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(54)发明名称

用于治疗目的新病毒颗粒

(57)摘要

本发明涉及一种病毒颗粒,其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段,其中所述S区段包含编码衍生自LCMV毒株WE的糖蛋白的开放阅读框,并且其中所述L区段包含编码衍生自LCMV毒株克隆13的L蛋白的开放阅读框。本发明还涉及相关的宿主细胞、生产此类病毒颗粒的方法、包含此类病毒颗粒的药物组合物和此类病毒颗粒的医药用途。

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1.一种病毒颗粒,其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含至少一个突变的氨基酸残基。

2.根据权利要求1所述的病毒颗粒,其中与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白在位置181和/或185处包含至少一个突变的氨基酸残基,其中优选地,与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含选自Arg 185→Trp和Ile 181→Met的至少一个突变。

3.根据权利要求1或2所述的病毒颗粒,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,所述L蛋白包含除Lys以外的氨基酸残基,优选地包含非碱性氨基酸残基,优选地包含中性亲水性氨基酸残基,优选地包含Asn或Gln,优选地包含Gln。

4.一种病毒颗粒,其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,所述L蛋白包含除Lys以外的氨基酸残基。

5.根据权利要求4所述的病毒颗粒,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,所述L蛋白包含非碱性氨基酸残基,优选地包含中性亲水性氨基酸残基,优选包含Asn或Gln,优选包含Gln。

6.根据权利要求4或5所述的病毒颗粒,其中与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含至少一个突变的氨基酸残基,其中优选地,与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白在位置181和/或185处包含至少一个突变的氨基酸残基,其中优选地,与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含选自Arg 185→Trp和Ile 181→Met的至少一个突变。

7.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段衍生自LCMV毒株WE或其变体,且其中所述L区段衍生自LCMV毒株克隆13或其变体。

8.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含编码与SEQ ID NO:6具有至少97%序列同一性的核蛋白的开放阅读框。

9.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含编码与SEQ ID NO:38具有至少90%序列同一性的Z蛋白的开放阅读框。

10.一种病毒颗粒,其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框和编码与SEQ ID NO:6具有至少97%序列同一性的核蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框和编码与SEQ ID NO:38具有至少90%序列同一性的Z蛋白的开放阅读框。

11.根据权利要求10所述的病毒颗粒,其中与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含至少一个突变的氨基酸残基,其中优选地,与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白在位置181和/或185处包含至少一个突变的氨基酸残基,其中优选地,与

SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含选自Arg 185→Trp和Ile 181→Met的至少一个突变。

12.根据权利要求10或11所述的病毒颗粒,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,所述L蛋白包含除Lys以外的氨基酸残基,优选地包含非碱性氨基酸残基,优选地包含中性亲水性氨基酸残基,优选地包含Asn或Gln,优选地包含Gln。

13.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够促进更强的肿瘤生长的降低。

14.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够促进更强的冷瘤生长的降低。

15.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够诱导更强的适应性免疫活化。

16.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒能够促进温肿瘤生长的降低,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述温肿瘤生长的降低至少一样强。

17.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒在全身施用后能够诱导降低的干扰素水平。

18.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够诱导更低浓度的一种或多种Th1-和促炎细胞因子。

19.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够诱导更低浓度的一种或多种Th1-和促炎细胞因子。

20.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE相比,所述病毒颗粒在小鼠中的致病性更低。

21.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够在小鼠中诱导降低的肝脏病状程度。

22.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒在神经元细胞中显示复制减少。

23.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE相比,所述病毒颗粒在肿瘤细胞中显示复制增加。

24.根据前述权利要求中任一项所述的病毒颗粒,其中与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒在健康器官中显示复制减少。

25.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含编码糖蛋白的开放阅读框,所述糖蛋白与SEQ ID NO:4或14所示的序列具有至少约98%、优选地至少约98.5%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.5%、优选地至少约99.7%的序列同一性,或优选地与SEQ ID NO:4或14所示的序列相同。

26.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含开放阅读框,所述开放阅读框包含与SEQ ID NO:3或13所示的序列具有至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%序列同一性的序列,或优选地包含与SEQ ID NO:3或13所示的序列相同的序列。

27.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含编码L蛋白的开放阅读框,所述L蛋白与SEQ ID NO:30或40所示的序列具有至少约91%,优选地至少约92%,优选地至少约93%,优选地至少约94%,优选地至少约95%,优选地至少约96%,优选地至少约97%,优选地至少约98%,优选地至少约99%,优选地至少约99.1%,优选地至少约99.2%,优选地至少约99.3%,优选地至少约99.4%,优选地至少约99.5%,优选地至少约99.6%,优选地至少约99.7%序列同一性,或优选地与SEQ ID NO:30或40所示的序列相同。

28.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含开放阅读框,所述开放阅读框包含与SEQ ID NO:29或39所示的序列具有至少约83%、优选地至少约84%、优选地至少约85%、优选地至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%、优选地至少约99.8%、优选地至少约99.9%序列同一性的序列,或优选地包含与SEQ ID NO:29或39所示的序列相同的序列。

29.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含编码核蛋白的开放阅读框,其中所述核蛋白与SEQ ID NO:6或16中任一所示的序列具有至少约98%、优选地98.5%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性,或优选地与SEQ ID NO:6或16中任一所示的序列相同。

30.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含开放阅读框,所述开放阅读框包含与SEQ ID NO:5或15所示的序列具有至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至

少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%序列同一性或优选地包含与SEQ ID NO:5或15所示的序列相同的序列。

31.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含编码Z蛋白的开放阅读框,所述Z蛋白与SEQ ID NO:28或38所示的序列具有至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性,或优选地与SEQ ID NO:28或38所示的序列相同。

32.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含开放阅读框,所述开放阅读框包含与SEQ ID NO:27或37所示的序列具有至少约84%、优选地至少约85%、优选地至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%序列同一性的序列或包含与SEQ ID NO:27或37所示的序列相同的序列。

33.根据前述权利要求中任一项所述的病毒颗粒,其中所述S区段包含与SEQ ID NO:1或11所示的序列具有至少约86%,优选地至少约87%,优选地至少约88%,优选地至少约89%,优选地至少约90%,优选地至少约91%,优选地至少约92%,优选地至少约93%,优选地至少约94%,优选地至少约95%,优选地至少约96%,优选地至少约97%,优选地至少约98%,优选地至少约99%,优选地至少约99.1%,优选地至少约99.2%,优选地至少约99.3%,优选地至少约99.4%,优选地至少约99.5%,优选地至少约99.6%,优选地至少约99.7%序列同一性,优选地至少约99.7%,优选地至少约99.8%,优选地至少约99.9%序列同一性的序列,或优选包含与SEQ ID NO:1或11所示的序列相同的序列。

34.根据前述权利要求中任一项所述的病毒颗粒,其中所述L区段包含与SEQ ID NO:21或31所示的序列具有至少约83%,优选地至少约84%,优选地至少约85%,优选地至少约86%,优选地至少约87%,优选地至少约88%,优选地至少约89%,优选地至少约90%,优选地至少约91%,优选地至少约92%,优选地至少约93%,优选地至少约94%,优选地至少约95%,优选地至少约96%,优选地至少约97%,优选地至少约98%,优选地至少约99%,优选地至少约99.1%,优选地至少约99.2%,优选地至少约99.3%,优选地至少约99.4%,优选地至少约99.5%,优选地至少约99.6%,优选地至少约99.7%序列同一性,优选地至少约99.7%,优选地至少约99.8%,优选地至少约99.9%序列同一性的序列,或优选地包含与SEQ ID NO:21或31所示的序列相同的序列。

35.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒是感染性的。

36.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒具有复制能力。

37.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒是减毒的。

38.根据前述权利要求中任一项所述的病毒颗粒,其中编码所述糖蛋白的ORF处于5'非

翻译区(UTR)的控制下。

39.根据前述权利要求中任一项所述的病毒颗粒,其中编码所述L蛋白的ORF处于3'非翻译区(UTR)的控制下。

40.根据前述权利要求中任一项所述的病毒颗粒,其中编码所述核蛋白的ORF处于3'非翻译区(UTR)的控制下。

41.根据前述权利要求中任一项所述的病毒颗粒,其中编码所述Z蛋白的ORF处于5'非翻译区(UTR)的控制下。

42.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒具有双区段基因组。

43.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒是沙粒病毒颗粒。

44.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒是LCMV颗粒。

45.根据前述权利要求中任一项所述的病毒颗粒,其中所述病毒颗粒不包含来自LCMV之外的生物的ORF。

46.一种宿主细胞,其包含前述权利要求中任一项所定义的LCMV S区段和LCMV L区段。

47.一种宿主细胞,其包含

(a)权利要求1-45中任一项定义的编码糖蛋白的ORF的、权利要求1-45中任一项定义的编码L蛋白的ORF的、权利要求1-45中任一项定义的编码核蛋白的ORF的和权利要求1-45中任一项定义的编码Z蛋白的ORF的cDNA;和/或

(b)权利要求1-45中任一项所定义的LCMV S区段和LCMV L区段的cDNA。

48.根据权利要求46或47所述的宿主细胞,其中所述宿主细胞是HEK293细胞。

49.一种生产权利要求1-45中任一项所述的病毒颗粒的方法,其包括在适于病毒颗粒形成的条件下培养权利要求46-48中任一项所述的宿主细胞。

50.根据权利要求49所述的方法,其还包括回收和/或纯化所述病毒颗粒。

51.一种药物组合物,其包含含有LCMV S区段和LCMV L区段的病毒颗粒,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。

52.根据权利要求51所述的药物组合物,其中所述病毒颗粒是权利要求1-45中任一项所述的病毒颗粒。

53.一种用在治疗中的包含LCMV S区段和LCMV L区段的病毒颗粒,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。

54.根据权利要求53所述用途的病毒颗粒,其中所述病毒颗粒是权利要求1-45中任一项所述的病毒颗粒。

55.根据权利要求53或54所述用途的病毒颗粒,其中所述用途为用在癌症的治疗中。

56.根据权利要求53-55中任一项所述用途的病毒颗粒,其中所述用途为用在人类受试者的治疗中。

57.根据权利要求53-56中任一项所述用途的病毒颗粒,其中所述用途为用在人类癌症的治疗中。

58.根据权利要求53-57中任一项所述用途的病毒颗粒,其中所述用途为用在冷肿瘤的

治疗中。

59.根据权利要求53-58中任一项所述用途的病毒颗粒,其中所述用途是为用在热肿瘤的治疗中。

60.根据权利要求53-59中任一项所述用途的病毒颗粒,其中所述用途为用在选自以下的肿瘤的治疗中:肛门癌、支气管癌、肺癌、子宫内膜癌、胆囊癌、膀胱癌、肝细胞癌、睾丸癌、结肠癌、结肠直肠癌、结肠直肠癌、肝细胞癌、睾丸癌、结肠癌、膀胱肿瘤、膀胱癌、膀胱肿瘤、肝细胞癌、肺癌、肺癌、子宫内膜癌、结肠直肠癌、直肠癌、喉癌、食管癌、胃癌、乳腺癌、肾癌、卵巢癌、胰腺癌、咽癌、口咽癌、前列腺癌、甲状腺癌、宫颈癌、血管肉瘤、软骨肉瘤、尤文肉瘤、纤维肉瘤、卡波西肉瘤、脂肪肉瘤、平滑肌肉瘤、恶性纤维化组织细胞瘤、淋巴瘤、白血病、神经性肉瘤、骨肉瘤和横纹肌肉瘤。

61.一种包含LCMV S区段和LCMV L区段的病毒颗粒在制备药物中的用途,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中所述药物优选用于癌症的治疗。

62.一种治疗疾病的方法,所述方法包括向有此需要的受试者施用有效量的包含LCMV S区段和LCMV L区段的病毒颗粒,其中S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中所述疾病优选为癌症。

用于治疗目的新病毒颗粒

[0001] 相关申请的交叉引用

[0002] 本申请要求2021年2月26日提交的欧洲专利申请EP 21159746.3的优先权的权益，其内容在此通过引用整体并入以用于所有目的。

技术领域

[0003] 本发明涉及一种病毒颗粒，其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段，其中所述S区段包含编码衍生自LCMV毒株WE的糖蛋白的开放阅读框，并且其中所述L区段包含编码衍生自LCMV毒株克隆13(Clone 13)的L蛋白的开放阅读框。本发明还涉及相关的宿主细胞、生产此类病毒颗粒的方法、包含此类病毒颗粒的药物组合物和此类病毒颗粒的医药用途。

背景技术

[0004] LCMV属于哺乳动物沙粒病毒属，并且可以普遍地自小鼠和其它啮齿动物中分离(Radoshitzky等，(2020)在D.M.Knipe和P.M.Howley(编辑)，Fields Virology中)。宫内感染导致后代持续感染而无临床症状，尽管病毒载量可能非常高(Radoshitzky等，(2020)在D.M.Knipe和P.M.Howley(编辑)，Fields Virology中)。受感染的动物终生通过尿液、唾液、鼻分泌物和粪便传播活病毒，导致暴露的幼稚啮齿动物的症状性感染。

[0005] 人类通过与感染的啮齿类动物或感染的啮齿类动物的分泌物紧密接触、通过实体器官移植或通过垂直经胎盘传播而感染LCMV。除了通过实体器官移植之外，人对人的水平传播尚未见报道。免疫系统完整的人的出生后感染通常是无症状的或导致轻度发热性疾病。很少观察到温和且可逆的神经症状。妊娠期间的感染增加了流产、严重CNS或眼部畸形的风险。神经后遗症包括痉挛性四肢轻瘫、智力迟钝、癫痫发作(seizures)和视力损伤。在免疫抑制的器官接受者中，LCMV感染可能是致命的，然而，迄今为止描述的病例少于20例。

[0006] LCMV毒株已被分成四种不同的谱系，将最常用的实验室毒株Armstrong和WE分组为谱系I(Radoshitzky等，(2020)在D.M.Knipe和P.M.Howley(编辑)，Fields Virology中)。这些实验室毒株对健康人群具有低致病潜力，但可在易感动物中引起实质性疾病和死亡。与由两种毒株及其衍生的衍生物在易感动物中引起的临床表现一致，将Armstrong毒株归类为嗜神经组织型，而将WE毒株归类为嗜内脏型。

[0007] LCMV基因组由两个命名为S(mall)和L(arge)的负链RNA区段组成。S区段编码表面糖蛋白(GP)和核壳蛋白(NP)，而L区段编码病毒聚合酶(LP)和Z蛋白(Radoshitzky等，(2020)在D.M.Knipe和P.M.Howley(编辑)，Fields Virology中)。

[0008] 一些LCMV WE株衍生物已被描述为实体瘤治疗的有效药剂(WO 2016/166285A1，WO 2020/053324A1)。然而，LCMV毒株WE具有默认的生物安全水平(BSL)3类，这将排除此类产品的使用，因为在BSL 3条件下生产和应用此类毒株实际上是不可能的。

[0009] 因此，存在未满足的提供具有更高减毒水平同时与LCMV毒株WE相比具有相当的或甚至改善的抗肿瘤性质的病毒的需求。因此，本发明的目的是提供可用于治疗的另外的和/

或改进的病毒。

发明内容

[0010] 本发明涉及一种病毒颗粒,其包含淋巴细胞性脉络丛脑膜炎病毒(LCMV)S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中与SEQ ID NO:4所示的糖蛋白序列相比,所述糖蛋白包含至少一个突变的氨基酸残基。

[0011] 本发明还涉及一种病毒颗粒,其包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,所述L蛋白包含除Lys以外的氨基酸残基。

[0012] 本发明还涉及一种病毒颗粒,其包含LCMV S区段和LCMV L区段,其中S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框和编码与SEQ ID NO:6具有至少97%序列同一性的核蛋白的开放阅读框,并且其中L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框和编码与SEQ ID NO:38具有至少90%序列同一性的Z蛋白的开放阅读框。

[0013] 本发明还涉及一种宿主细胞,其包含本发明病毒颗粒中所含的LCMV S区段和LCMV L区段的宿主细胞。

[0014] 本发明还涉及一种宿主细胞,其包含(a)本发明的病毒颗粒中包含的编码糖蛋白的ORF的、编码L蛋白的ORF的、编码核蛋白的ORF的和编码Z蛋白的ORF的cDNA;和/或本发明的病毒颗粒中包含的LCMV S区段和LCMV L区段的cDNA。

[0015] 本发明还涉及一种生产本发明的病毒颗粒的方法,其包括在适于病毒颗粒形成的条件下培养本发明的宿主细胞。

[0016] 本发明还涉及一种药物组合物,其包含含有LCMV S区段和LCMV L区段的病毒颗粒,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。

[0017] 本发明还涉及一种用在治疗中、特别是用在癌症的治疗中的包含LCMV S区段和LCMV L区段的病毒颗粒,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。

附图说明

[0018] 图1:携带鼠B16肿瘤的B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,肿瘤生长测量7天并在第7天测量肿瘤质量(n=5只动物/组),将单因素ANOVA和Dunnett's多重比较检验用于统计。

[0019] 图2:携带鼠B16肿瘤的B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自肿瘤的CD8T细胞(n=5只动物/组)。

[0020] 图3:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自肿瘤的病毒特异性(GP33)CD8T细胞(n=5只动物/组)。

[0021] 图4:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,肿瘤生长测量11天(n=4只动物/组),将t-检验用于统计。

[0022] 图5:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第11天通过流式细胞术测量肿瘤浸润T细胞($CD3^+$)(n=4只动物/组)。

[0023] 图6:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第11天通过流式细胞术测量肿瘤浸润细胞毒性T细胞($CD3^+CD8^+$)(n=4只动物/组)。

[0024] 图7:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第11天对LCMV(NP蛋白+)CD8 T细胞($CD8^+$)进行肿瘤免疫组织化学(IHC)(n=(3)4只动物/组)。

[0025] 图8:通过HEK293T和人肿瘤细胞系H1975(肺)、SkMM(骨髓瘤)、Ma-Mel-51(黑素瘤)、C643(甲状腺)和鼠肿瘤细胞系MC-57(纤维肉瘤)和B16F10(黑素瘤)中的流式细胞术(NP蛋白),MOI=0.1的野生型(WE,克隆13)和重组病毒体外复制20小时。

[0026] 图9:通过在MC57细胞、人肿瘤细胞系H1975(肺)、Mame186a和51(黑素瘤)、C643(甲状腺)、鼠肿瘤细胞系511950(胰腺)、Tramp-C2(前列腺)、B16.F10(黑素瘤)和鼠树突细胞系JAWSII中的集落形成测定,MOI=0.1的野生型(WE)和重组WE-C113病毒体外复制24小时或48小时。

[0027] 图10:通过在人原代神经元、鼠肿瘤细胞系MC-57(纤维肉瘤)、鼠MC57G细胞、人肺腺癌细胞系A549和人甲状腺癌细胞系FTC133中的体外复制测定,MOI=0.1的野生型(WE)和重组病毒体外复制48小时,线:初始接种物。

[0028] 图11:衍生自骨髓的树突细胞。

[0029] 图12:以2×10E4 PFU/动物静脉注射处理Bl/6小鼠,注射后第1天和第3天的血清细胞因子。虚线表示检测下限。

[0030] 图13:以2×10E4 PFU/动物静脉注射处理Bl/6小鼠,注射后第1天和第3天的血清细胞因子。虚线表示检测下限。

[0031] 图14:在第0天以2×10E6 PFU/动物静脉注射LCMV野生型(WE,克隆13,ARM)和重组(克隆13L,WE S)毒株的小鼠品系(n=3只动物/组)。

[0032] 图15:在第0天以2×10E6 PFU/动物静脉注射LCMV野生型(WE,克隆13,ARM)和重组(克隆13L,WE S)毒株的小鼠品系(n=3只动物/组)。

[0033] 图16:在第0天以2×10E6 PFU/动物静脉注射LCMV野生型(WE,克隆13,ARM)和重组(克隆13L,WE S)毒株的小鼠品系(n=3只动物/组)。

[0034] 图17:在第0天以2×10E6 PFU/动物静脉注射LCMV野生型(WE,克隆13,ARM)和重组(克隆13L,WE S)毒株的小鼠品系(n=3只动物/组)。

[0035] 图18:在以2×10E4 PFU/动物静脉注射治疗携带B16黑素瘤的Bl/6动物,注射7天后的ALT/AST血清水平。.

[0036] 图19:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,第7天的来自指定器官的集落形成分析(n=5只动物/组)。

[0037] 图20:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,第11天的来自指定器官的空斑形成试验(n=4只动物/组)。

[0038] 图21:通过人肿瘤细胞系H1975(肺)、GIST-T1(胃肠的)、Ma-Mel-86a和51(黑素瘤)和鼠肿瘤细胞系MC-57G(纤维肉瘤)中的流式细胞术(NP蛋白),MOI=0.1的野生型(WE)和重组病毒体外复制20小时。线:LCMV毒株WE的复制。

[0039] 图22:通过人肿瘤细胞系H1975(肺)、Gist-T1(胃肠的)、Mamel86a和51(黑素瘤)和鼠肿瘤细胞系MC-57G(纤维肉瘤)中的流式细胞术(NP蛋白),MOI=0.1的野生型(WE)和重组病毒体外复制20小时。线:LCMV毒株WE的复制。

[0040] 图23:接种分化的人肌肉成肌细胞、人骨骼肌成肌细胞(SkMM)、肺腺癌细胞系A549和鼠纤维肉瘤细胞系MC57G(100.000个细胞/孔),并使其感染MOI=0.1的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)、I181M-Cl13(L)或R185W-Cl13(L)感染。20小时后,对细胞进行LCMV核蛋白(NP,克隆VL4)的细胞内染色。通过流式细胞术分析感染LCMV的细胞(LCMV NP^+)的百分比。线:LCMV毒株WE的复制。

[0041] 图24:通过在人原代神经元以及作为比较的鼠肿瘤细胞系MC57G(纤维肉瘤)中的复制测定,MOI=0.1的野生型(WE)和重组病毒体外复制48小时,线:初始接种物。

[0042] 图25:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,肿瘤生长测量7天并在第7天测量肿瘤质量(n=5只动物/组),将单因素ANOVA和Dunnett's多重比较检验用于统计。

[0043] 图26:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自dLN和肿瘤的病毒特异性(GP33)和CD8 T细胞(n=5只动物/组)。

[0044] 图27:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自dLN和肿瘤的病毒特异性(GP33)和CD8 T细胞(n=5只动物/组)。

[0045] 图28:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自dLN和肿瘤的病毒特异性(GP33)和CD8 T细胞(n=5只动物/组)。

[0046] 图29:携带鼠B16肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,在第7天通过流式细胞术分析来自dLN和肿瘤的病毒特异性(GP33)和CD8 T细胞(n=5只动物/组)。

[0047] 图30:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,肿瘤生长测量11天(n=4只动物/组),将t-检验用于统计

[0048] 图31:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,除了由于实验错误的P52-FP7-Cl13(L)组(n=3)外(其值接近/低于对照),在第11天通过流式细胞术测量肿瘤T细胞,n=4只动物/臂。

[0049] 图32:携带鼠MC38肿瘤的Bl/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,除了由于实验错误的P52-FP7-Cl13(L)组(n=3)外(其值接近/低于

对照),在第11天通过流式细胞术测量肿瘤T辅助细胞,n=4只动物/臂。

[0050] 图33:携带鼠MC38肿瘤的B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,除了由于实验错误的P52-FP7-C113(L)组(n=3)外(其值接近/低于对照),在第11天通过流式细胞术测量肿瘤细胞毒性T细胞,n=4只动物/臂。

[0051] 图34:幼稚(naïve)B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,第2和4天进行细胞因子LegendPlex(n=3只动物/组)。

[0052] 图35:携带鼠B16肿瘤的B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,第7天的来自指定器官的空斑形成试验(n=5只动物/组)。

[0053] 图36:携带鼠MC38肿瘤的B1/6小鼠,在第0天以2×10E4 PFU/动物静脉注射LCMV野生型(WE)和重组毒株,第11天的来自指定器官的空斑形成试验(n=4只动物/组)。

[0054] 图37:以1.5×10^{6}个细胞/mL的密度,用MOI=0.001的LCMV毒株WE-C113(L)、P52-C113(L)或P52-WE(L)感染FreeStyle 293-F悬浮细胞。在感染后12、24、30、34、40、48、72和96小时收获上清液。通过空斑形成试验分析上清液中的LCMV滴度。

[0055] 图38:LCMV毒株A.WE,B.P52,C.Armstrong和D.克隆13的L区段、S区段、GPC、NP、ZP和LP的核酸和氨基酸序列。

具体实施方式

[0056] 本申请的发明人相信WE毒株的致病性可以总是由位于L区段上的元件决定,而WE和其它LCMV毒株的S区段对致病性没有贡献。因此,认为用诸如Armstrong毒株、克隆13毒株的另一种LCMV毒株及它们的衍生物的相应区段取代WE毒株的L区段将产生一种重新组合的实验室毒株,其不再显示原始致病特征,包括在NHP和其它易感动物中的肝脏致病性。

[0057] 本申请的发明人惊奇地发现,与LCMV WE毒株相比,包含被认为对致病性没有贡献的LCMV WE株的S区段的元件或其衍生物和被认为对致病性没有贡献的克隆13或Armstrong毒株的L区段的元件或其衍生物的病毒毒株(特别是在肿瘤治疗中)具有改善的性质。这种病毒毒株不再能够在NHP、啮齿动物或豚鼠中诱导包括肝脏疾病的LCMV特异性疾病(Riviere等,(1985)Journal of virology,55:704-09;Riviere等,(1986)Med Microbiol Immunol,175:191-2;Baccala等,(2014)Proc Natl Acad Sci USA,111:8925-30;Oldstone等,(2018)Proceedings of the National Academy of Sciences,115:E7814)。

[0058] 本申请的发明人对幼稚和易感啮齿动物进行的研究确实证明,与LCMV WE毒株相比,本发明的重新组合的病毒具有降低的致病性(包括肝脏致病性)(实施例16、17、18、19和35)。这些结果确实证实本发明的病毒颗粒可以产生基于病毒的产物,这些产品可以在生产和临床研究期间得到安全处理,原因在于野生型LCMV毒株的致病性得到降低,所述致病性包括肝脏致病性和嗜神经性(实施例10、21、24)。

[0059] 由于在不同来源的细胞中的复制能力严重降低(高达>100倍)(实施例8和9),本发明的病毒颗粒可显示出在幼稚动物体内诱导致病细胞因子的潜力大大降低,同时可能不存在任何诱导器官致病性的迹象(实施例12-17)。值得注意的是,在实施例8中,仅包含WE毒株衍生的S区段元件和克隆13毒株衍生的L区段元件的病毒颗粒,而不是包含克隆13毒株衍生的S区段元件和WE毒株衍生的L区段元件的病毒颗粒显示减弱的复制,这支持了WE和克隆13毒株的致病性分别由其L或S区段决定的假设。

[0060] 当感染LCMV时,表现出对病毒诱导的病状的易感性((Schnell等,(2012)PLoS Pathog,8:e1003073))的FVB小鼠品系易患出血热样疾病,包括血小板减少症和肝细胞坏死。重要的是,FVB小鼠中的疾病模拟了猕猴中的LCMV疾病和阿根廷出血热的临床症状(Schnell等,(2012)PLoS Pathog,8:e1003073)。然而,与LCMV毒株WE、克隆13和Armstrong不同,在实施例14-17中,感染本发明的病毒颗粒既不导致动物体重减轻,也不导致肝脏病状(liver pathology)或出血热样疾病的任何其它症状。

[0061] 本发明的病毒颗粒用于临床开发的一个重要且令人惊讶的特征是尽管它们是减毒的,但它们保持或甚至增强了WE毒株的强抗肿瘤作用(Kalkavan等,(2017)Nat Commun,8:14447)。本发明的病毒颗粒可以具有另外的修饰以增加其肿瘤趋性(实施例21-23)。此类修饰可包括GP的位置181和/或185的突变,特别是Arg 185→Trp和/或Ile 181→Met。实际上,此类病毒颗粒在鼠肿瘤模型中(实施例25)可表现出强的抗肿瘤作用,但可具有衍生它的WE-克隆13株的减毒表型(实施例34和38)。据报道,LCMV的致病性主要由免疫系统的抗病毒功能决定(directed),并与感染器官中病毒复制的强度相关(Lang等,(2010)Cell Physiol Biochem,26:263-72)。与WE毒株相比,此类修饰的病毒颗粒可以导致更强的早期LCMV定向T细胞应答,这是主要的抗病毒免疫效应机制,并且其器官分布在感染早期就已经得到控制(实施例35)。

[0062] 在先前的出版物中,由于先天性(Th1和促炎细胞因子)和适应性(CD8T细胞)免疫应答的过度调节和失调,将LCMV描述为能够诱导器官损伤(例如肝)(Lang等,(2010)Cell Physiol Biochem,26:263-72;Schnell等,(2012)PLoS Pathog,8:e1003073;Oldstone等,(2018)Proceedings of the National Academy of Sciences,115:E7814)。本申请的发明人惊奇地发现-尽管观察到与野生型LCMV毒株Armstrong、克隆13和WE的细胞因子应答相似的模式-本发明病毒颗粒的免疫应答强度显著更低。这一观察结果对于IFN-α特别重要,对于IFN-α,在感染早期的高细胞因子水平与各动物模型中的器官损伤有关(Schnell等,(2012)PLoS Pathog,8:e1003073)。相对地,本发明的病毒颗粒可在感染早期诱导显著更低的IFN-α和IFN-γ水平(实施例12和13),这强烈表明了显著更低的IFN介导的有害作用的可能性(Baccala等,(2014)Proc Natl Acad Sci USA,111:8925-30)。此外,感染后的不同时间点(第1天和第3天),促炎细胞因子IL-6和TNF-α以及IL-10也可显著降低,这表明病毒控制增强(Lang等,(2010)Cell Physiol Biochem,26:263-72;Schnell等,(2012)PLoS Pathog,8:e1003073)。

[0063] 总之,本发明的病毒颗粒,尽管保持或甚至增强了它们的抗肿瘤功效,但仍表现出了强的减毒的表型,并表现出了甚至更强的体内减毒免疫表型。

[0064] 因此,本发明涉及一种含有LCMV S区段和LCMV L区段的病毒颗粒。S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。

[0065] S区段还可以包含编码核蛋白的开放阅读框。该核蛋白可与SEQ ID NO:6具有至少97%的序列同一性。

[0066] L区段还可包括L区段。该L区段可包含编码与SEQ ID NO:38具有至少90%序列同一性的Z蛋白的开放阅读框。

[0067] 优选地,本发明的病毒颗粒为沙粒病毒颗粒,更优选地为淋巴细胞性脉络丛脑膜

炎病毒(LCMV)颗粒。

[0068] 野生型沙粒病毒基因组区段和ORF是本领域已知的。具体地,沙粒病毒基因组由S区段和L区段组成。S区段携带编码GP和NP的ORF。L区段编码L蛋白和Z蛋白。两个区段的侧翼是各自的5'和3'UTR。

[0069] 优选地,本发明的病毒颗粒包含与野生型沙粒病毒的基因组区段对应的基因组区段。这意味着S区段携带编码GP和NP的ORF,和L区段编码L蛋白和Z蛋白。在S区段上,编码糖蛋白的ORF在5'非翻译区(UTR)的控制下,核蛋白在3'UTR的控制下。在L区段上,编码L蛋白的ORF在3'UTR的控制下,编码Z蛋白的ORF在5'UTR的控制下。因此,优选地,本公开的病毒颗粒的基因位于它们的天然位置。因此,优选地,本发明的病毒颗粒具有双区段基因组。优选地,本发明病毒颗粒的基因组由本文所述的一个L区段和一个S区段组成。LCMV S区段的说明性实例示于SEQ ID NO:1、11、21和31所示的LCMV L区段的说明性实例示于SEQ ID NO:2、12、22和32。

[0070] LCMV的几种毒株是本发明的一部分。如本文所用,LCMV"WE"、"毒株WE"、"WE毒株"等是指具有SEQ ID NO:1和2所示的基因组区段的LCMV。如本文所用,LCMV"P52"、"P52-WE"、"毒株P52"、"P52毒株"等是指毒株WE的变体/衍生物,其具有SEQ ID NO:11和12所示的基因组区段。如本文所用,LCMV"Armstrong"、"毒株Armstrong"、"Armstrong毒株"等是指LCMV毒株Armstrong 53b,其具有SEQ ID NO:21和22所示的基因组区段。如本文所用,LCMV"克隆13"、"C113"、"毒株克隆13"、"克隆13毒株"等是指具有SEQ ID NO:31和32所示的基因组区段的LCMV。

[0071] 术语"糖蛋白"、"GP"和"G蛋白"可互换使用,指LCMV衍生的糖蛋白,其被认为介导受体结合和膜融合。糖蛋白的说明性实例示于SEQ ID NO:4、14、24和34。编码糖蛋白的基因的说明性实例示于SEQ ID NO:3、13、23和33。

[0072] 术语"L蛋白"和"LP"可互换使用,指LCMV衍生的RNA聚合酶L。L蛋白的说明性实例示于SEQ ID NO:10、20、30和40。编码L蛋白的基因的说明性实例示于SEQ ID NO:9、19、29和39。

[0073] 术语"核蛋白"、"N蛋白"和"NP"可互换使用,指LCMV衍生的核蛋白。核蛋白的说明性实例示于SEQ ID NO:6、16、26和36。编码核蛋白的基因的说明性实例示于SEQ ID NO:5、15、25和35。

[0074] 术语"Z蛋白"或"ZP"可互换使用,指LCMV衍生的小环指蛋白Z(small RING finger protein Z)。Z蛋白的说明性实例示于SEQ ID NO:8、18、28和38。编码Z蛋白的基因的说明性实例示于SEQ ID NO:7、17、27和37。

[0075] 本发明的病毒颗粒包含糖蛋白,其中与SEQ ID NO:4所示的糖蛋白序列相比,该糖蛋白可包含至少一个突变的氨基酸残基。例如,与SEQ ID NO:4所示的糖蛋白序列相比,该糖蛋白可在位置181和/或185处包含至少一个突变的氨基酸残基。然而优选地,与SEQ ID NO:4相比,该糖蛋白在两个位置都包含突变。在这些位置处的优选突变选自Arg 185→Trp和Ile 181→Met。因此,病毒颗粒可以具有任何一个突变或优选地两个突变。

[0076] 不希望受理论束缚,认为糖蛋白中一个或两个上述突变的存在可以改善LCMV的功能(例如抗肿瘤活性),而与其它突变(特别是LCMV的其它基因或蛋白中的其它突变)的存在无关。

[0077] 本发明的病毒颗粒包含L蛋白,其中在对应于SEQ ID NO:40的线性多肽序列的位置1079处,该L蛋白包含除Lys以外的氨基酸残基。优选地,在该位置的氨基酸残基是非碱性氨基酸残基,更优选地为中性亲水性氨基酸残基,甚至更优选地为Asn或Gln,最优选地为Gln。

[0078] 术语"氨基酸"或"氨基酸残基"通常是指具有其本领域公认定义的氨基酸,例如选自以下的氨基酸:丙氨酸(Ala或A);精氨酸(Arg或R);天冬酰胺(Asn或N);天冬氨酸(Asp或D);半胱氨酸(Cys或C);谷氨酰胺(Gln或Q);谷氨酸(Glu或E);甘氨酸(Gly或G);组氨酸(His或H);异亮氨酸(Ile或I):亮氨酸(Leu或L);赖氨酸(Lys或K);甲硫氨酸(Met或M);苯丙氨酸(Phe或F);脯氨酸(Pro或P);丝氨酸(Ser或S);苏氨酸(Thr或T);色氨酸(Trp或W);酪氨酸(Tyr或Y);和缬氨酸(Val或V),但可视需要使用经修饰、合成或罕见的氨基酸。基于一般侧链性质,将天然存在的残基分为以下的组:(1)疏水性:甲硫氨酸、丙氨酸、缬氨酸、亮氨酸、异亮氨酸;(2)中性亲水性:半胱氨酸、丝氨酸、苏氨酸、天冬酰胺、谷氨酰胺;(3)酸性:天冬氨酸、谷氨酸;(4)碱性:组氨酸、赖氨酸、精氨酸;(5)影响链取向的残基:甘氨酸、脯氨酸;和(6)芳香族:色氨酸、酪氨酸、苯丙氨酸。在一些实施方案中,置换可能需要将这些类别中一类的成员换成另一类。

[0079] 本发明的病毒颗粒包含S区段和L区段,其中S区段优选衍生自LCMV毒株WE或其变体,且其中L区段优选衍生自LCMV毒株克隆13或其变体。

[0080] L区段的变体可以与原L区段的序列具有至少约83%、优选地至少约84%、优选地至少约85%、优选地至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性、优选地至少约99.7%、优选地至少约99.8%、优选地至少约99.9%的序列同一性。

[0081] 本文公开的病毒颗粒可具有包含下述序列或优选地由下述序列组成的L区段,所述序列与SEQ ID NO:21或31所示的序列具有至少约83%、优选地至少约84%、优选地至少约85%、优选地至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性,优选地至少约99.7%、优选地至少约99.8%、优选地至少约99.9%的序列同一性,或优选地与SEQ ID NO:21或31所示的序列相同。

[0082] S区段的变体可以与原S区段的序列具有至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少

约99.6％、优选地至少约99.7％的序列同一性，优选地至少约99.7％、优选地至少约99.8％、优选地至少约99.9％的序列同一性。

[0083] 本文公开的病毒颗粒可具有包含这样序列或优选由该序列组成的S区段，所述序列与SEQ ID NO:1或11所示的序列具有至少约86％、优选地至少约87％、优选地至少约88％、优选地至少约89％、优选地至少约90％、优选地至少约91％、优选地至少约92％、优选地至少约93％、优选地至少约94％、优选地至少约95％、优选地至少约96％、优选地至少约97％、优选地至少约98％、优选地至少约99％、优选地至少约99.1％、优选地至少约99.2％、优选地至少约99.3％、优选地至少约99.4％、优选地至少约99.5％、优选地至少约99.6％、优选地至少约99.7％的序列同一性，优选地至少约99.7％、优选地至少约99.8％、优选地至少约99.9％的序列同一性，或优选地与SEQ ID NO:1或11所示的序列相同。

[0084] 本发明的包含LCMV的病毒颗粒优选包含S区段和LCMV L区段，其中所述S区段包含编码与SEQ ID NO:4具有至少97％序列同一性的糖蛋白的开放阅读框和编码与SEQ ID NO:6具有至少97％序列同一性的核蛋白的开放阅读框，并且其中所述L区段包含编码与SEQ ID NO:40具有至少90％序列同一性的L蛋白的开放阅读框和编码与SEQ ID NO:38具有至少90％序列同一性的Z蛋白的开放阅读框。

[0085] 本文公开的编码糖蛋白的开放阅读框可以编码与SEQ ID NO:4或14所示的序列具有至少约98％、优选地至少约98.5％、优选地至少约99％、优选地至少约99.1％、优选地至少约99.2％、优选地至少约99.3％、优选地至少约99.4％、优选地至少约99.5％、优选地至少约99.5％、优选地至少约99.7％序列同一性的序列，或优选地编码与SEQ ID NO:4或14所示的序列相同的序列。

[0086] 本文公开的编码糖蛋白的开放阅读框可以包含与SEQ ID NO:3或13所示的序列具有至少约87％、优选地至少约88％、优选地至少约89％、优选地至少约90％、优选地至少约91％、优选地至少约92％、优选地至少约93％、优选地至少约94％、优选地至少约95％、优选地至少约96％、优选地至少约97％、优选地至少约98％、优选地至少约99％、优选地至少约99.1％、优选地至少约99.2％、优选地至少约99.3％、优选地至少约99.4％、优选地至少约99.5％、优选地至少约99.6％、优选地至少约99.7％序列同一性的序列，或优选地与SEQ ID NO:3或13所示的序列相同的序列。

[0087] 本文公开的编码L蛋白的开放阅读框可以编码与SEQ ID NO:30或40所示的序列具有至少约91％、优选地至少约92％、优选地至少约93％、优选地至少约94％、优选地至少约95％、优选地至少约96％、优选地至少约97％、优选地至少约98％、优选地至少约99％、优选地至少约99.1％、优选地至少约99.2％、优选地至少约99.3％、优选地至少约99.4％、优选地至少约99.5％、优选地至少约99.6％、优选地至少约99.7％序列同一性的序列，或优选地与SEQ ID NO:30或40所示的序列相同的序列。

[0088] 本文公开的编码L蛋白的开放阅读框可以与SEQ ID NO:29或39所示的序列具有至少约83％、优选地至少约84％、优选地至少约85％、优选地至少约86％、优选地至少约87％、优选地至少约88％、优选地至少约89％、优选地至少约90％、优选地至少约91％、优选地至少约92％、优选地至少约93％、优选地至少约94％、优选地至少约95％、优选地至少约96％、优选地至少约97％、优选地至少约98％、优选地至少约99％、优选地至少约99.1％、优选地至少约99.2％、优选地至少约99.3％、优选地至少约99.4％、优选地至少约99.5％、优选地

至少约99.6%、优选地至少约99.7%、优选地至少约99.8%、优选地至少约99.9%的序列同一性,或优选地与SEQ ID NO:29或39所示的序列相同。

[0089] 本文公开的编码核蛋白的开放阅读框可以编码与SEQ ID NO:6或16中任一项所示的序列具有至少约98%、优选地至少约98.5%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%序列同一性的序列或优选地与SEQ ID NO:6或16中任一项所示的序列相同的序列。

[0090] 本文公开的编码核蛋白的开放阅读框可以与SEQ ID NO:5或15所示的序列具有至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性,或优选地与SEQ ID NO:5或15所示的序列相同。

[0091] 本文公开的编码Z蛋白的开放阅读框可以编码与SEQ ID NO:28或38所示的序列具有至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%序列同一性的序列,或优选地与SEQ ID NO:28或38所示的序列相同的序列。

[0092] 本文公开的编码Z蛋白的开放阅读框可以与SEQ ID NO:27或37所示的序列具有至少约84%、优选地至少约85%、优选地至少约86%、优选地至少约87%、优选地至少约88%、优选地至少约89%、优选地至少约90%、优选地至少约91%、优选地至少约92%、优选地至少约93%、优选地至少约94%、优选地至少约95%、优选地至少约96%、优选地至少约97%、优选地至少约98%、优选地至少约99%、优选地至少约99.1%、优选地至少约99.2%、优选地至少约99.3%、优选地至少约99.4%、优选地至少约99.5%、优选地至少约99.6%、优选地至少约99.7%的序列同一性,或与SEQ ID NO:27或37所示的序列相同。

[0093] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4或14(其中SEQ ID NO:14是优选的)具有至少98.5%序列同一性的糖蛋白的开放阅读框,和编码与SEQ ID NO:6或16(其中SEQ ID NO:16是优选的)具有至少98.5%序列同一性的核蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:30或40(其中SEQ ID NO:40是优选的)具有至少95%序列同一性的L蛋白的开放阅读框,和编码与SEQ ID NO:28或38(其中SEQ ID NO:38是优选的)具有至少95%序列同一性的Z蛋白的开放阅读框。

[0094] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4或14(其中SEQ ID NO:14是优选的)具有至少98%序列同一性的糖蛋白的开放阅读框,和编码与SEQ ID NO:6或16(其中SEQ ID NO:16是优选的)具有至少98%序列同一性的核蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:30或40(其中SEQ ID NO:40是优选的)具有至少98%序列同一性的L蛋白的开放阅读框,和编码与SEQ ID NO:28或38(其中SEQ ID NO:38是优选的)具有至少98%序列同一性的Z蛋白的开放阅读框。

[0095] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4或14(其中SEQ ID NO:14是优选的)具有至少99%序列同一性的糖蛋白的开放阅读框,和编码与SEQ ID NO:6或16(其中SEQ ID NO:16是优选的)具有至少99%序列同一性的核蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:30或40(其中SEQ ID NO:40是优选的)具有至少99%序列同一性的L蛋白的开放阅读框,和编码与SEQ ID NO:28或38(其中SEQ ID NO:38是优选的)具有至少99%序列同一性的Z蛋白的开放阅读框。

[0096] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码具有SEQ ID NO:4或14(其中SEQ ID NO:14是优选的)所示序列的糖蛋白的开放阅读框,和编码具有SEQ ID NO:6或16(其中SEQ ID NO:16是优选的)所示序列的核蛋白的开放阅读框,并且其中所述L区段包含编码具有SEQ ID NO:30或40(其中SEQ ID NO:40是优选的)所示序列的L蛋白的开放阅读框,和编码具有SEQ ID NO:28或38(其中SEQ ID NO:38是优选的)所示序列的Z蛋白的开放阅读框。

[0097] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码具有SEQ ID NO:4所示序列的糖蛋白的开放阅读框和编码具有SEQ ID NO:6所示序列的核蛋白的开放阅读框,并且其中所述L区段包含编码具有SEQ ID NO:40所示序列的L蛋白的开放阅读框和编码具有SEQ ID NO:38所示序列的Z蛋白的开放阅读框。

[0098] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码具有SEQ ID NO:14所示序列的糖蛋白的开放阅读框,和编码具有SEQ ID NO:16所示序列的核蛋白的开放阅读框,并且其中所述L区段包含编码具有SEQ ID NO:40所示序列的L蛋白的开放阅读框,和编码具有SEQ ID NO:38所示序列的Z蛋白的开放阅读框。

[0099] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码具有SEQ ID NO:4所示序列的糖蛋白的开放阅读框和编码具有SEQ ID NO:6所示序列的核蛋白的开放阅读框,并且其中所述L区段包含编码具有SEQ ID NO:30所示序列的L蛋白的开放阅读框和编码具有SEQ ID NO:28所示序列的Z蛋白的开放阅读框。

[0100] 优选的病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码具有SEQ ID NO:14所示序列的糖蛋白的开放阅读框,和编码具有SEQ ID NO:16所示序列的核蛋白的开放阅读框,并且其中所述L区段包含编码具有SEQ ID NO:30所示序列的L蛋白的开放阅读框,和编码具有SEQ ID NO:28所示序列的Z蛋白的开放阅读框。

[0101] 优选地,本公开的病毒颗粒不包含异源ORF。本上下文中的“异源ORF”是指来自LCMV之外的生物体的ORF和/或编码人工或合成蛋白的ORF。

[0102] 本文所用的术语“核酸”通常可以指DNA或RNA。DNA和RNA的不同之处在于它们的碱基。DNA中腺嘌呤的互补碱基是胸腺嘧啶,而RNA中是尿嘧啶。为了简化起见,在本申请中腺嘌呤的相应碱基表示为“t”,根据上下文,其可以指胸腺嘧啶(DNA中)或尿嘧啶(RNA中)。

[0103] 如本文在核酸的上下文中所用,术语“编码(“encoding”或“encode(s)”)”涉及一种具有这样序列的核酸,该序列可以翻译成由该核酸编码的特定氨基酸序列。核酸序列可以涵盖编码链的序列,也可以涵盖与编码链互补的链的序列。

[0104] 关于本文公开的序列的“序列同一性百分比(%)”被定义为:在将序列进行比对并引入间隔(如有必要,以获得最大序列同一性百分数)之后,且不将任何保守置换认为是序列同一性的一部分,候选序列中与参考序列中的氨基酸残基或核苷酸成对相同的氨基酸残

基或核苷酸的百分数。用于确定氨基酸序列同一性百分比目的的比对可通过本领域技术范围内的各种方式来实现,例如使用公共可用的计算机软件,例如BLAST、ALIGN或Megalign(DNASTAR)软件。本领域技术人员可以确定用于测量比对的适当参数,包括在被比较序列的全长上实现最大比对所需的任何算法。本文所公开的核苷酸序列也是如此。为了确定序列同一性,(例如RNA中的)尿嘧啶可以被认为与(例如DNA中的)胸腺嘧啶相同。

[0105] 如本文所用,术语“减毒”涉及病毒在给定宿主(细胞)内复制的能力降低、在健康器官中复制的能力降低和/或诱导细胞因子的能力降低。优选地,本发明的病毒颗粒是减毒的。

[0106] 如本文所用,术语“感染性”涉及病毒感染,即进入给定宿主细胞的能力。优选地,本发明的病毒颗粒是具有感染性的。

[0107] 术语“有复制能力”是指病毒具有在感染的细胞中扩增和表达其遗传物质的能力,并且能够在未遗传工程化的正常细胞中产生进一步的子代。特别地,有复制能力的病毒不需要被工程化以表达能够复制的病毒基因的宿主细胞。优选地,本发明的病毒颗粒是有复制能力的。

[0108] 如本文所用,术语“致病性”涉及病毒引起疾病的能力,即病毒对生物体伤害的能力。

[0109] 本发明的病毒颗粒能够促进肿瘤生长的降低,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述肿瘤生长的降低至少是一样强或甚至更强。特别地,优选地如在基本上如实施例1所述的分析中所测量的,与LCMV毒株WE和/或包含与病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述病毒颗粒能够促进更强的冷肿瘤生长的降低。

[0110] 本发明的病毒颗粒能够诱导适应性免疫活化,优选地如在基本上如实施例3所述的分析中所测量的,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述适应性免疫活化至少是一样强或甚至更强。

[0111] 本发明的病毒颗粒能够促进温肿瘤生长的降低,优选地如在基本上如实施例4中所述的分析中所测量的,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,所述温肿瘤生长的降低至少一样强。

[0112] 如本文所用的,可互换使用“热”或“温”肿瘤涉及具有T细胞炎症表型的肿瘤。这些肿瘤显示出炎症的迹象,意味着肿瘤已经被T细胞浸润以对抗癌细胞。典型地为热肿瘤的癌症的实例包括黑素瘤、膀胱癌、肾癌、头颈癌和非小细胞肺癌。

[0113] 如本文所用,“冷肿瘤”涉及具有非T细胞炎症表型的肿瘤,其具有低T细胞浸润或其尚未被T细胞浸润。由于缺乏T细胞,在这些肿瘤中用免疫治疗药物难以激发免疫应答。典型地为冷肿瘤的癌症的实例包括乳腺癌、卵巢癌、前列腺癌、胰腺癌和成成胶质细胞瘤。在Gajewski等,(2017)Adv Exp Med Biol.1036:19-31和Maleki Vareki(2018)Journal for ImmunoTherapy of Cancer 6:157中描述了热肿瘤和冷肿瘤之间的差异。

[0114] 优选地如在基本如实施例12所述的分析中测定的,与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒在(优选全身)施用后能够诱导降低的干扰素水平。优选地,所述干扰素选自IFN-α和IFN-β。

[0115] 优选地,如在基本上如实施例13所述的分析中所测量的,与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒能够诱导更低浓度的一种或多种Th1-和促炎细胞因子。优选地,所述细胞因子选自IL-6、IL-10、TNFα和IFNγ。

[0116] 优选地,如在基本上如实施例13所述的分析中所测量的,与LCMV毒株WE、Armstrong、克隆13和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒能够诱导更低浓度的一种或多种Th1-和促炎细胞因子。优选地,所述细胞因子选自IL-6、IL-10、TNFα和IFNγ。

[0117] 优选地,如在FVB/N小鼠中在基本上如实施例14所述的分析中所测量的,与LCMV毒株WE相比,本发明的病毒颗粒在小鼠中的致病性更低。

[0118] 优选地,如在基本上如实施例18所述的分析中所测量的,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒能够在小鼠中诱导降低的肝脏病状程度。

[0119] 优选地,如在基本上如实施例15所述的分析中所测定的,与LCMV毒株WE和包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒可以能够在小鼠中诱导降低程度的血小板减少症,或在小鼠(例如FVB/N小鼠)中诱导不可检测的血小板减少症。

[0120] 优选地,如在基本上如实施例24所述的分析中所测量的,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒可以在健康细胞(如神经元细胞)中显示复制减少。

[0121] 优选地,如在基本如实施例24所述的分析中测量的,与LCMV毒株WE相比,本发明的病毒颗粒在肿瘤细胞中显示复制增加。

[0122] 优选地,如在基本如实施例35所述的分析中测量的,与LCMV毒株WE和/或包含与所述病毒颗粒相同的S区段和如SEQ ID NO:2所示的L区段的病毒颗粒相比,本发明的病毒颗粒可以在健康器官中显示复制减少。

[0123] 本发明还涉及一种宿主细胞,其包含针对本发明病毒颗粒所述的LCMV S区段和LCMV L区段。

[0124] 本发明还涉及一种宿主细胞,其包含编码针对本发明病毒颗粒所述的糖蛋白的ORF的、编码针对本发明病毒颗粒所述的L蛋白的ORF的、编码针对本发明病毒颗粒所述的核蛋白的ORF的和编码针对本发明病毒颗粒所述的Z蛋白的ORF的cDNA。

[0125] 本发明还涉及一种宿主细胞,其包含针对本发明病毒颗粒所述的LCMV S区段和LCMV L区段的cDNA。

[0126] 用于生产cDNA的技术是分子生物学和DNA操作和生产的常见且常规的技术。可以使用本领域技术人员已知的任何克隆技术。这些技术是熟知的,并且可由技术人员在诸如Sambrook和Russell,Molecular Cloning:Alaboratory Manual,3rd edition,Cold Spring Harbor Laboratory N.Y.(2001)的实验手册中获得。

[0127] 可以将本文所述的cDNA引入质粒。本文所述的cDNA可以是DNA表达载体的一部分,或者可以引入DNA表达载体中,并任选地引入宿主细胞中。本文所述的cDNA或包含该cDNA的质粒或载体优选包含启动子。启动子的具体实例包括RNA聚合酶I启动子、RNA聚合酶II启动

子、RNA聚合酶III启动子、T7启动子、SP6启动子或T3启动子。

[0128] 宿主细胞可以是任何适于克隆、表达、增殖或生产病毒颗粒的宿主细胞。宿主细胞可以是原核的或真核的,所述原核的比如大肠杆菌(E.coli)或枯草芽孢杆菌,所述真核的比如酿酒酵母、巴斯德毕赤酵母、SF9或High5昆虫细胞、永生化哺乳动物细胞系(例如HEK细胞、BHK细胞、HeLa细胞或CHO细胞)或原代哺乳动物细胞。优选的宿主细胞包括HEK细胞,特别是HEK293细胞,例如HEK293T(CVCL_0063)或FreeStyle 293-F(CVCL_D603)。FreeStyle 293-F细胞是商购可获得的,例如,从Thermo Fisher ScientificInc.(目录号12338026)商购获得。优选的宿主细胞还包括BHK细胞,如BHK-21细胞(CVCL_1914)。优选的宿主细胞还包括WHO Vero RCB 10-87细胞(ATCC CCL 81)。

[0129] 本发明还涉及生产本发明的病毒颗粒的方法。该方法包括在适于病毒颗粒形成的条件下培养本发明的宿主细胞。

[0130] 生产病毒颗粒的方法可进一步包括向宿主细胞中引入本文所述的cDNA。生产病毒颗粒的方法还可以包括回收和/或纯化病毒颗粒。这种回收和/或纯化方法是本领域技术人员熟知的。

[0131] 本发明还涉及一种药物组合物,其包含本文公开的病毒颗粒。优选地,所述病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。该药物组合物可进一步包含药学上可接受的赋形剂或载体。载体可以例如选自水、水性盐溶液、水性缓冲液、细胞培养基和至少两种前述载体的组合。

[0132] 本发明还涉及本文公开的病毒颗粒,其用在治疗中。优选地,所述病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。本文公开的病毒颗粒可用在癌症或肿瘤的治疗中。

[0133] 本发明还涉及一种所公开的病毒颗粒在制备药物中的用途。优选地,所述病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。优选地,所述药物用在癌症或肿瘤的治疗中。

[0134] 本发明还涉及一种治疗疾病的方法,所述方法包括向受试者施用本文公开的病毒颗粒。优选地,受试者是有此需要的。优选地,以有效量施用病毒颗粒。优选地,所述病毒颗粒包含LCMV S区段和LCMV L区段,其中所述S区段包含编码与SEQ ID NO:4具有至少97%序列同一性的糖蛋白的开放阅读框,并且其中所述L区段包含编码与SEQ ID NO:40具有至少90%序列同一性的L蛋白的开放阅读框。优选地,所述疾病为癌症或肿瘤。

[0135] “受试者”是脊椎动物,优选地为哺乳动物,更优选地为人。本文所用的术语“哺乳动物”是指归类为哺乳动物的任何动物,包括但不限于人、家畜和农场动物,以及动物园动物、运动动物或宠物动物,例如小鼠、绵羊、狗、马、猫、牛、大鼠、猪、猿(如食蟹猴)等,仅举几个说明性实例。优选地,本文的哺乳动物是人。癌症或肿瘤可以是人或鼠癌症或肿瘤,优选地为人癌症或肿瘤。

[0136] “有效量”是足以产生有益或所需结果的量。有效量可以在一次或多次施用中施

用。

[0137] 癌症或肿瘤可以是本文公开的任何癌症或肿瘤。通常,癌症或肿瘤可以选自癌(carcinoma)、黑素瘤、胚细胞瘤、淋巴瘤和肉瘤。

[0138] 在本公开的上下文中,术语“癌(carcinoma)”应当理解为意指上皮来源的恶性瘤变。优选地,所述癌选自肛门癌、支气管癌、肺癌、子宫内膜癌、胆囊癌、膀胱癌、肝细胞癌、睾丸癌、结肠癌、结肠直肠癌、直肠癌、喉癌、食道癌、胃癌、乳腺癌、肾癌、卵巢癌、胰腺癌、咽癌、口咽癌、前列腺癌、甲状腺癌和宫颈癌。

[0139] 在本公开的上下文中,术语“肉瘤”应当理解为意指中胚层来源的恶性瘤变。肉瘤可以选自血管肉瘤、软骨肉瘤、尤文肉瘤、纤维肉瘤、卡波西肉瘤、脂肪肉瘤、平滑肌肉瘤、恶性纤维组织细胞瘤、神经源性肉瘤、骨肉瘤和横纹肌肉瘤。

[0140] 在本公开的上下文中,术语“黑素瘤”应理解为意指黑素细胞来源的恶性瘤变。

[0141] 在本公开的上下文中,术语“淋巴瘤”应当理解为意指淋巴细胞来源的恶性瘤变。

[0142] 在本公开的上下文中,术语“胚细胞瘤”应当理解为意指胚胎来源的恶性瘤变。

[0143] 待治疗的癌症或肿瘤可以是冷肿瘤。优选的冷瘤包括乳腺癌、卵巢癌、前列腺癌、胰腺癌和成胶质细胞瘤。

[0144] 待治疗的癌症或肿瘤可以是热肿瘤。优选的热肿瘤包括黑素瘤、膀胱癌、肾癌、头颈癌和非小细胞肺癌。

[0145] 优选的待治疗的癌症或肿瘤包括黑素瘤、结肠癌、纤维肉瘤、胰腺癌、甲状腺癌、肺癌、腺癌和胃肠癌。

[0146] 一般而言,本文公开的病毒颗粒可以通过技术人员已知的任何合适途径施用。施用通常包括肠内和肠胃外施用。肠胃外施用可以包括局部施用,例如肌内、腹膜内、皮下或肿瘤内施用。或者,肠胃外施用可以包括全身施用,特别是例如通过注射或输注的静脉内施用。

[0147] 除非另有说明,否则在一系列要素之前的术语“至少”应理解为是指该系列中的每个要素。本领域技术人员将认识到或能够使用不超过常规实验来确定与本文所述的本发明的特定实施方案相当的许多等同物。这些等同物意欲涵盖在本发明中。

[0148] 本文无论何处所用的术语“和/或”包括“和”、“或”以及“由所述术语连接的要素的全部或任何其它组合”的含义。

[0149] 本文使用的术语“约”或“近似地”是指在给定值或范围的20%内,优选在10%内,更优选在5%内。然而,它也包括所述具体的数字,例如约20包括20。

[0150] 除非上下文另有要求,否则贯穿本说明书和权利要求书,措辞“包含(comprise)”及其变形,例如“包含(comprises)”和“包含(comprising)”将被理解为意指涵盖所述整数或步骤或整数组或步骤的集合,但不排除任何其它整数或步骤或整数组或步骤的集合。当在本文使用时,术语“包含(comprising)”可被术语“含有(containing)”或“包括(including)”替代,或者有时当用于本文时被术语“具有(having)”替代。

[0151] 当在本文中使用时,“由…组成(consisting of)”排除未在要求保护的要素中具体提到的任一要素、步骤或成分。当在本文使用时,“基本上由....组成”不排除对权利要求的基本和新特征没有重大影响的材料或步骤。

[0152] 在本文每个实例中术语,“包含(comprising)”、“基本上由…组成(consisting

essentially of)”和“由…组成(consisting of)”中的任何一个可以用另外两个术语中的任一个代替。例如术语“包含(comprising)”意指也为“基本上由…组成(consisting essentially of)”和“由…组成(consisting of)”提供明确的支持,术语“基本上由…组成(consisting essentially of)”意指也为“包含(comprising)”和“由…组成(consisting of)”提供明确的支持,术语“由…组成(consisting of)”意指也为“基本上由…组成(consisting essentially of)”和“包含(comprising)”提供明确的支持。

[0153] 实施例

[0154] 鼠

[0155] 通过使用野生型动物在C57BL/6背景下进行抗肿瘤作用的分析。对于LCMV诱导作用的体内分析,使用野生型小鼠品系C57BL/6、BALB/C或FVB/N。C57BL/6和BALB/C品系对LCMV引起的致死性感染有抗性。FVB/N小鼠代表了一种高度易感的小鼠品系,其在感染LCMV毒株克隆13后发展出血热样疾病。在LCMV处理后观察体质并测量体重。

[0156] 细胞系

[0157] MC57G(CVCL_4985)是一种鼠纤维肉瘤细胞系,其显示强LCMV复制。Tramp-C2是一种鼠前列腺细胞系(CVCL_3615)。B16(CVCL_F936)和B16-F10(B16F10,CVCL_0159)是鼠黑素瘤细胞系。B16-Ova代表了相应的表达卵清蛋白作为抗原的B16细胞系。MC-38(MC38,CVCL_B288)是鼠结肠腺癌细胞系。JAWSII是一种鼠的自发永生化细胞系,其可以通过用GM-CSF(CVCL_3727)处理而分化成树突样细胞。511950为一种传代少于20次的遗传工程化的小鼠原代胰腺癌细胞系(Mazur等,(2015)Nature medicine 21(10):1163-1171)。骨髓来源的树突状细胞(BMDC)是在GM-CSF的存在下从小鼠骨髓分化而来。

[0158] C643(CVCL_5969)是人未分化甲状腺癌细胞系。NCI-H1975(H1975,CVCL_1511)是一种人肺腺癌细胞系。A549是人腺癌细胞系(CVCL_0023)。FTC133是人甲状腺癌细胞系(CVCL_1219)。GIST-T1是一种衍生自胸腔积液的人胃肠肿瘤细胞系(CVCL_4976)。Hek293T(CVCL_0063)是人胚胎肾细胞系,其显示强LCMV复制。FreeStyle 293-F(CVCL_D603)是在Freestyle培养基中繁殖的、Hek293细胞的衍生物。FreeStyle 293-F细胞是LCMV生产所需的生产细胞系。

[0159] UKE-Ma-Mel-51(Mamel51,CVCL_A186)和UKE-Ma-Mel-86a(Ma-Mel-86a,CVCL_A221)是由Prof.Dr.Paschen,Klinik für Dermatologie,UK Essen提供的衍生自淋巴结转移的人原代黑素瘤细胞系。从Prof.Dr.Gopalakrishnan,HHU Düsseldorf提供的人神经元祖细胞(NPC)中分化原代人神经元。SkMM(人骨骼肌成肌细胞,Lonza CC-2580)是人的原代骨骼肌成肌细胞。在SkGM-2、马血清、谷氨酰胺、庆大霉素和地塞米松的存在下,从SkMM分化肌管。通过用抗肌球蛋白4AK(eBioscience,Clone MF-20)染色来验证分化。

[0160] BHK-21细胞代表自发永生化的成纤维细胞仓鼠细胞系(CVCL_1914)。

[0161] 病毒

[0162] LCMV毒株WE获自Prof.Zinkernagel(Experimental Immunology,Zurich,Switzerland)的实验室并且自2008年起已在L929细胞或BHK-21细胞中繁殖。

[0163] LCMV毒株克隆13和Armstrong 53b分别获自S.Basta,Queens University和R.M.Zinkernagel,University of Zurich。如(Flatz等,(2006)Proc Natl Acad Sci USA103(12):4663-4668)所述,通过瞬时转染完全从质粒中获得LCMV重组体

(reassortants)WE-Cl13(L)、P52-Cl13(L)、P52-WE(L)和Cl13-WE(L)。该病毒由LCMV毒株WE或WE衍生的P52的S-区段和LCMV毒株克隆13或WE的L-区段组成。病毒在BHK-21或Freestyle293F细胞上繁殖。

[0164] 重组病毒的产生

[0165] LCMV重组和重组体病毒完全由质粒产生。用编码LCMV S区段、L区段的质粒以及编码L聚合酶和核蛋白的辅助质粒瞬时转染BHK-21细胞。使用WE S区段和克隆13L区段质粒产生LCMV重组体WE-Cl13(L)。使用LCMV P52 S区段质粒和克隆13L区段质粒获得LCMV P52-Cl13(L),所述LCMV P52 S区段质粒在糖蛋白中具有两个编码突变,I181M和R185W。使用LCMV P52 S区段质粒和LCMV WE L区段质粒产生LCMV P52-WE(L)。使用LCMV克隆13S区段质粒和WE L区段质粒产生Cl13-WE(L)。

[0166] 通过免疫荧光离体测定LCMV感染的细胞和肿瘤组织中免疫细胞的浸润

[0167] 使用免疫组织荧光检测LCMV处理的或对照处理的荷瘤小鼠的肿瘤组织中的LCMV和免疫细胞分布。将肿瘤活检样品切成7μm厚的切片,用荧光染料标记的抗-LCMV-NP抗体(克隆VL4)和抗CD8抗体(eBioscience)染色,用荧光显微镜(Keyence)观察,用集成的CCD照相机拍照。

[0168] 通过空斑形成试验测定上清液或器官中的LCMV

[0169] 为了分析LCMV复制能力,将肿瘤和原代细胞接种在24孔板中(100.000个细胞/孔),并在所示MOI下用LCMV感染。感染后24小时、48小时或72小时收获上清液。通过每mL接种1.5×10^{6}个细胞并用MOI=0.001的LCMV感染来进行通过FreeStyle 293-F细胞生产LCMV的分析。感染后12、24、30、34、40、48、72和96小时后收获上清液。在感染的荷瘤和非荷瘤动物中进行LCMV生物分布的分析。将感染小鼠的器官解剖并在细胞培养基中匀浆。将上清液滴定并在MC57G细胞上温育(100.000个细胞/孔)。3至4小时后加入甲基纤维素覆盖层。用抗-LCMV-NP抗体(克隆VL4)染色LCMV感染的空斑。对空斑计数,并以每mL上清液或每个器官的病毒滴度来确定感染性颗粒。

[0170] 通过流式细胞术测定LCMV感染的细胞

[0171] 为了分析肿瘤和原代细胞中LCMV的感染性,将细胞接种在96孔板中,用MOI=0.1的LCMV感染或不处理并在冰上孵育1小时。1小时后,将细胞转移至37℃下。感染后20小时,收获细胞,并使用荧光标记的LCMV NP抗体(克隆VL4)进行细胞内LCMV染色。通过流式细胞术(LSR Fortessa,BD)分析细胞,结果以LCMV感染细胞的百分比或平均荧光强度(MFI)示出。

[0172] 通过流式细胞术测定细胞因子产生

[0173] 通过测定血清中的细胞因子来分析LCMV的免疫活化强度。因此,通过LegendPlex,根据制造商的方案(BioLegend)分析具有或不具有肿瘤的幼稚或感染小鼠的血清。

[0174] 临床化学

[0175] 通过测量丙氨酸氨基转移酶(ALT)和天冬氨酸氨基转移酶(AST)来确定LCMV对肝脏病状的诱导。在LCMV感染后的不同天对小鼠放血并提取血清。在Zentrallabor,Universitätsklinkum Essen或Zentralinstitut fürKlinische Chemie und Laboratoriumsdiagnostik,HHU Düsseldorf进行ALT和AST值的分析。

[0176] 通过流式细胞术分析免疫细胞

[0177] 为了确定LCMV治疗的效果,通过流式细胞术(LSR Fortessa,BD)分析免疫细胞。通过其特定尺寸和粒度来检测血小板。用CD8、CD4、CD3(eBioscience)的特异性荧光标记抗体染色T细胞。用四聚体染色法(NIH,四聚体设备(Tetramer Facility))染色LCMV特异性T细胞。

[0178] 肿瘤生长和治疗

[0179] 为了测定LCMV治疗的抗肿瘤效果,将1×10^6哥肿瘤细胞(100μL)皮下注射到C57BL/6小鼠(6-12周龄)的右侧或左侧。在可见肿瘤形成后,将动物进行LCMV或对照处理,并测定平均肿瘤体积。通过测量肿瘤的总重量(以g计)进行肿瘤块的终点分析。

[0180] 统计分析

[0181] 对于柱形图,使用未配对的双样品Student's t-检验比较平均值。使用采用Skidak多重比较检验的双因素ANOVA比较肿瘤生长曲线。数据以平均值±SEM示出。统计学显著性的水平确定为$p<0.05$。

[0182] 研究

[0183] 实施例1

[0184] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=5只动物/组)。肿瘤生长测量7天。在结束时获取肿瘤质量(d7)(图1)。

[0185] 由此证明,与野生型LCMV毒株WE相比,LCMV WE-CL13(L)在非免疫原性冷B16黑素瘤肿瘤模型中显示了增加的抗肿瘤作用。该模型是冷肿瘤的一个实例。

[0186] 实施例2

[0187] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。将肿瘤驻留的细胞毒性$CD8^+$T细胞用荧光标记的抗体(CD8 eBioscience)染色,并通过流式细胞术分析(图2)。

[0188] 由此证明,LCMV毒株WE-Cl13(L)增强了向肿瘤组织中的T细胞浸润。

[0189] 实施例3

[0190] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。在感染后第7天,通过流式细胞术分析肿瘤驻留的细胞毒性,抗病毒$CD8^+$GP33-四聚体阳性T细胞(图3)。

[0191] 由此证明,与野生型LCMV毒株WE相比,LCMV毒株WE-Cl13(L)诱导更强的适应性免疫活化。

[0192] 实施例4

[0193] 用MC38结肠癌细胞皮下处理C57BL/6小鼠。肿瘤形成后,通过静脉注射使小鼠感染$2x10^4$ PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=4只动物/组)。观察肿瘤生长达11天(图4)。

[0194] 由此证明,在免疫原性温MC38肿瘤模型中,LCMV毒株WE-Cl13(L)显示强的肿瘤生长抑制作用。这是针对温肿瘤的模型。

[0195] 实施例5

[0196] 用MC38结肠癌细胞皮下处理C57BL/6小鼠。肿瘤形成后,通过静脉注射使小鼠感染$2x10^4$ PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=4只动物/组)。在感染后第11天解剖肿瘤组织。将肿瘤浸润T细胞($CD3^+$)通过荧光标记的抗体(CD3,eBioscience)染色并通过流式细胞术测量(实施例5)。

[0197] 由此证明,LCMV毒株WE-Cl13(L)诱导了向肿瘤的强T细胞浸润。

[0198] 实施例6

[0199] 用MC38细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$PFU的LCMV毒株WE或WE-Cl13(L),或者对其进行对照处理(n=4只动物/组)。在感染后第11天解剖肿瘤组织。将肿瘤浸润细胞毒性T细胞($CD3^+CD8^+$)通过荧光标记的抗体(CD3,CD8,eBioscience)染色并通过流式细胞术分析(图6)。

[0200] 由此证明,LCMV毒株WE-Cl13(L)强烈增强向肿瘤中的细胞毒性T细胞浸润。

[0201] 实施例7

[0202] 用MC38细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$PFU的LCMV毒株WE(n=4)或WE-Cl13(L)(n=3),或者对其进行对照处理(n=4)。对肿瘤组织进行组织学分析。用LCMV核蛋白(LCMV NP,克隆VL4)和$CD8^+$T细胞(CD8)的荧光标记抗体染色肿瘤切片(7μm)(图7)。

[0203] 由此证明,LCMV毒株WE-Cl13(L)增强向肿瘤中的细胞毒性T细胞浸润,而与特定的局部病毒存在无关。

[0204] 实施例8

[0205] 接种C643、H1975、Ma-Mel-51、SkMM、B16F10、MC57G和HEK293T细胞(100.000个细胞/孔),并使它们感染MOI=0.1的LCMV毒株WE、克隆13、WE-Cl13(L)(WE S-区段,克隆13L-区段)和克隆13-WE(L)(克隆13S-区段,WE L区段)。将细胞培养20小时,并通过荧光标记的抗体(NP,克隆VL4)对LCMV核蛋白的存在进行细胞内染色。通过流式细胞术分析来自所有细胞的感染细胞的百分比(图8)。

[0206] 由此证明,克隆13L-区段负责病毒在所有肿瘤细胞系上的减毒,但不强烈降低生产细胞系HEK293的感染。

[0207] 实施例9

[0208] 接种C643、Ma-Mel-86a、Ma-Mel-51、511950、B16F10、Tramp-C2和JAWSII细胞(100.000个细胞/孔),并使它们感染MOI=0.1的LCMV毒株WE和WE-Cl13(L)。感染24和48小时后,收集上清液,并通过LCMV集落形成测定(focus forming assay)来分析LCMV复制(实施例9)。

[0209] 由此证明,在肿瘤细胞和抗原呈递细胞(JAWSII)上,LCMV毒株WE-Cl13(L)复制能力减弱。

[0210] 实施例10

[0211] 接种原代人神经元、鼠MC57G细胞、人肺腺癌细胞系A549和人甲状腺癌细胞系FTC133(100.000个细胞/孔),并使它们感染MOI=0.1的LCMV WE和WE-Cl13(L)。48小时后收集上清液,并通过集落形成测定来分析LCMV复制(图10)。

[0212] 由此证明,与LCMV毒株WE相比,LCMV毒株WE-Cl13(L)在易感肿瘤细胞(如鼠纤维肉瘤细胞系MC57G)中显示缺乏嗜神经性和同时增强的复制,和在人癌细胞系A549和FTC133中

显示强健的复制。

[0213] 实施例11

[0214] 用LCMV毒株WE和WE-Cl13感染衍生自骨髓的树突细胞。收获上清液,并通过商业干扰素αELISA-试剂盒分析干扰素α蛋白(图11)。

[0215] 由此证明,在体外感染树状细胞后,LCMV毒株WE-Cl13(L)与LCMV WE诱导相似的干扰素应答。

[0216] 实施例12

[0217] 通过静脉注射使C57BL/6小鼠感染2×10^4PFU的LCMV毒株Armstrong(Arm,n=3)、WE(n=3)、WE-Cl13(L)(n=3)或克隆13(Cl13,n=3),或不对其进行处理(n=12)。在感染后第1天和第3天取血。通过LegendPlex测定(BioLegend)分析IFNα和IFNβ的血清细胞因子浓度(图12)。

[0218] 由此证明,在全身给药后,LCMV WE-Cl13(L)重组体在小鼠中诱导降低的干扰素水平。

[0219] 实施例13

[0220] 通过静脉注射使C57BL/6小鼠感染2×10^4PFU的LCMV毒株Armstrong(Arm,n=3)、WE(n=3)、WE-Cl13(L)(n=3)或克隆13(Cl13,n=3),或不对其进行处理(n=12)。在感染后第1天和第3天取血。通过LegendPlex测定(BioLegend)分析IL-6、IL-10、TNFα和IFNγ的血清细胞因子浓度(图13)。

[0221] 由此证明,LCMV毒株WE-CL13(L)在小鼠中诱导更低浓度的Th1-和促炎细胞因子。

[0222] 实施例14

[0223] 通过静脉注射使野生型C57BL/6或BALB/c小鼠或高度易感小鼠品系FVB/N感染2×10^6PFU的LCMV毒株WE、Cl13(克隆13)、Arm(Armstrong)或WE-Cl13(L)(n=3)。在14天的时间跨度内测量体重。按照感染当天的体重的百分比来分析体重(图14)。

[0224] 由此证明,与野生型LCMV毒株WE相比,LCMV重组体WE-Cl13(L)在高度易感的小鼠品系FVB/N中不诱导致死病状。

[0225] 实施例15

[0226] 通过静脉注射使野生型C57BL/6或BALB/c小鼠或高度易感小鼠品系FVB/N感染2×10^6PFU的LCMV毒株WE、Cl13(克隆13)、Arm(Armstrong)或WE-Cl13(L)(N=3)。在第3、6和9天对小鼠放血。通过流式细胞术测量全血中的血小板(凝血细胞)。分析每微升血液的血小板总数(图15)。

[0227] 由此证明,LCMV毒株WE-Cl13(L)在高度易感FVB/N和其它小鼠品系中不诱导血小板减少症。

[0228] 实施例16

[0229] 通过静脉注射使野生型C57BL/6或BALB/c小鼠或高度易感小鼠品系FVB/N感染2×10^6PFU的LCMV毒株WE、Cl13(克隆13)、Arm(Armstrong)或WE-Cl13(L)(N=3)。在第3、6、9和14天对小鼠放血。分析了丙氨酸氨基转移酶(ALT)的血清水平(图16)。

[0230] 由此表明,LCMV WE-Cl13(L)在高度易感FVB/N和其它小鼠品系中不诱导肝脏病状。

[0231] 实施例17

[0232] 通过静脉注射使野生型C57BL/6或BALB/c小鼠或高度易感小鼠品系FVB/N感染2×10^6PFU的LCMV毒株WE、Cl13(克隆13)、Arm(Armstrong)或WE-Cl13(L)(N=3)。在第3、6、9和14天对小鼠放血。分析了天冬氨酸转氨酶(AST)的血清水平(图17)。

[0233] 由此表明,LCMV WE-Cl13(L)在高度易感FVB/N和其它小鼠品系中不诱导肝脏病状。

[0234] 实施例18

[0235] 将B16黑素瘤肿瘤细胞皮下注射至C57BL/6小鼠。用2×10^4PFU的LCMV毒株WE(n=4)或WE-Cl13(L)(n=5)处理小鼠或对其进行对照处理(n=6)。在感染后第7天抽血,并分析作为肝脏病状指标的ALT和AST血清水平(图18)。

[0236] 由此证明,在肿瘤中存在LCMV复制时,在全身施用后,LCMV毒株WE-CL13(L)不诱导肝脏病状。

[0237] 实施例19

[0238] 将表达OVA的B16肿瘤细胞皮下注射至C57BL/6小鼠。用2×10^4PFU的LCMV毒株WE或WE-Cl13(L)静脉注射处理小鼠或对其进行对照处理(n=5)。在处理后第7天处死小鼠,通过集落形成测定分析脾、肝、肺、肾和脑中LCMV颗粒的复制(图19)。

[0239] 由此表明,LCMV毒株WE-Cl13(L)在健康器官中显示显著降低的复制。

[0240] 实施例20

[0241] 将鼠MC38肿瘤细胞皮下移植到C57BL/6小鼠中。通过静脉内注射2×10^4PFU的LCMV毒株WE(n=4)或WE-Cl13(L)(n=4)处理小鼠或对照处理小鼠。在感染后第11天,通过集落形成测定分析肿瘤组织的LCMV复制(图20)。

[0242] 由此证明,在肿瘤组织中,LCMV毒株WE-Cl13(L)与LCMV毒株WE同等地复制。

[0243] 实施例21

[0244] 接种原代人神经元、肺腺癌细胞系H1975、胃肠道癌细胞系GIST-T1,原代黑素瘤细胞系Ma-Mel-86a,鼠纤维肉瘤MC57G和原代黑素瘤细胞系Ma-Mel-51(100.00个细胞/孔),并使它们感染MOI=0.1的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L)。20小时后,对细胞进行LCMV核蛋白(NP,克隆VL4)的细胞内染色。通过流式细胞术分析感染LCMV的细胞(LCMV NP^+)的百分比(图21)。

[0245] 由此证明,LCMV重组体LCMV WE-Cl13(L)和LCMV P52-Cl13(L)在人神经元中不复制,但LCMV毒株P52-Cl13(L)在人和鼠肿瘤细胞中显示增加的感染性和复制。

[0246] 实施例22

[0247] 接种原代人神经元、肺腺癌细胞系H1975、胃肠道癌细胞系GIST-T1、原代黑素瘤细胞系Ma-Mel-86a、鼠纤维肉瘤MC57G和原代黑素瘤细胞系Ma-Mel-51(100.00个细胞/孔),并使它们感染MOI=0.1的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L)。20小时后,对细胞进行LCMV核蛋白(NP,克隆VL4)的细胞内染色。通过流式细胞术分析感染LCMV的细胞的荧光强度以研究细胞中的复制能力(图22)。

[0248] 由此证明,LCMV毒株P52-Cl13(L)在人和鼠肿瘤细胞中显示增强的复制。

[0249] 实施例23

[0250] 接种分化的人肌肉成肌细胞、人骨骼肌成肌细胞(SkMM)、肺腺癌细胞系A549和鼠纤维肉瘤细胞系MC57G(100.000个细胞/孔),并使它们感染MOI=0.1的LCMV毒株WE、WE-

Cl13(L)、P52-Cl13(L)、I181M-Cl13(L)或R185W-Cl13(L)。20小时后,对细胞进行LCMV核蛋白(NP,克隆VL4)的细胞内染色。通过流式细胞术分析感染LCMV的细胞(LCMV NP^+)的百分比(图23)。

[0251] 由此表明,LCMV糖蛋白中位置181和185处的突变增强了人和鼠癌细胞中的复制和感染性,但不增加对健康人肌肉细胞的趋性。

[0252] 实施例24

[0253] 检测原代人神经元和鼠纤维肉瘤MC57G细胞的LCMV复制潜力。以100.000个细胞/孔接种并使它们感染MOI=0.1的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L)。感染48小时后收集上清液。通过集落形成测定分析病毒滴度(图24)。

[0254] 由此证明,与野生型LCMV毒株WE相比,重组体LCMV毒株WE-Cl13(L)和P52-Cl13(L)不显示对健康人神经元的趋性,但在鼠癌细胞中显示增强的复制。

[0255] 实施例25

[0256] 用鼠黑素瘤B16细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染2×10^4PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。肿瘤生长测量7天。在结束时测量肿瘤质量(d7)(图25)。

[0257] 由此证明,与野生型LCMV毒株WE相比,LCMV毒株WE-CL13(L)和P52-Cl13(L)显示增强的抗肿瘤作用。

[0258] 实施例26

[0259] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。将肿瘤引流淋巴结(tumor draining lymph node)驻留的细胞毒性$CD8^+$T细胞通过荧光标记的抗-CD8抗体(eBioscience)染色,并通过流式细胞术分析(图26)。

[0260] 由此证明,LCMV毒株WE-CL13(L)和P52-Cl13(L)增强肿瘤引流淋巴结中的细胞毒性T细胞积累。

[0261] 实施例27

[0262] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。在感染后第7天,肿瘤引流淋巴结驻留的细胞毒性,抗病毒$CD8^+$GP33-四聚体阳性T细胞通过荧光标记的抗体(eBioscience,NIH)染色并通过流式细胞术分析(图27)。

[0263] 由此证明,LCMV毒株P52-Cl13(L)增加了肿瘤引流淋巴结中的病毒特异性T细胞的积累。

[0264] 实施例28

[0265] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染$2x10^4$ PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。肿瘤驻留的细胞毒性$CD8^+$T细胞通过荧光标记的抗-CD8抗体(eBioscience)染色,并通过流式细胞术分析(图28)。

[0266] 由此证明,LCMV毒株WE-CL13(L)和P52-Cl13(L)增强肿瘤中的细胞毒性T细胞积累。

[0267] 实施例29

[0268] 用B16黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染2x10^4 PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天,肿瘤引流淋巴结驻留的细胞毒性,抗病毒$CD8^+$GP33-四聚体阳性T细胞通过荧光标记的抗体(eBioscience,NIH)染色并通过流式细胞术分析(图29)。

[0269] 由此证明,用LCMV毒株P52-Cl13(L)处理强烈增强了肿瘤组织中的抗病毒T细胞积累。

[0270] 实施例30

[0271] 用鼠MC38结肠癌细胞皮下处理C57BL/6小鼠。在可见肿瘤形成后,用2×10^4PFU的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)静脉注射处理小鼠或对其进行对照处理(n=4)。测量肿瘤体积直到感染后11天(图30)。

[0272] 由此证明,LCMV毒株P52-Cl13(L)诱导强肿瘤生长抑制。

[0273] 实施例31

[0274] 用鼠MC38结肠癌细胞皮下处理C57BL/6小鼠。在可见肿瘤形成后,用2×10^4PFU的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)静脉注射处理小鼠或对其进行对照处理(n=4)。在第11天解剖肿瘤。将T细胞用荧光抗-CD3抗体(eBioscience)染色,并通过流式细胞术分析(图31)。

[0275] 由此证明,与LCMV毒株WE、WE-Cl13(L)和对照处理的肿瘤相比,LCMV毒株P52-Cl13(L)显示出在肿瘤组织中T细胞积累增加的明显趋势。

[0276] 实施例32

[0277] 用鼠MC38结肠癌细胞皮下处理C57BL/6小鼠。在可见肿瘤形成后,用2×10^4PFU的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)静脉注射处理小鼠或对其进行对照处理(n=4)。在第11天解剖肿瘤。将T辅助细胞用荧光抗-CD3和抗-CD4抗体(eBioscience)染色,并通过流式细胞术分析(图32)。

[0278] 因此,表明与用野生型LCMV毒株WE处理的肿瘤或对照处理的肿瘤相比,LCMV毒株WE-Cl13(L)和P52-Cl13(L)诱导向肿瘤组织中的更强的T辅助细胞浸润。

[0279] 实施例33

[0280] 用鼠MC38结肠癌细胞皮下处理C57BL/6小鼠。在可见肿瘤形成后,用2×10^4PFU的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)静脉注射处理小鼠或对其进行对照处理(n=4)。在第11天解剖肿瘤。将细胞毒性T细胞用荧光抗-CD3和抗CD8抗体(eBioscience)染色,并通过流式细胞术分析(图33)。

[0281] 由此证明,与对照处理相比,LCMV毒株P52-Cl13(L)增强了肿瘤中的细胞毒性T细胞积累。

[0282] 实施例34

[0283] 通过静脉注射使C57BL/6小鼠感染2×10^4PFU/鼠的LCMV毒株WE、WE-Cl13(L)、P52-Cl13(L)或未对其进行处理(n=3)。在感染后第2天和第4天取血。通过LegendPlex测定(BioLegend)分析IFNα、TNFα和IFNγ的血清细胞因子水平(图34)。

[0284] 由此证明,与野生型LCMV毒株WE和克隆13相比,LCMV重组体毒株WE-Cl13(L)和P52-Cl13(L)诱导降低的全身细胞因子水平。

[0285] 实施例35

[0286] 用B16-Ova黑素瘤细胞皮下处理C57BL/6小鼠,并通过静脉注射使其感染2×10^4PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L),或者对其进行对照处理(n=5只动物/组)。在感染后第7天处死小鼠。通过集落形成测定分析脾、肝、肺、肾、脑和肿瘤组织的LCMV复制(图35)。

[0287] 由此表明,LCMV重组体P52-Cl13(L)在健康器官中显示复制减少,同时在肿瘤组织中显示可度量(measurable)的复制。

[0288] 实施例36

[0289] 将MC38肿瘤细胞皮下移植到C57BL/6小鼠。在可见肿瘤形成后,用2×10^4PFU的LCMV毒株WE、WE-Cl13(L)或P52-Cl13(L)静脉注射处理小鼠。在感染后第11天,解剖肿瘤,通过集落形成测定分析LCMV复制(图36)。

[0290] 由此证明,与毒株WE和WE-Cl13(L)相比,LCMV毒株P52-CL13(L)在小鼠肿瘤组织中的持续时间更短。

[0291] 实施例37

[0292] 以1.5×10^6细胞/mL的密度,用MOI=0.001的LCMV毒株WE-Cl13(L)、P52-Cl13(L)或P52-WE(L)感染FreeStyle 293-F悬浮细胞。在感染后12、24、30、34、40、48、72和96小时收获上清液。通过集落形成测定分析上清液中的LCMV滴度(图37)。

[0293] 由此证明,FreeStyle 293-F细胞显示LCMV重组体WE-CL13(L)和P52-Cl13(L)的复制增强,并显示了用于生产LCMV重组体的理想生产细胞系。

[0294] 本文示例性所描述的实施方式可以适当地在没有本文中未具体公开的任何一种或多种要素、一种或多种限制的情况下实施。因此,本文所采用的术语和表达被用作为描述的术语而非限制,并且无意图在使用这些术语和表达时,排除掉显示和描述的特征的任何等同物或其部分,而是认可各种修改可以在本发明要求保护的范围内。因此,应当理解的是,虽然这些实施方式已通过优选的实施方式和任选的特征而被具体公开,本领域技术人员可以寻求其修改和变化,并且这样的修改和变化被认为是在本发明的范围内。每个较窄种类和亚属分组落入一般性公开范围内,也形成本发明的一部分。这包括本发明的一般描述,且具有从该种类中取出任何主题的条件或负面限制,而不管该去除的材料是否在本文中具体陈述。此外,当特征是以马库什组的形式描述时,本领域技术人员将认识到,本发明还由此以该马库什组中任何单独成员或亚组的形式描述。

[0295] 等同物:本领域技术人员使用不超过常规实验就会认识到或者能够确定本文描述的本发明的具体实施方式的许多等同物。以下的权利要求意欲涵盖这些等同物。

[0296] 应当理解,本发明不限于本文所述的特定方法、方案、材料、试剂和物质等,因此它们是可以变化的。本文所用的术语仅用于描述特定实施方案的目的,而不是要限制本发明的范围,本发明的范围仅由权利要求书限定。

[0297] 本说明书全文中引用的所有出版物(包括所有专利、专利申请、科学出版物、制造商的说明书、使用说明书等)均通过引用以其整体并入本文。本文中的任何内容都不应被解释为承认本发明由于先前的发明而无权早于所述公开。如果通过引用并入的材料与本说明书相矛盾或不一致,则说明书将取代任何所述材料。

[0298] 进一步的实施方式将由以下的权利要求书中变得显而易见。

序列表

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<210> 3
<211> 1497
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE
<400> 3

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<210> 4
<211> 498
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE
<400> 4

Met Gly Gln Ile Val Thr Met Phe Glu Ala Leu Pro His Ile Ile Asp
1 5 10 15

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

325 330 335
Glu Ser Ala Leu His Val Phe Lys Thr Thr Val Asn Ser Leu Ile Ser
340 345 350
Asp Gln Leu Leu Met Arg Asn His Leu Arg Asp Leu Met Gly Val Pro
355 360 365
Tyr Cys Asn Tyr Ser Lys Phe Trp Tyr Leu Glu His Ala Lys Thr Gly
370 375 380
Glu Thr Ser Val Pro Lys Cys Trp Leu Val Thr Asn Gly Ser Tyr Leu
385 390 395 400
Asn Glu Thr His Phe Ser Asp Gln Ile Glu Gln Glu Ala Asp Asn Met
405 410 415
Ile Thr Glu Met Leu Arg Lys Asp Tyr Ile Lys Arg Gln Gly Ser Thr
420 425 430
Pro Leu Ala Leu Met Asp Leu Leu Met Phe Ser Thr Ser Ala Tyr Leu
435 440 445
Ile Ser Ile Phe Leu His Leu Val Lys Ile Pro Thr His Arg His Ile
450 455 460
Lys Gly Gly Ser Cys Pro Lys Pro His Arg Leu Thr Asn Lys Gly Ile
465 470 475 480
Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Lys Thr Ile Trp Lys
485 490 495
Arg Arg

<210> 5
<211> 1677
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE
<400> 5

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aagtctacat caaagaaaaa tgttctgaaa gtgggaagac ttagtgcaga ggaattgatg 300
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<210> 6
<211> 558
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE
<400> 6

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

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

450 455 460

Asp Ser Gln Asn Arg Arg Asp Ile Lys Leu Ile Asp Val Glu Met Thr
465 470 475 480

Lys Glu Ala Ser Arg Glu Tyr Glu Asp Lys Val Trp Asp Lys Tyr Gly
485 490 495

Trp Leu Cys Lys Met His Thr Gly Val Val Arg Asp Lys Lys Lys Lys
500 505 510

Glu Ile Thr Pro His Cys Ala Leu Met Asp Cys Ile Ile Phe Glu Ser
515 520 525

Ala Ser Lys Ala Arg Leu Pro Asp Leu Lys Thr Val His Asn Ile Leu
530 535 540

Pro His Asp Leu Ile Phe Arg Gly Pro Asn Val Val Thr Leu
545 550 555

<210> 7

<211> 273

<212> DNA

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE

<400> 7

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ttgccagaca ccacctatct tggtcctcta aattgtaaat catgttggca gaaatttgac 120

agcttggtta gatgccatga ccactatctt tgcagacact gtctgaatct cctgctgtca 180

gtttccgaca gatgtcctct ctgtaagtat ccactgccaa ccaaactgaa ggtgtcaaca 240

gtcccaagct ccccacctcc ctatgaggag tga 273

<210> 8

<211> 90

<212> PRT

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE

<400> 8

Met Gly Gln Gly Lys Ser Lys Glu Glu Arg Asp Thr Ser Asn Thr Gly
1 5 10 15

Arg Ala Glu Leu Leu Pro Asp Thr Thr Tyr Leu Gly Pro Leu Asn Cys
20 25 30

Lys Ser Cys Trp Gln Lys Phe Asp Ser Leu Val Arg Cys His Asp His
35 40 45

Tyr Leu Cys Arg His Cys Leu Asn Leu Leu Leu Ser Val Ser Asp Arg
50 55 60

Cys Pro Leu Cys Lys Tyr Pro Leu Pro Thr Lys Leu Lys Val Ser Thr
65 70 75 80

Val Pro Ser Ser Pro Pro Pro Tyr Glu Glu

85 90

<210> 9

<211> 6630

<212> DNA

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株WE

<400> 9

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gagggactca aattgttatc acgctgtata gagatagaca gtgcagacaa aagtggttgc 180
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ccaggactgc cactcatcat ccctgatggt tataagttga ttgacaattc ccttattctt 300
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Ile Arg Ser Cys Pro Asp Leu Lys Asp Ser Leu Ile Asp Ile Glu Thr

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

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Ser Asp Phe Ser Ser Thr Ser Leu Met Asp Lys Leu Lys Glu Asp Leu

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Arg Thr Ile Phe Gly Thr Gly Glu Lys Val Leu Leu Ser Ala Lys Phe

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755 760 765

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835 840 845

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885 890 895

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1790 1795 1800

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1820 1825 1830

Asn Phe Leu Lys Gln Val Tyr Phe Glu Ser Phe Val Arg Glu Phe

1835 1840 1845

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1865 1870 1875

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1880 1885 1890

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1895 1900 1905

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1910 1915 1920

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atggactgca tcatttttga gagtgcttcc aaggcaagac tccctgatct aaaaaccgtt 1620
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<210> 16
<211> 558
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株P52-WE
<400> 16

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Arg Arg Glu Leu Gln Ser Phe Thr Ser Asp Val Lys Ala Ala Val Ile
20 25 30
Lys Asp Ala Thr Ser Leu Leu Asn Gly Leu Asp Phe Ser Glu Val Ser
35 40 45
Asn Val Gln Arg Ile Met Arg Lys Glu Arg Arg Asp Asp Lys Asp Leu
50 55 60

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

370 375 380
Gly Arg Phe Asn Asp Pro Val Glu Ile Ala Ile Phe Gln Pro Gln Asn
385 390 395 400
Gly Gln Phe Ile His Phe Tyr Arg Glu Pro Thr Asp Gln Lys Gln Phe
405 410 415
Lys Gln Asp Ser Lys Tyr Ser His Gly Met Asp Leu Ala Asp Leu Phe
420 425 430
Asn Ala Gln Pro Gly Leu Thr Ser Ser Val Ile Gly Ala Leu Pro Gln
435 440 445
Gly Met Val Leu Ser Cys Gln Gly Ser Asp Asp Ile Arg Lys Leu Leu
450 455 460
Asp Ser Gln Asn Arg Arg Asp Ile Lys Leu Ile Asp Val Glu Met Thr
465 470 475 480
Lys Glu Ala Ser Arg Glu Tyr Glu Asp Lys Val Trp Asp Lys Tyr Gly
485 490 495
Trp Leu Cys Lys Met His Thr Gly Val Val Arg Asp Lys Lys Lys Lys
500 505 510
Glu Ile Thr Pro His Cys Ala Leu Met Asp Cys Ile Ile Phe Glu Ser
515 520 525
Ala Ser Lys Ala Arg Leu Pro Asp Leu Lys Thr Val His Asn Ile Leu
530 535 540
Pro His Asp Leu Ile Phe Arg Gly Pro Asn Val Val Thr Leu
545 550 555

<210> 17
<211> 273
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株P52-WE
<400> 17
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agcttggtta gatgccatga ccactatctt tgcagacact gtctgaatct cctgctgtca 180
gtttccgaca gatgtcctct ctgtaagtat ccactgccaa ccaaactgaa ggtgtcaaca 240
gtcccaagct ccccacctcc ctatgaggag tga 273

<210> 18
<211> 90
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株P52-WE
<400> 18
Met Gly Gln Gly Lys Ser Lys Glu Glu Arg Asp Thr Ser Asn Thr Gly

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

<210> 19
<211> 6630
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株P52-WE
<400> 19

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gagggactca aattgttatc acgctgtata gagatagaca gtgcagacaa aagtggttgc 180
atacacaacc acgatgacaa atctgttgaa acaatcctaa tagactctgg gattgtgtgt 240
ccaggactgc cactcatcat ccctgatggt tataagttga ttgacaattc ccttattctt 300
cttgaatgtt ttgttagaag cacaccagct agttttgaaa agaagttcat tgaggacacc 360
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<210> 20
<211> 2209
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株P52-WE
<400> 20

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

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

500 505 510

Gln Leu Gly Ser Val Arg Tyr Gln Val Val Glu Cys Lys Glu Val Phe
515 520 525

Cys Gln Ile Ile Lys Leu Asp Ser Glu Glu Tyr His Leu Leu Tyr Gln
530 535 540

Lys Thr Gly Glu Ser Ser Arg Cys Tyr Ser Ile Gln Gly Pro Asp Gly
545 550 555 560

His Leu Ile Ser Phe Tyr Ala Asp Pro Lys Arg Phe Phe Leu Pro Ile
565 570 575

Phe Ser Asp Glu Val Leu His Asn Met Ile Asp Thr Met Ile Ser Trp
580 585 590

Ile Arg Ser Cys Pro Asp Leu Lys Asp Ser Leu Ile Asp Ile Glu Thr
595 600 605

Ala Leu Arg Thr Leu Ile Leu Leu Met Leu Thr Asn Pro Thr Lys Arg
610 615 620

Asn Gln Lys Gln Val Gln Asn Ile Arg Tyr Leu Val Met Ala Ile Val
625 630 635 640

Ser Asp Phe Ser Ser Thr Ser Leu Met Asp Lys Leu Lys Glu Asp Leu
645 650 655

Ile Thr Pro Ala Glu Lys Val Val Tyr Arg Leu Leu Arg Phe Leu Ile
660 665 670

Arg Thr Ile Phe Gly Thr Gly Glu Lys Val Leu Leu Ser Ala Lys Phe
675 680 685

Lys Phe Met Leu Asn Val Ser Tyr Leu Cys His Leu Ile Thr Lys Glu
690 695 700

Thr Pro Asp Arg Leu Thr Asp Gln Ile Lys Cys Phe Glu Lys Phe Phe
705 710 715 720

Glu Pro Lys Ser Glu Phe Gly Phe Phe Val Asn Pro Lys Glu Thr Ile
725 730 735

Thr Pro Glu Glu Glu Cys Val Phe Tyr Glu Gln Met Lys Lys Phe Thr
740 745 750

Gly Lys Asp Ile Asp Cys Gln His Ser Thr Pro Gly Val Asn Leu Glu
755 760 765

Ile Phe Ser Met Met Val Ser Ser Phe Asn Asn Gly Thr Leu Ile Leu
770 775 780

Lys Gly Glu Lys Arg Leu Asn Asn Leu Asp Pro Met Thr Asn Ser Gly
785 790 795 800

Cys Ala Thr Ala Leu Asp Leu Ala Ser Asn Lys Ser Val Val Val Asn
805 810 815

Lys His Leu Asn Gly Glu Arg Leu Leu Glu Tyr Asp Phe Asn Lys Leu
820 825 830
Leu Val Ser Ala Val Ser Gln Ile Thr Glu Gly Phe Met Arg Lys Gln
835 840 845
Lys Tyr Lys Leu Arg His Ser Asp Tyr Glu Tyr Lys Val Ser Lys Leu
850 855 860
Val Ser Arg Leu Val Ile Gly Ser Arg Lys Thr Glu Val Asp Lys Leu
865 870 875 880
Glu Asp Asp Pro Val Asp Val Cys Phe Glu Gly Glu Glu Glu Thr Ser
885 890 895
Phe Phe Arg Ser Leu Glu Asp Lys Val Ser Ser Thr Ile Thr Arg Tyr
900 905 910
Asn Arg Gly Thr Arg Leu Asn Glu Gly Gln Gly Glu Gly Glu Phe Lys
915 920 925
Asn Thr Lys Gly Leu His His Leu Gln Ile Ile Leu Ser Gly Lys Arg
930 935 940
Ala Tyr Leu Arg Lys Val Ile Leu Ser Glu Ile Ser Phe His Leu Val
945 950 955 960
Glu Asp Phe Asp Pro Ser Cys Leu Thr Asn Asp Asp Met Arg Phe Ile
965 970 975
Cys Glu Ala Val Glu Gly Ser Thr Glu Leu Ser Pro Leu Tyr Phe Thr
980 985 990
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<210> 23
<211> 1497
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b
<400> 23

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tgtgggatat tcgcattgat cagtttccta cttctggctg gcaggtcctg tggcatgtac 180
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cagagccagt gtagaacctt cagaggtaga gtcctagata tgtttagaac tgccttcggg 600
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<210> 24
<211> 498
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b
<400> 24

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

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

Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Lys Thr Val Trp Lys
485 490 495

Arg Arg

<210> 25

<211> 1677

<212> DNA

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b

<400> 25

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cagagcttca catcagatgt gaaggctgct gtcattaagg atgcaaccaa ccttctgaat 120
gggttggact tctctgaggt cagcaatgtt cagaggatca tgaggaagga aaagagagat 180
gacaaagacc tacagagact cagaagtctc aaccagactg tacattctct tgtggattta 240
aagtcaacat caaagaagaa tgttttgaaa gtggggaggc tcagtgcaga agaactgatg 300
tctcttgcgg ctgaccttga gaagctgaag gccaagatca tgaggtctga aaggccccag 360
gcttcagggg tatatatggg gaacttaaca acacagcaac tagaccaaag atctcagatc 420
ctacagatag ttgggatgag aaagcctcag cagggtgcaa gtggtgtggt aagagtttgg 480
gatgtgaaag actcatcact tttgaacaat caatttggca caatgccaag tctaactatg 540
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aagcacccag ttctgggggt catcactgaa cagcagtcca gcatcaacat ttctggctat 720
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atggactgca tcatttttga aagcgcctcc aaagcaaggc tcccagatct gaaaactgtt 1620
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<210> 26

<211> 558

<212> PRT

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b

<400> 26

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

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

<210> 27
<211> 273
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b
<400> 27
atgggtcaag gcaagtccag agaggagaaa ggcaccaata gtacaaacag ggccgaaatc 60

ctaccagata ccacctatct tggcccttta agctgcaaat cttgctggca gaaatttgac 120
agcttggtaa gatgccatga ccactacctt tgcaggcact gtttaaacct tctgctgtca 180
gtatccgaca ggtgtcctct ttgtaaatat ccattaccaa ccagattgaa gatatcaaca 240
gccccaagct ctccacctcc ctacgaagag taa 273

<210> 28
<211> 90
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b
<400> 28

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

<210> 29
<211> 6633
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株Armstrong 53b
<400> 29

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aggttgtcaa ggcagaaact caactttctg ggacaaaggg aacccagaat ggttctgatt 120
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gactctatga aaattctgaa agatgcgagg tcaactcata atgatgaaat tatgaggatg 660
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cttttcagca ggtttagaag agatttagaa agtgggaaat taaagagaaa ctttcagaaa 780

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Arg Glu Pro Arg Met Val Leu Ile Glu Gly Leu Lys Leu Leu Ser Arg
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Cys Ile Glu Ile Asp Ser Ala Asp Lys Ser Gly Cys Thr His Asn His
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Asp Asp Lys Ser Val Glu Thr Ile Leu Val Glu Ser Gly Ile Val Cys
65 70 75 80
Pro Gly Leu Pro Leu Ile Ile Pro Asp Gly Tyr Lys Leu Ile Asp Asn
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Ser Leu Ile Leu Leu Glu Cys Phe Val Arg Ser Thr Pro Ala Ser Phe
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Glu Lys Lys Phe Ile Glu Asp Thr Asn Lys Leu Ala Cys Ile Arg Glu
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Val Phe Glu Glu Ser Glu Tyr Phe Arg Leu Cys Glu Ser Leu Lys Thr
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260 265 270
Leu Tyr Glu Asn Leu Ala Asp Ser Asp Asp Ile Leu Thr Leu Ser Arg
275 280 285
Glu Ala Val Glu Ser Cys Pro Leu Met Arg Phe Ile Thr Ala Glu Thr
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Arg Arg Gln Leu Leu Asn Leu Asp Val Leu Cys Leu Ser Ser Leu Ile
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Cys Cys Tyr Ser Ser Val Asn Asp Arg Leu Val Ser Phe His Ser Thr
370 375 380
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385 390 395 400
Phe Arg Lys Val Ser Phe Glu Glu Leu Phe Arg Ala Ser Ile Ser Glu
405 410 415
Phe Ile Ala Lys Ile Gln Lys Cys Leu Leu Val Val Gly Leu Ser Phe

420 425 430

Glu His Tyr Gly Leu Ser Glu His Leu Glu Gln Glu Cys His Ile Pro

435 440 445

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450 455 460

Tyr Tyr Thr Lys Phe Glu Asp Tyr Asn Phe Gln Pro Ser Thr Glu Gln

465 470 475 480

Leu Lys Asn Ile Gln Ser Leu Arg Arg Leu Ser Ser Val Cys Leu Ala

485 490 495

Leu Thr Asn Ser Met Lys Thr Ser Ser Val Ala Arg Leu Arg Gln Asn

500 505 510

Gln Ile Gly Ser Val Arg Tyr Gln Val Val Glu Cys Lys Glu Val Phe

515 520 525

Cys Gln Val Ile Lys Leu Asp Ser Glu Glu Tyr His Leu Leu Tyr Gln

530 535 540

Lys Thr Gly Glu Ser Ser Arg Cys Tyr Ser Ile Gln Gly Pro Asp Gly

545 550 555 560

His Leu Ile Ser Phe Tyr Ala Asp Pro Lys Arg Phe Phe Leu Pro Ile

565 570 575

Phe Ser Asp Glu Val Leu Tyr Asn Met Ile Asp Ile Met Ile Ser Trp

580 585 590

Ile Arg Ser Cys Pro Asp Leu Lys Asp Cys Leu Thr Asp Ile Glu Val

595 600 605

Ala Leu Arg Thr Leu Leu Leu Leu Met Leu Thr Asn Pro Thr Lys Arg

610 615 620

Asn Gln Lys Gln Val Gln Ser Val Arg Tyr Leu Val Met Ala Ile Val

625 630 635 640

Ser Asp Phe Ser Ser Thr Ser Leu Met Asp Lys Leu Arg Glu Asp Leu

645 650 655

Ile Thr Pro Ala Glu Lys Val Val Tyr Lys Leu Leu Arg Phe Leu Ile

660 665 670

Lys Thr Ile Phe Gly Thr Gly Glu Lys Val Leu Leu Ser Ala Lys Phe

675 680 685

Lys Phe Met Leu Asn Val Ser Tyr Leu Cys His Leu Ile Thr Lys Glu

690 695 700

Thr Pro Asp Arg Leu Thr Asp Gln Ile Lys Cys Phe Glu Lys Phe Phe

705 710 715 720

Glu Pro Lys Ser Gln Phe Gly Phe Phe Val Asn Pro Lys Glu Ala Ile

725 730 735

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755 760 765
Ala Phe Ser Leu Met Val Ser Ser Phe Asn Asn Gly Thr Leu Ile Phe
770 775 780
Lys Gly Glu Lys Lys Leu Asn Ser Leu Asp Pro Met Thr Asn Ser Gly
785 790 795 800
Cys Ala Thr Ala Leu Asp Leu Ala Ser Asn Lys Ser Val Val Val Asn
805 810 815
Lys His Leu Asn Gly Glu Arg Leu Leu Glu Tyr Asp Phe Asn Lys Leu
820 825 830
Leu Val Ser Ala Val Ser Gln Ile Thr Glu Ser Phe Val Arg Lys Gln
835 840 845
Lys Tyr Lys Leu Ser His Ser Asp Tyr Glu Tyr Lys Val Ser Lys Leu
850 855 860
Val Ser Arg Leu Val Ile Gly Ser Lys Gly Glu Glu Thr Gly Arg Ser
865 870 875 880
Glu Asp Asn Leu Ala Glu Ile Cys Phe Asp Gly Glu Glu Glu Thr Ser
885 890 895
Phe Phe Lys Ser Leu Glu Glu Lys Val Asn Thr Thr Ile Ala Arg Tyr
900 905 910
Arg Arg Gly Arg Arg Ala Asn Asp Lys Gly Asp Gly Glu Lys Leu Thr
915 920 925
Asn Thr Lys Gly Leu His His Leu Gln Leu Ile Leu Thr Gly Lys Met
930 935 940
Ala His Leu Arg Lys Val Ile Leu Ser Glu Ile Ser Phe His Leu Val
945 950 955 960
Glu Asp Phe Asp Pro Ser Cys Leu Thr Asn Asp Asp Met Lys Phe Ile
965 970 975
Cys Glu Ala Val Glu Gly Ser Thr Glu Leu Ser Pro Leu Tyr Phe Thr
980 985 990
Ser Val Ile Lys Asp Gln Cys Gly Leu Asp Glu Met Ala Lys Asn Leu
995 1000 1005
Cys Arg Lys Phe Phe Ser Glu Asn Asp Trp Phe Ser Cys Met Lys
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1130 1135 1140

Glu Ser Phe Ser Ser Phe Phe Ser Gly Ser Cys Leu Asn Asn Asp

1145 1150 1155

Lys Glu Phe Glu Asn Ala Ile Leu Ser Met Thr Ile Asn Val Arg

1160 1165 1170

Glu Gly Phe Leu Asn Tyr Ser Met Asp His Ser Lys Trp Gly Pro

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Met Met Cys Pro Phe Leu Phe Leu Met Phe Leu Gln Asn Leu Lys

1190 1195 1200

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Pro Val Val Asn Ala Met Met Lys Ser Tyr Val Lys Ser Lys Leu

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Arg Gln Tyr Phe Glu Met Gly Ile Val Pro Ser His Ile Ser Ser

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Tyr Gly Leu Leu Ser Glu Arg Phe Ile Asn Tyr Cys Ile Gly Val

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1580 1585 1590
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1625 1630 1635

Asp Asp His Val Thr Arg Val Cys Asn Arg Asp Gly Ile Thr Leu

1640 1645 1650

Tyr Ile Cys Asp Lys Gln Ser His Pro Glu Ala His Arg Asp His

1655 1660 1665

Ile Cys Leu Leu Arg Pro Leu Leu Trp Asp Tyr Ile Cys Ile Ser

1670 1675 1680

Leu Ser Asn Ser Phe Glu Leu Gly Val Trp Val Leu Ala Glu Pro

1685 1690 1695

Thr Lys Gly Lys Asn Asn Ser Glu Asn Leu Thr Leu Lys His Leu

1700 1705 1710

Asn Pro Cys Asp Tyr Val Ala Arg Lys Pro Glu Ser Ser Arg Leu

1715 1720 1725

Leu Glu Asp Lys Val Asn Leu Asn Gln Val Ile Gln Ser Val Arg

1730 1735 1740

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1745 1750 1755

Ser Asp Met Ser Ser Lys Asn Met Arg Trp Ser Pro Arg Ile Lys

1760 1765 1770

Phe Leu Asp Leu Cys Val Leu Ile Asp Ile Asn Ser Glu Ser Leu

1775 1780 1785

Ser Leu Ile Ser His Val Val Lys Trp Lys Arg Asp Glu His Tyr

1790 1795 1800

Thr Val Leu Phe Ser Asp Leu Ala Asn Ser His Gln Arg Ser Asp

1805 1810 1815

Ser Ser Leu Val Asp Glu Phe Val Val Ser Thr Arg Asp Val Cys

1820 1825 1830

Lys Asn Phe Leu Lys Gln Val Tyr Phe Glu Ser Phe Val Arg Glu

1835 1840 1845

Phe Val Ala Thr Thr Arg Thr Leu Gly Asn Phe Ser Trp Phe Pro

1850 1855 1860

His Lys Glu Met Met Pro Ser Glu Asp Gly Ala Glu Ala Leu Gly

1865 1870 1875

Pro Phe Gln Ser Phe Val Ser Lys Val Val Asn Lys Asn Val Glu

1880 1885 1890

Arg Pro Met Phe Arg Asn Asp Leu Gln Phe Gly Phe Gly Trp Phe

1895 1900 1905

Ser Tyr Arg Met Gly Asp Val Val Cys Asn Ala Ala Met Leu Ile

1910 1915 1920

Arg Gln Gly Leu Thr Asn Pro Lys Ala Phe Lys Ser Leu Lys Asp
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1940 1945 1950
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1955 1960 1965
Leu Arg Lys Phe Ser Leu Ile Phe Leu Val Arg Cys Gln Leu Gln
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1985 1990 1995
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2000 2005 2010
Arg Thr Asp Ser Val Phe Lys Val Asn Asp Gly Val Phe Asp Ile
2015 2020 2025
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2105 2110 2115
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2120 2125 2130
His Leu Leu Gly Ser Glu Ile Ser Val Ile Leu Gln Glu Leu Cys
2135 2140 2145
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2165 2170 2175
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2210

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<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13

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<400> 32

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<210> 33
<211> 1497
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13
<400> 33
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<210> 34
<211> 498
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13
<400> 34

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Glu Val Ile Asn Ile Val Ile Ile Val Leu Ile Val Ile Thr Gly Ile
20 25 30
Lys Ala Val Tyr Asn Phe Ala Thr Cys Gly Ile Phe Ala Leu Ile Ser
35 40 45
Phe Leu Leu Leu Ala Gly Arg Ser Cys Gly Met Tyr Gly Leu Lys Gly
50 55 60
Pro Asp Ile Tyr Lys Gly Val Tyr Gln Phe Lys Ser Val Glu Phe Asp
65 70 75 80

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

385 390 395 400
Asn Glu Thr His Phe Ser Asp Gln Ile Glu Gln Glu Ala Asp Asn Met
405 410 415
Ile Thr Glu Met Leu Arg Lys Asp Tyr Ile Lys Arg Gln Gly Ser Thr
420 425 430
Pro Leu Ala Leu Met Asp Leu Leu Met Phe Ser Thr Ser Ala Tyr Leu
435 440 445
Val Ser Ile Phe Leu His Leu Val Lys Ile Pro Thr His Arg His Ile
450 455 460
Lys Gly Gly Ser Cys Pro Lys Pro His Arg Leu Thr Asn Lys Gly Ile
465 470 475 480
Cys Ser Cys Gly Ala Phe Lys Val Pro Gly Val Lys Thr Val Trp Lys
485 490 495
Arg Arg

<210> 35
<211> 1677
<212> DNA
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13
<400> 35

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<210> 36
<211> 558
<212> PRT
<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13
<400> 36

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

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

515 520 525

Ala Ser Lys Ala Arg Leu Pro Asp Leu Lys Thr Val His Asn Ile Leu
530 535 540

Pro His Asp Leu Ile Phe Arg Gly Pro Asn Val Val Thr Leu
545 550 555

<210> 37

<211> 273

<212> DNA

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13

<400> 37

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ctaccagata ccacctatct tggcccttta agctgcaaat cttgctggca gaaatttgac 120

agcttggtaa gatgccatga ccactacctt tgcaggcact gtttaaacct tctgctgtca 180

gtatccgaca ggtgtcctct ttgtaaatat ccattaccaa ccagattgaa gatatcaaca 240

gccccaagct ctccacctcc ctacgaagag taa 273

<210> 38

<211> 90

<212> PRT

<213> 淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆13

<400> 38

Met Gly Gln Gly Lys Ser Arg Glu Glu Lys Gly Thr Asn Ser Thr Asn
1 5 10 15

Arg Ala Glu Ile Leu Pro Asp Thr Thr Tyr Leu Gly Pro Leu Ser Cys
20 25 30

Lys Ser Cys Trp Gln Lys Phe Asp Ser Leu Val Arg Cys His Asp His
35 40 45

Tyr Leu Cys Arg His Cys Leu Asn Leu Leu Leu Ser Val Ser Asp Arg
50 55 60

Cys Pro Leu Cys Lys Tyr Pro Leu Pro Thr Arg Leu Lys Ile Ser Thr
65 70 75 80

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Ser Ser Leu Val Asp Glu Phe Val Val Ser Thr Arg Asp Val Cys
1820 1825 1830
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1835 1840 1845

Phe Val Ala Thr Thr Arg Thr Leu Gly Asn Phe Ser Trp Phe Pro

1850 1855 1860

His Lys Glu Met Met Pro Ser Glu Asp Gly Ala Glu Ala Leu Gly

1865 1870 1875

Pro Phe Gln Ser Phe Val Ser Lys Val Val Asn Lys Asn Val Glu

1880 1885 1890

Arg Pro Met Phe Arg Asn Asp Leu Gln Phe Gly Phe Gly Trp Phe

1895 1900 1905

Ser Tyr Arg Met Gly Asp Val Val Cys Asn Ala Ala Met Leu Ile

1910 1915 1920

Arg Gln Gly Leu Thr Asn Pro Lys Ala Phe Lys Ser Leu Lys Asp

1925 1930 1935

Leu Trp Asp Tyr Met Leu Asn Tyr Thr Lys Gly Val Leu Glu Phe

1940 1945 1950

Ser Ile Ser Val Asp Phe Thr His Asn Gln Asn Asn Thr Asp Cys

1955 1960 1965

Leu Arg Lys Phe Ser Leu Ile Phe Leu Val Arg Cys Gln Leu Gln

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Asn Pro Gly Val Ala Glu Leu Leu Ser Cys Ser His Leu Phe Lys

1985 1990 1995

Gly Glu Ile Asp Arg Arg Met Leu Asp Glu Cys Leu His Leu Leu

2000 2005 2010

Arg Thr Asp Ser Val Phe Lys Val Asn Asp Gly Val Phe Asp Ile

2015 2020 2025

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Glu Pro Val Pro Leu Thr Val Lys Met Gly Ala Leu Phe Glu Gly

2075 2080 2085

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Asp Val Leu Gly Asn Leu Phe Leu His Arg Phe Arg Thr Gly Glu

2120 2125 2130

His Leu Leu Gly Ser Glu Ile Ser Val Ile Leu Gln Glu Leu Cys
2135 2140 2145
Ile Asp Arg Ser Ile Leu Leu Ile Pro Leu Ser Leu Leu Pro Asp
2150 2155 2160
Trp Phe Ala Phe Lys Asp Cys Arg Leu Cys Phe Ser Lys Ser Arg
2165 2170 2175
Ser Thr Leu Met Tyr Glu Thr Val Gly Gly Arg Phe Arg Leu Lys
2180 2185 2190
Gly Arg Ser Cys Asp Asp Trp Leu Gly Gly Ser Val Ala Glu Asp
2195 2200 2205
Ile Asp
2210

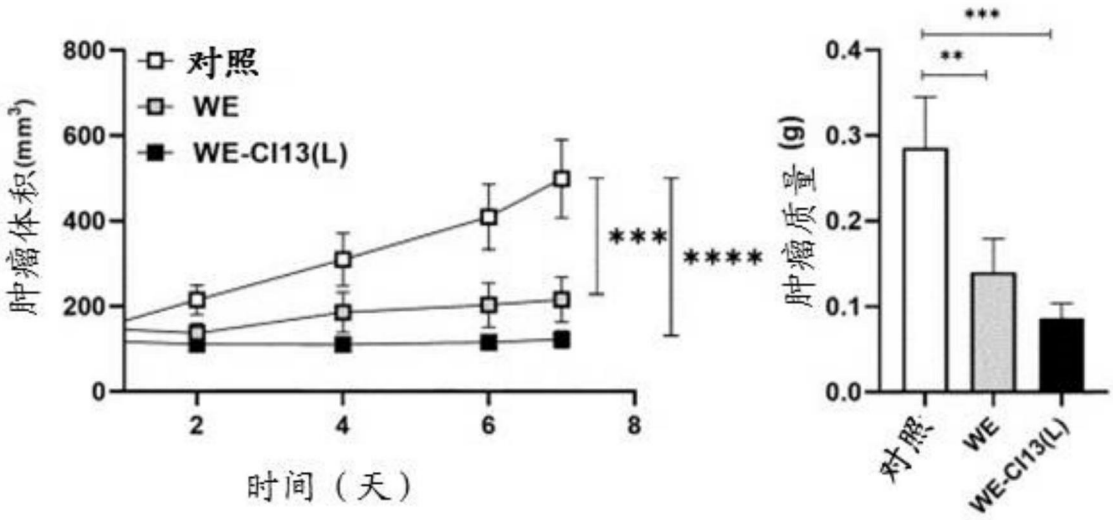

对照
WE
WE-CI13(L)
肿瘤体积(mm³)
800
600
400
200
0
2
4
6
8
时间（天）
***
****
肿瘤质量 (g)
0.4
0.3
0.2
0.1
0.0
**
***
对照
WE
WE-CI13(L)

图1

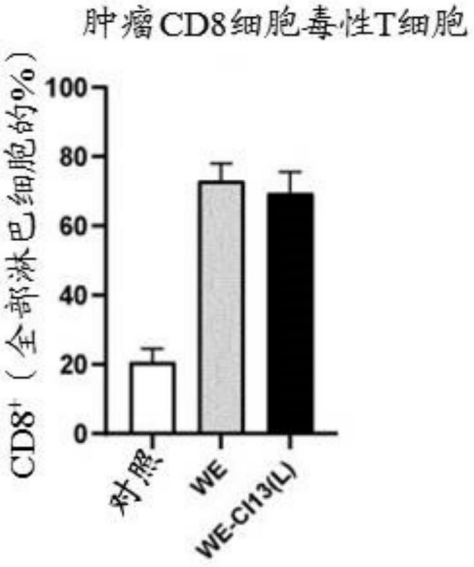

肿瘤CD8细胞毒性T细胞
CD8⁺（全部淋巴细胞的%）
100
80
60
40
20
0
对照
WE
WE-CI13(L)

图2

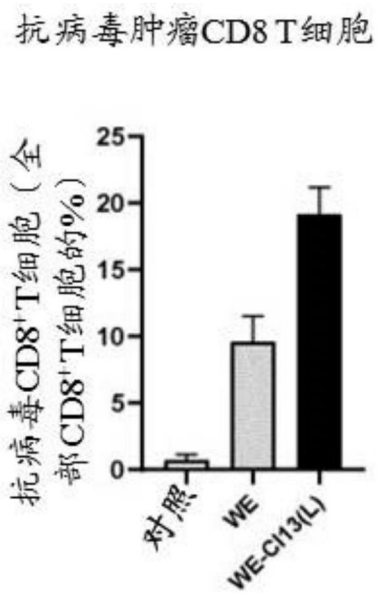

抗病毒肿瘤CD8 T细胞
抗病毒CD8+T细胞（全部CD8+T细胞的%）
25
20
15
10
5
0
对照
WE
WE-CI13(L)

图3

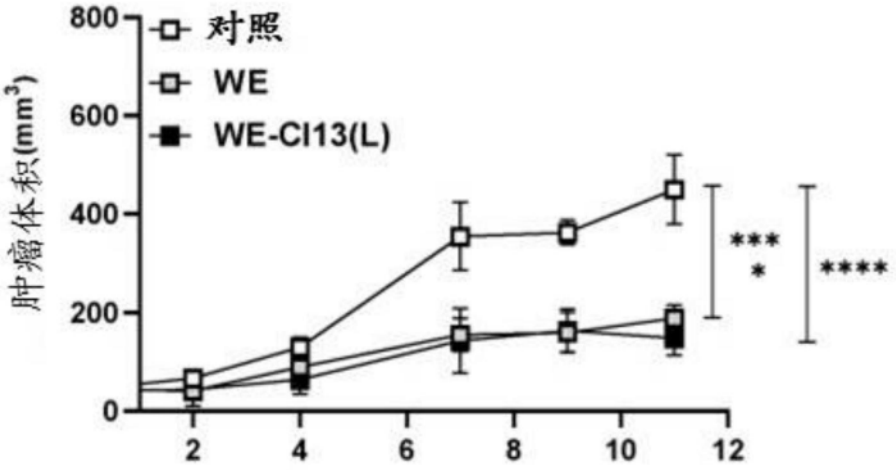

肿瘤体积(mm3)
800
600
400
200
0
对照
WE
WE-CI13(L)
2
4
6
8
10
12
***
*
****

图4

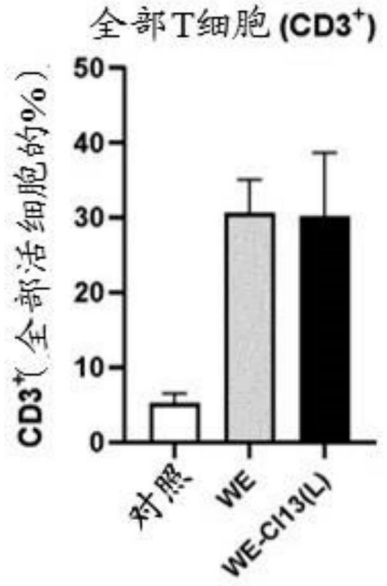

全部T细胞 (CD3+)
CD3+（全部活细胞的%）
50
40
30
20
10
0
对照
WE
WE-CI13(L)

图5

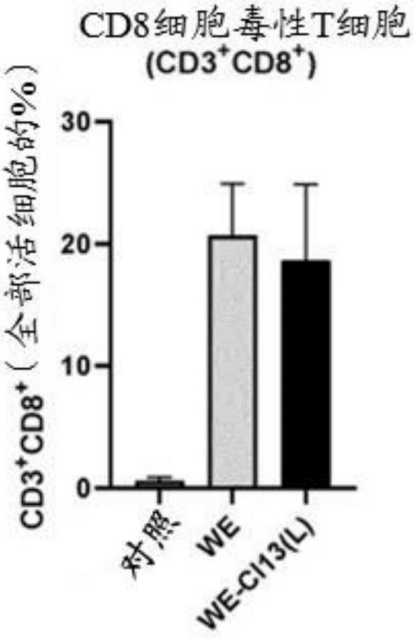

CD8细胞毒性T细胞
(CD3+CD8+)
CD3+CD8+（全部活细胞的%）
30
20
10
0
对照
WE
WE-CI13(L)

图6

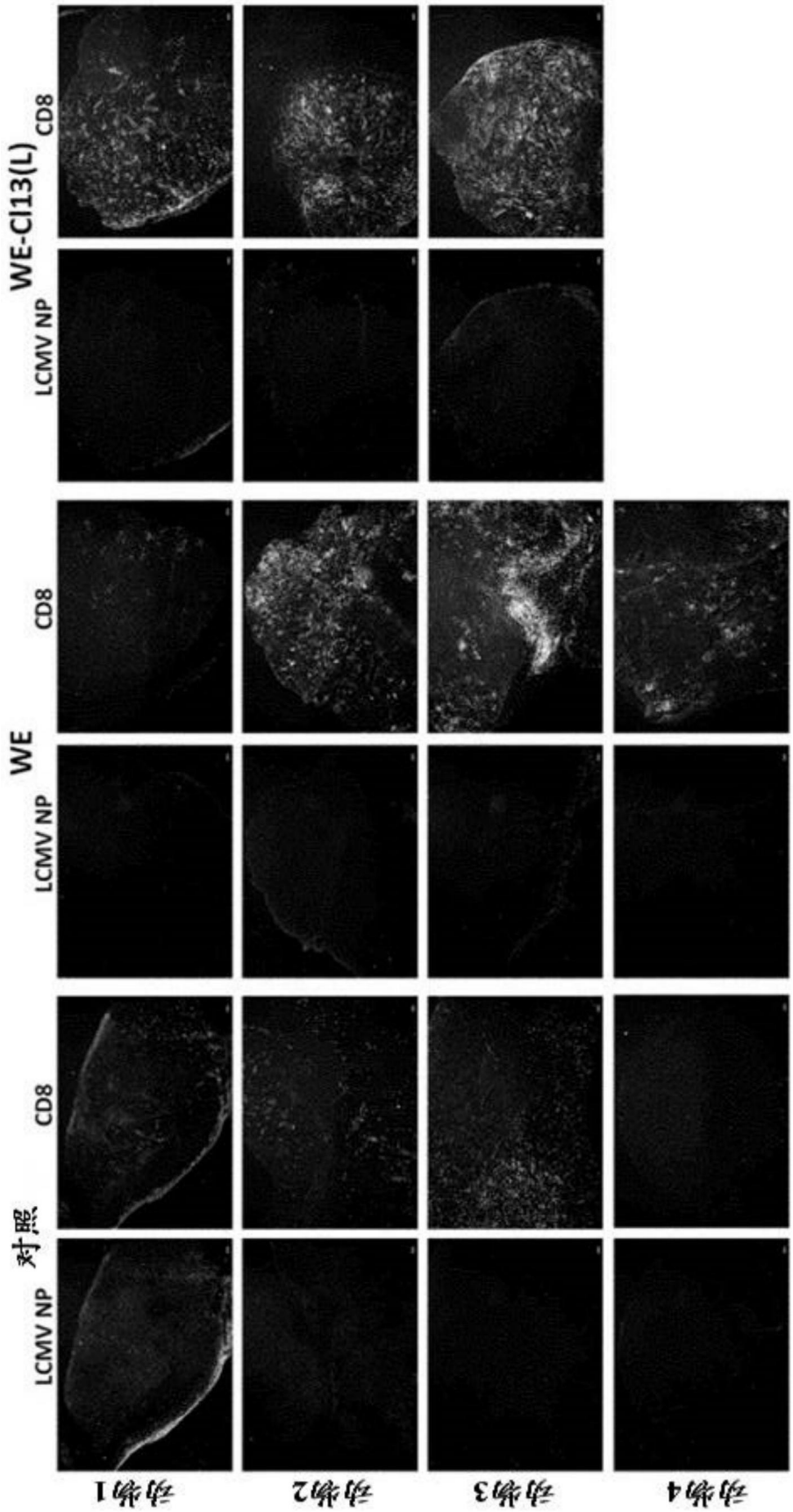

WE-Cl13(L)
CD8
LCMV NP
WE
CD8
LCMV NP
对照
CD8
LCMV NP
动物1
动物2
动物3
动物4

图7

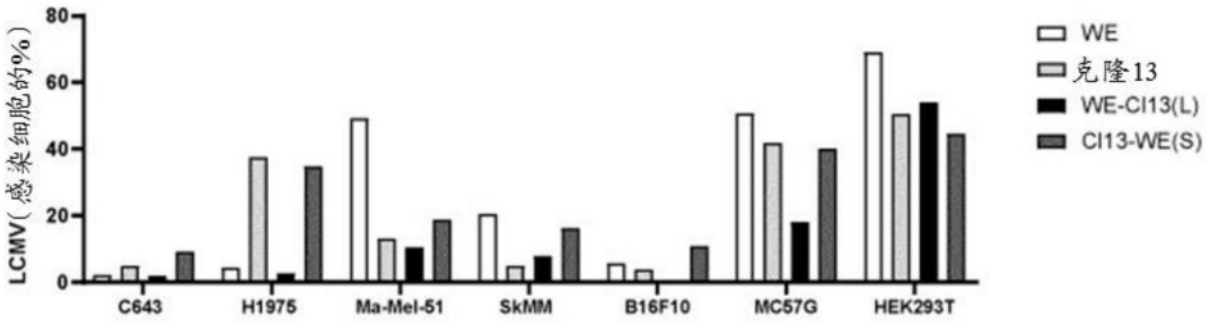

LCMV(感染细胞的%)
80
60
40
20
0
C643
H1975
Ma-Mel-51
SkMM
B16F10
MC57G
HEK293T
WE
克隆13
WE-Cl13(L)
Cl13-WE(S)

图8

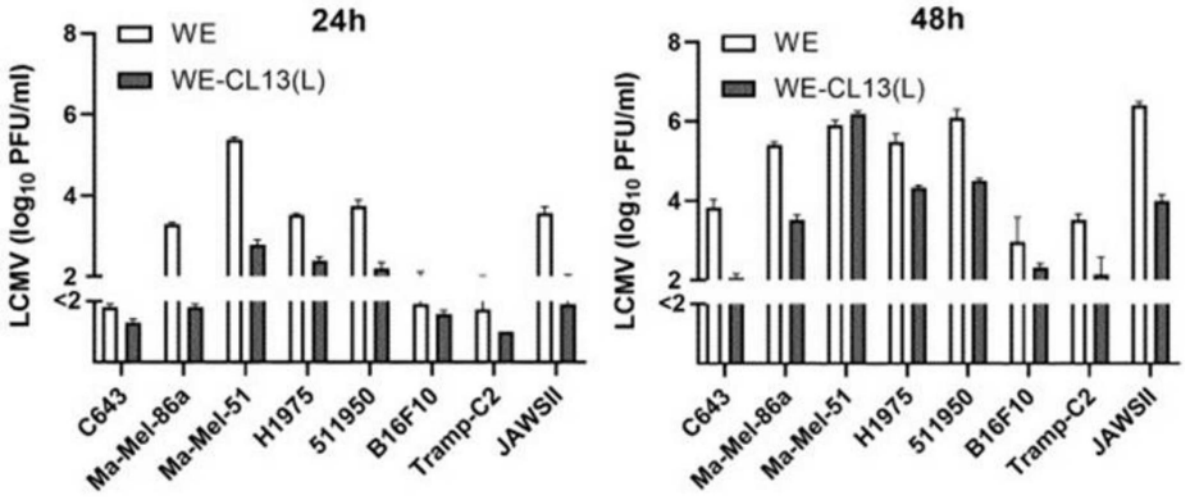

24h
48h
WE
WE-CL13(L)
LCMV (log10 PFU/ml)
8
6
4
2
<2
C643
Ma-Mel-86a
Ma-Mel-51
H1975
511950
B16F10
Tramp-C2
JAWSII

图9

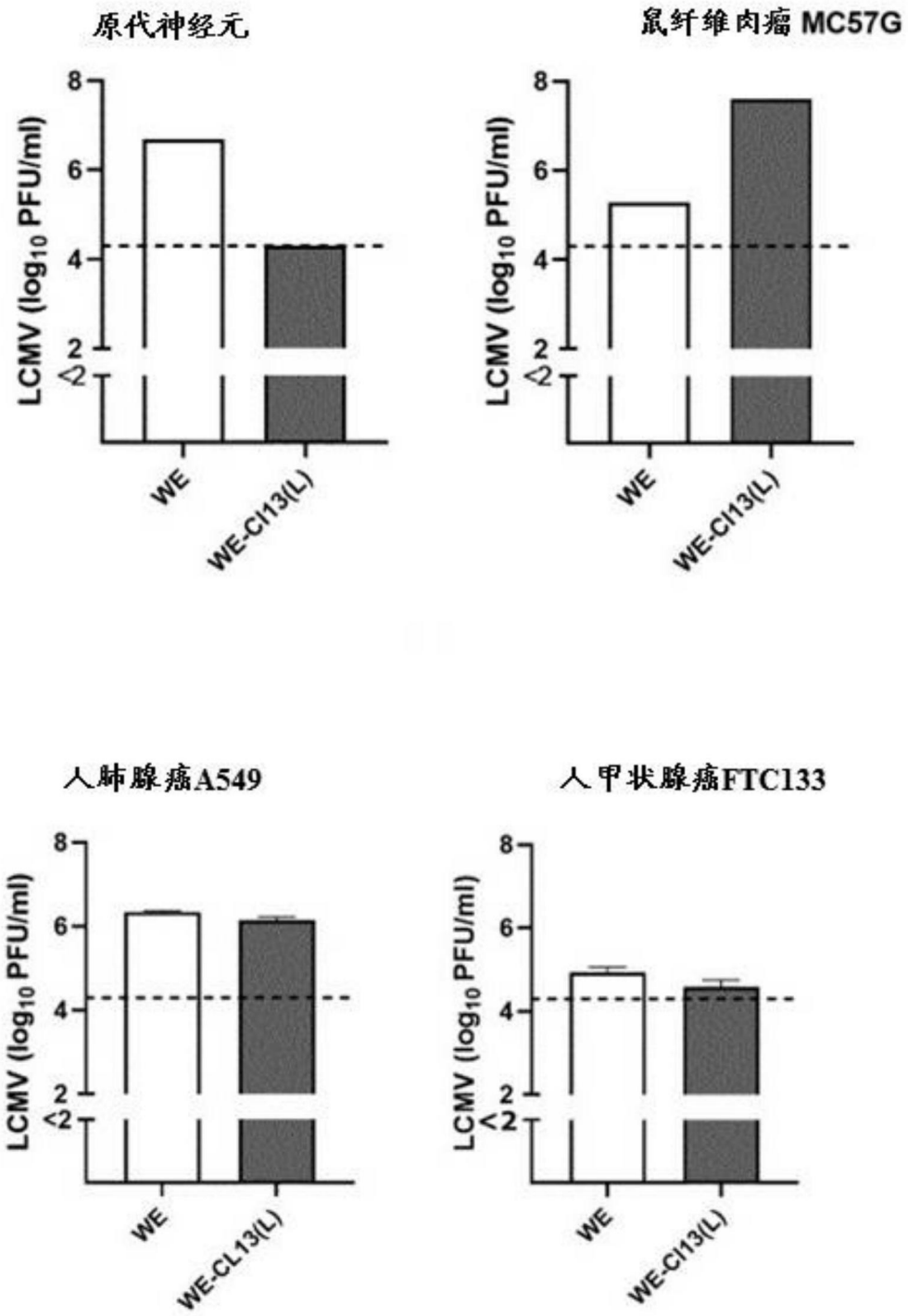

原代神经元
鼠纤维肉瘤 MC57G
人肺腺癌A549
人甲状腺癌FTC133
LCMV (log10 PFU/ml)
8
6
4
2
<2
WE
WE-Cl13(L)
WE-CL13(L)

图10

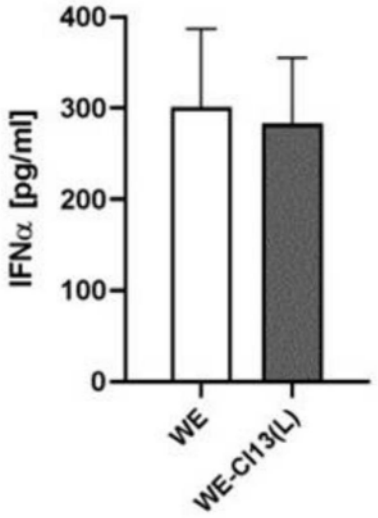

400
300
200
100
0
IFNα [pg/ml]
WE
WE-Cl13(L)

图11

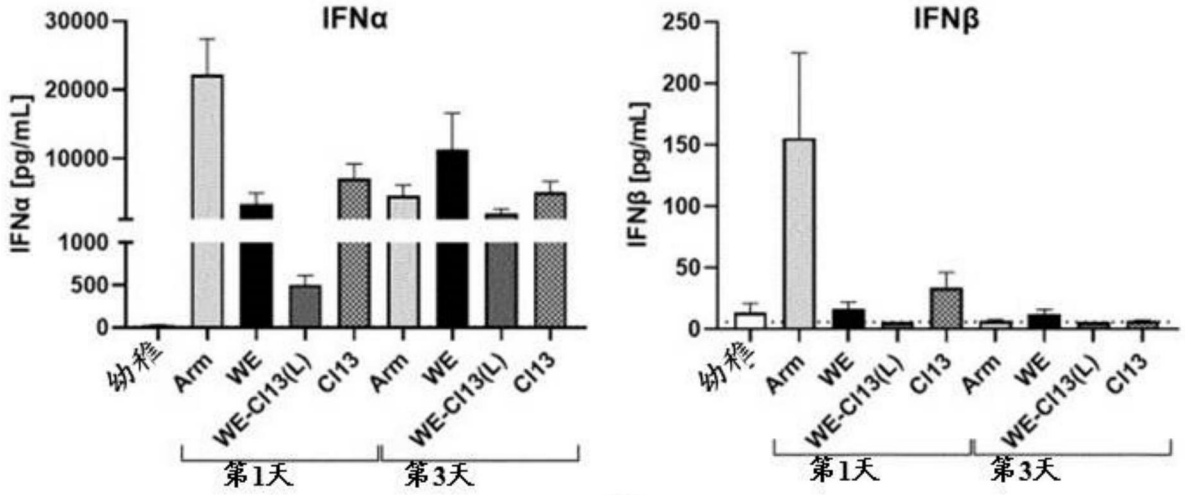

IFNα
30000
20000
10000
1000
500
0
IFNα [pg/mL]
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
Cl13
第1天
第3天
IFNβ
250
200
150
100
50
0
IFNβ [pg/mL]
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
Cl13
第1天
第3天

图12

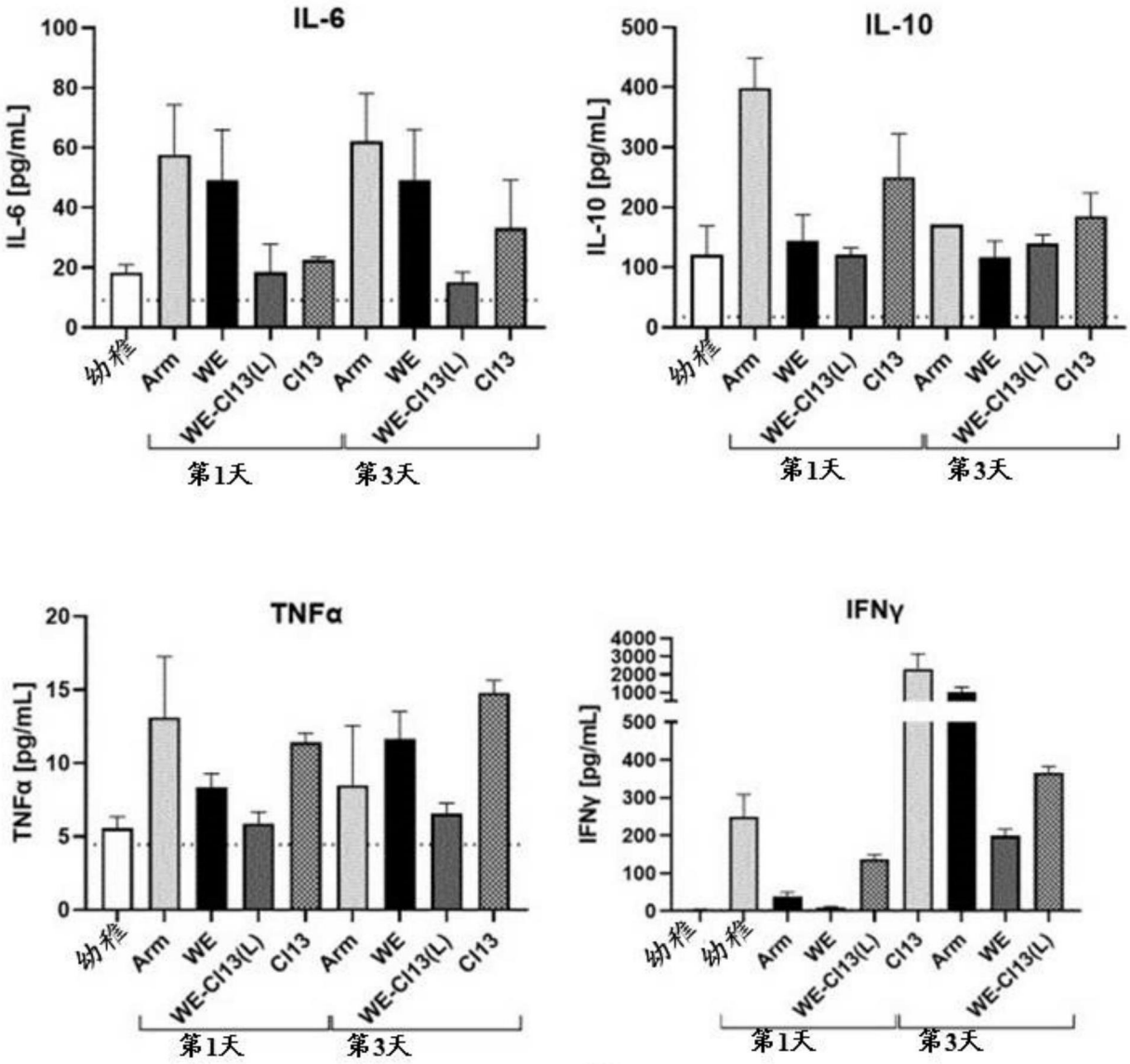

IL-6
IL-6 [pg/mL]
100
80
60
40
20
0
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
Cl13
第1天
第3天
IL-10
IL-10 [pg/mL]
500
400
300
200
100
0
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
Cl13
第1天
第3天
TNFα
TNFα [pg/mL]
20
15
10
5
0
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
Cl13
第1天
第3天
IFNγ
IFNγ [pg/mL]
4000
3000
2000
1000
500
400
300
200
100
0
幼稚
幼稚
Arm
WE
WE-Cl13(L)
Cl13
Arm
WE
WE-Cl13(L)
第1天
第3天

图13

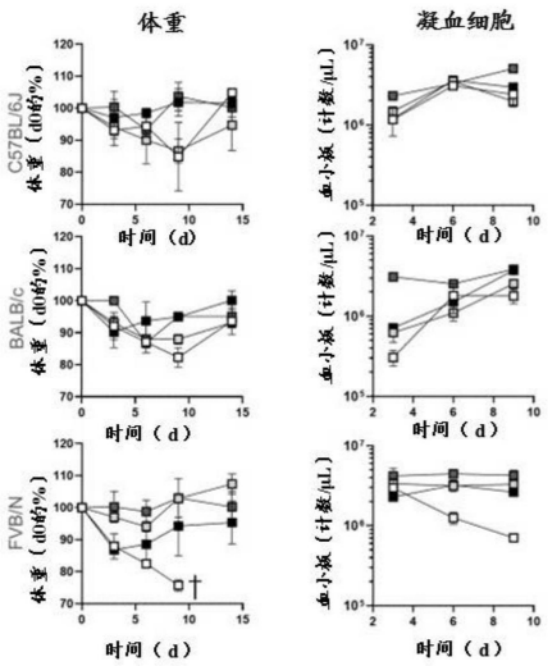


图14

图15

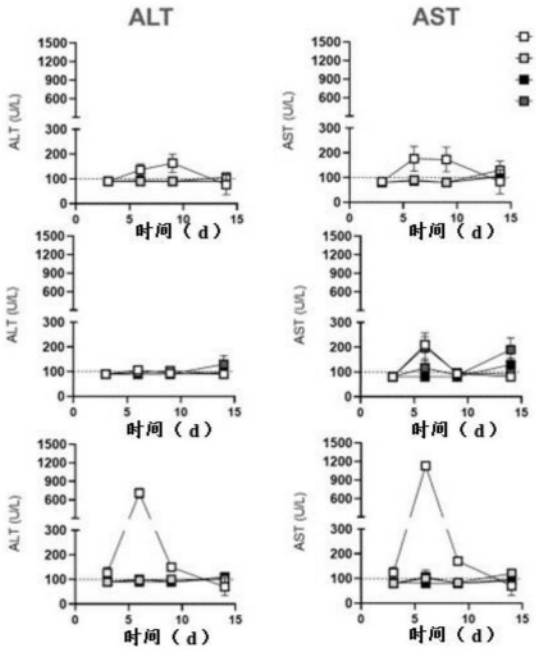


图16

图17

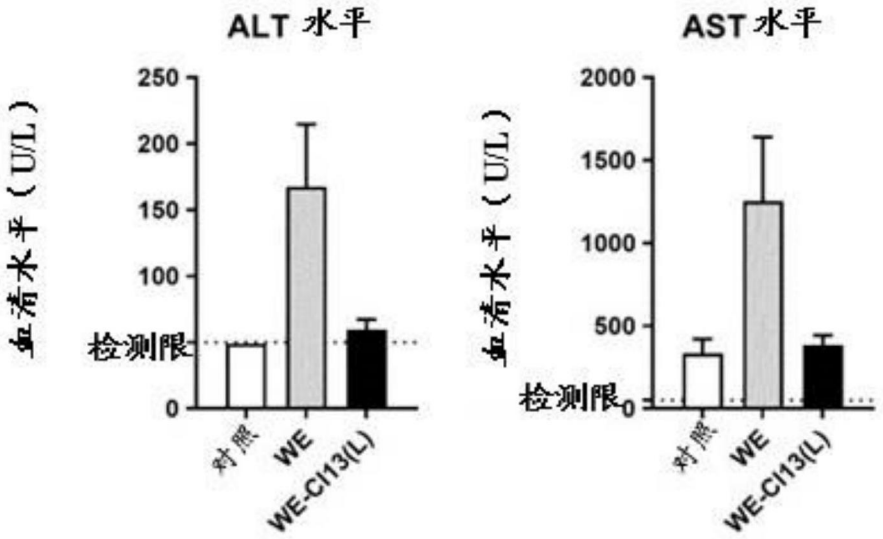


图18

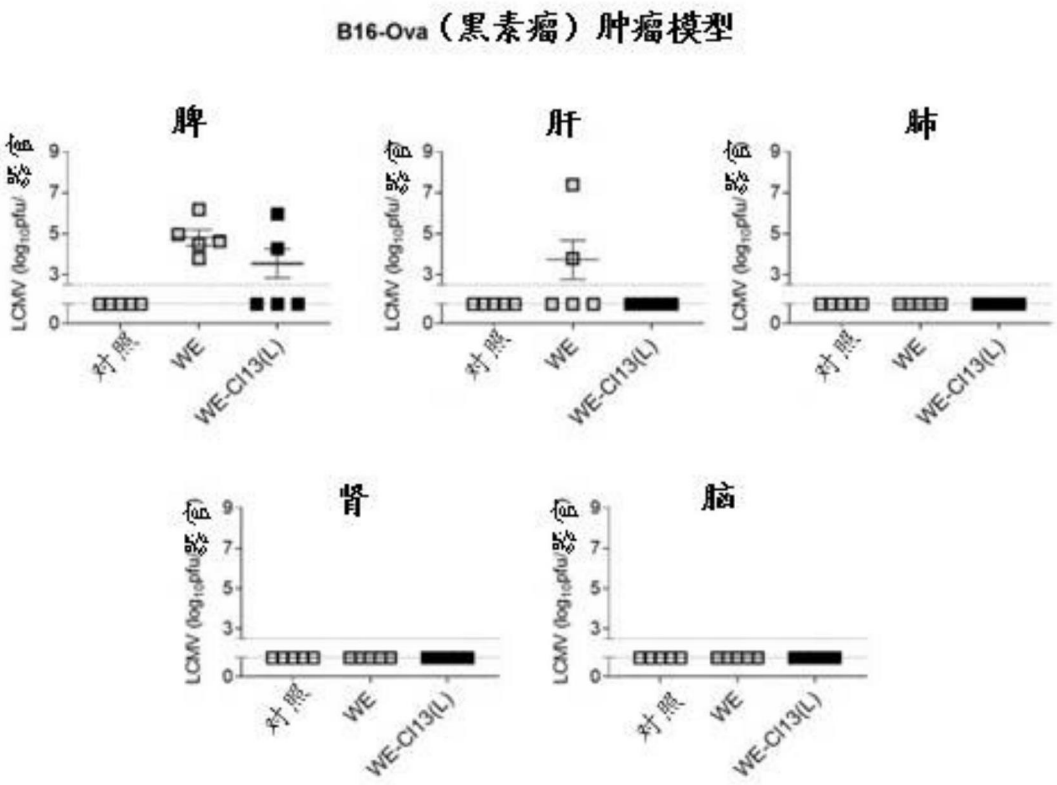

B16-Ova（黑素瘤）肿瘤模型
脾
肝
肺
肾
脑
LCMV (log10pfu/肿瘤)
对照
WE
WE-CI13(L)

图19

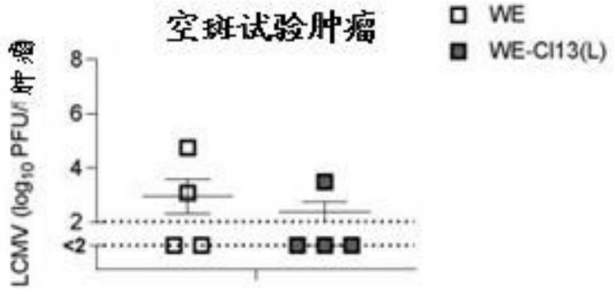

MC38（结肠）肿瘤模型
空斑试验肿瘤
WE
WE-CI13(L)
LCMV (log10 PFU/肿瘤)

图20

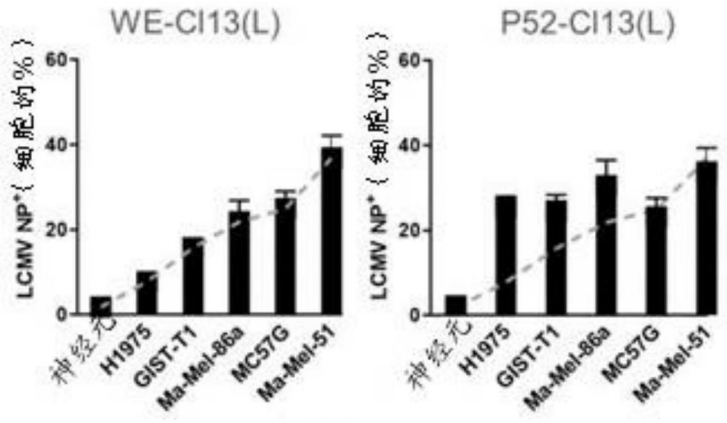

WE-CI13(L)
P52-CI13(L)
LCMV NP+{ 细胞的% }
60
40
20
0
神经元
H1975
GIST-T1
Ma-Mel-86a
MC57G
Ma-Mel-51

图21

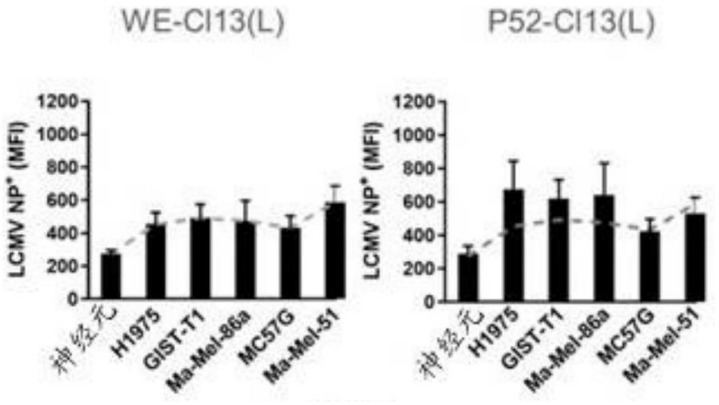

WE-CI13(L)
P52-CI13(L)
LCMV NP+ (MFI)
1200
1000
800
600
400
200
0
神经元
H1975
GIST-T1
Ma-Mel-86a
MC57G
Ma-Mel-51

图22

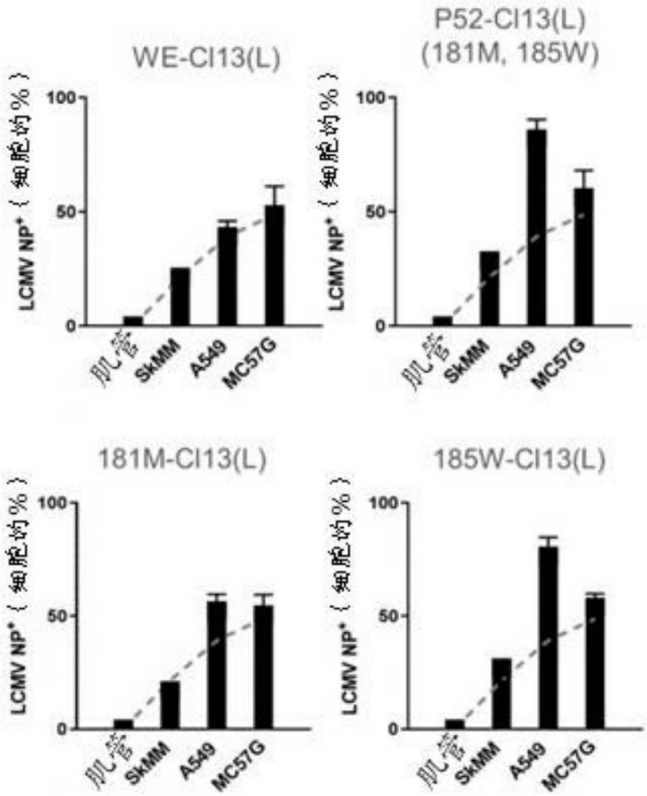

WE-CI13(L)
P52-CI13(L)
(181M, 185W)
181M-CI13(L)
185W-CI13(L)
LCMV NP+（细胞的%）
100
50
0
肌管
SkMM
A549
MC57G

图23

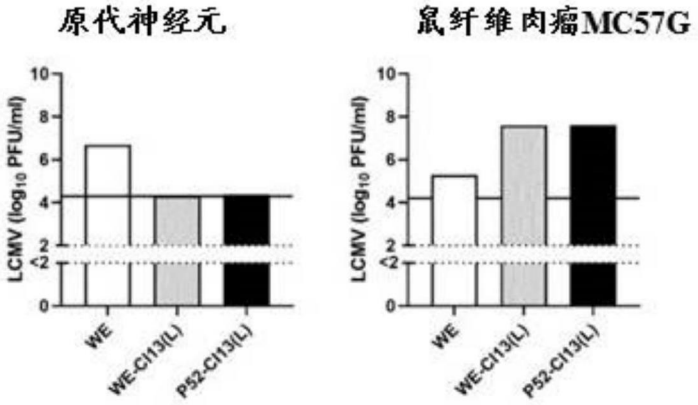

原代神经元
鼠纤维肉瘤MC57G
LCMV (log10 PFU/ml)
10
8
6
4
2
<2
0
WE
WE-CI13(L)
P52-CI13(L)

图24

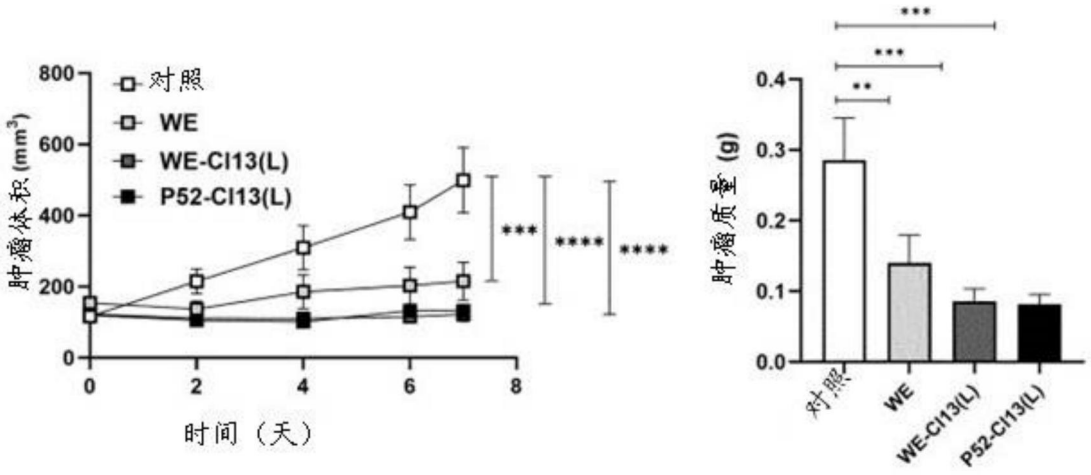


图25

肿瘤引流淋巴结

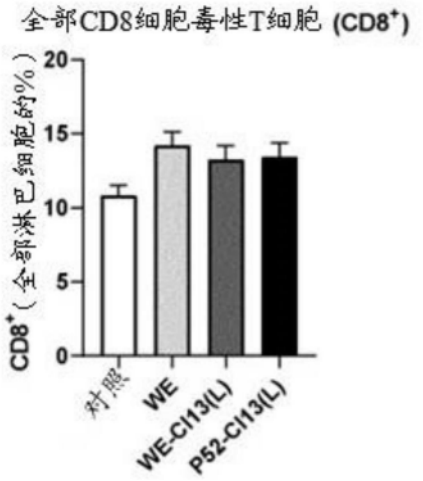


图26

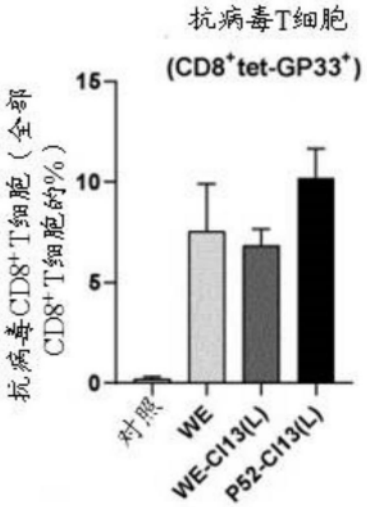


图27

肿瘤

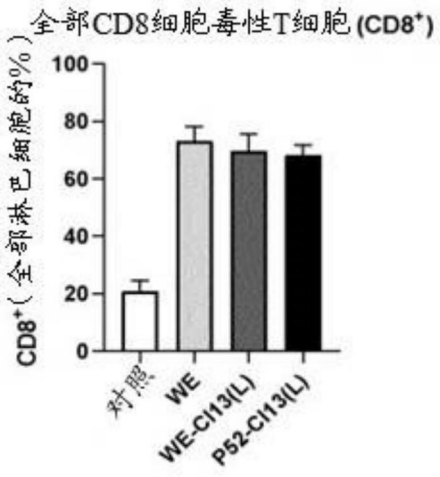


图28

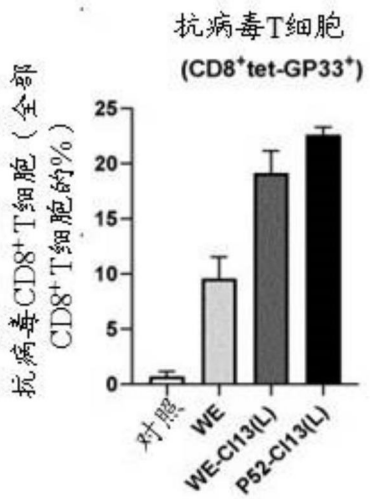
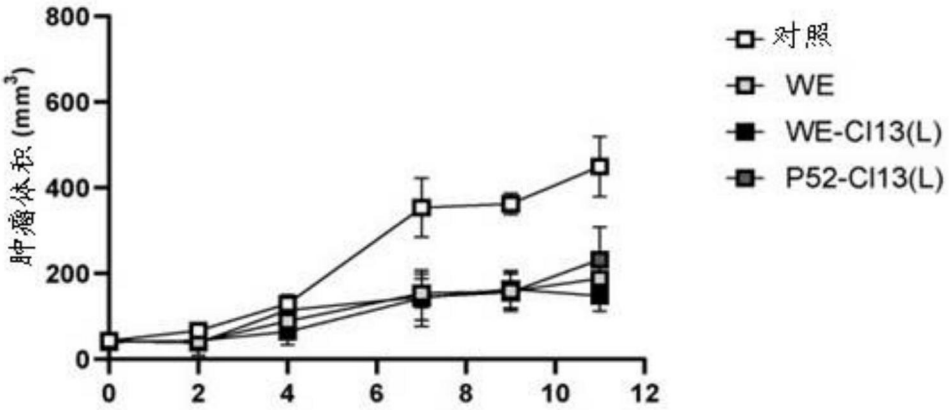


图29



Ctrl. vs.	第7天	第9天	第11天
WE	*	**	**
WE-CI13(L)	ns	**	**
P52-CI13(L)	ns	**	ns

图30

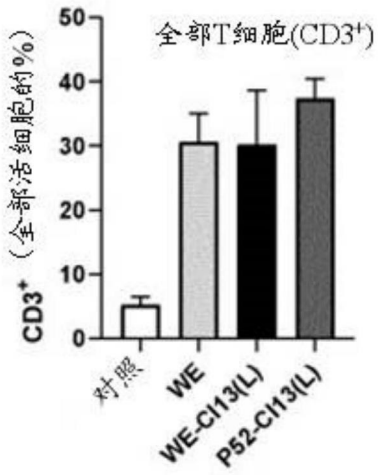

全部T细胞(CD3+)
CD3+（全部活细胞的%）
50
40
30
20
10
0
对照
WE
WE-CI13(L)
P52-CI13(L)

图31

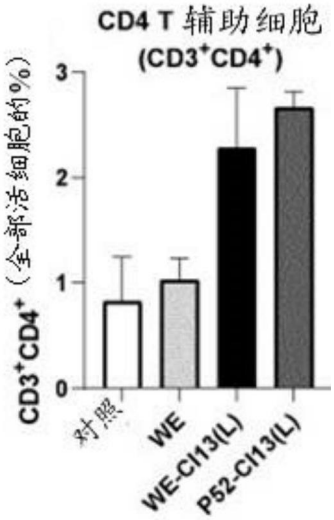

CD4 T 辅助细胞
(CD3+CD4+)
CD3+CD4+（全部活细胞的%）
3
2
1
0
对照
WE
WE-CI13(L)
P52-CI13(L)

图32

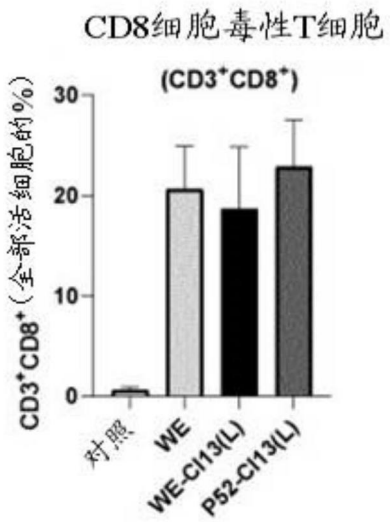

CD8细胞毒性T细胞
(CD3+CD8+)
CD3+CD8+(全部活细胞的%)
30
20
10
0
对照
WE
WE-CI13(L)
P52-CI13(L)

图33

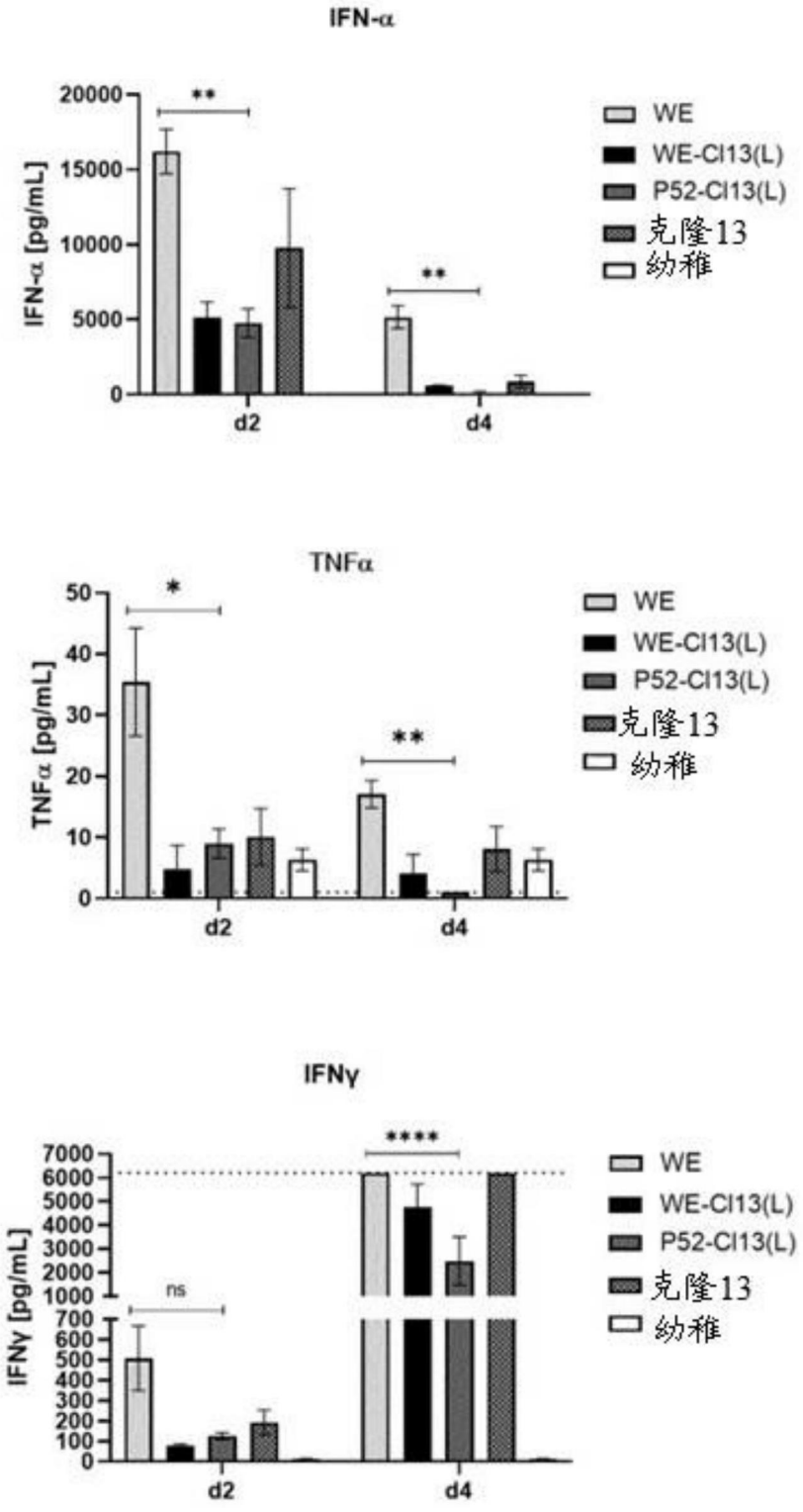

IFN-α
IFN-α [pg/mL]
20000
15000
10000
5000
0
**
**
d2
d4
WE
WE-CI13(L)
P52-CI13(L)
克隆13
幼稚
TNFα
TNFα [pg/mL]
50
40
30
20
10
0
*
**
d2
d4
WE
WE-CI13(L)
P52-CI13(L)
克隆13
幼稚
IFNγ
IFNγ [pg/mL]
7000
6000
5000
4000
3000
2000
1000
700
600
500
400
300
200
100
0
ns
****
d2
d4
WE
WE-CI13(L)
P52-CI13(L)
克隆13
幼稚

图34

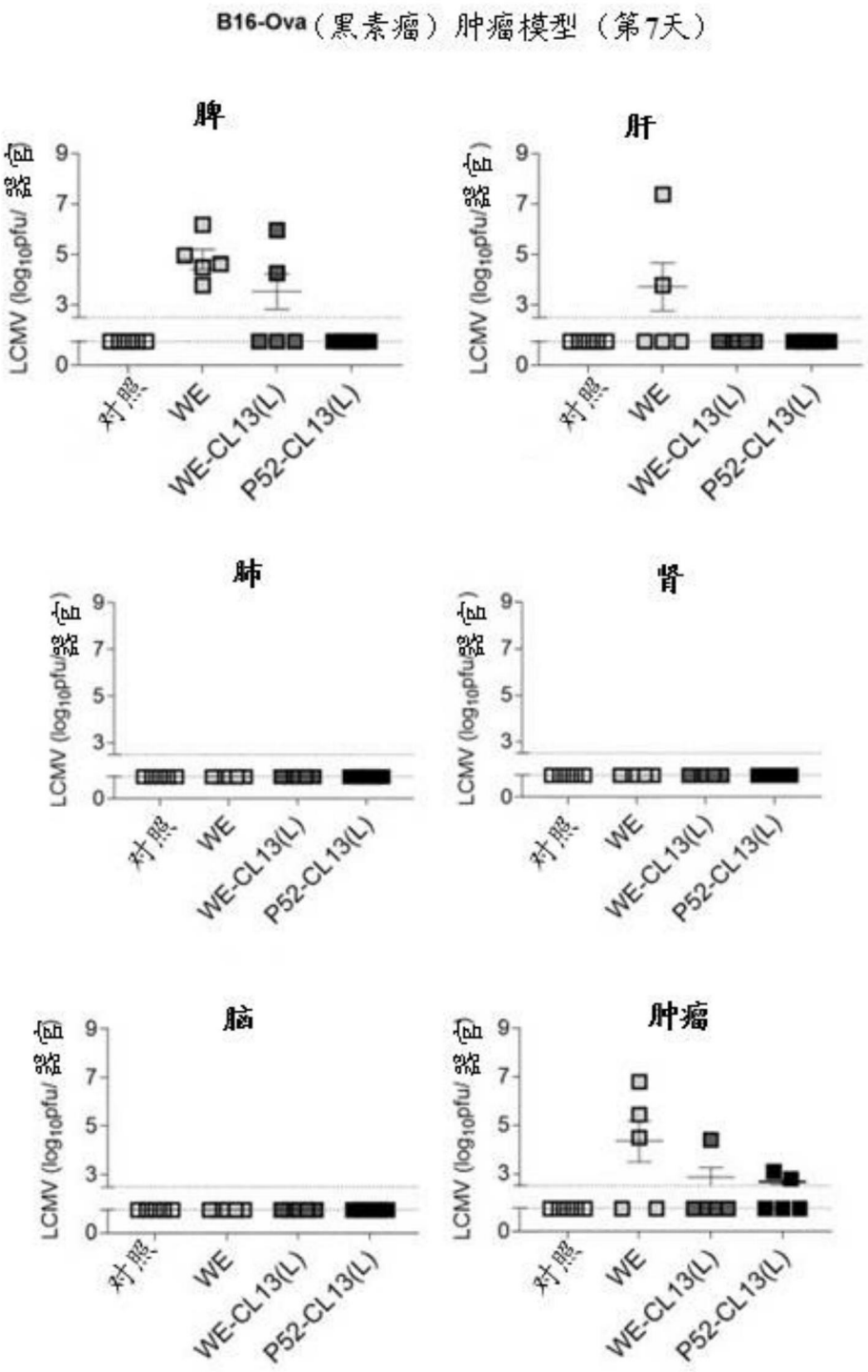

B16-Ova（黑素瘤）肿瘤模型（第7天）
脾
肝
肺
肾
脑
肿瘤
LCMV (log10pfu/脏)
9
7
5
3
0
对照
WE
WE-CL13(L)
P52-CL13(L)

图35

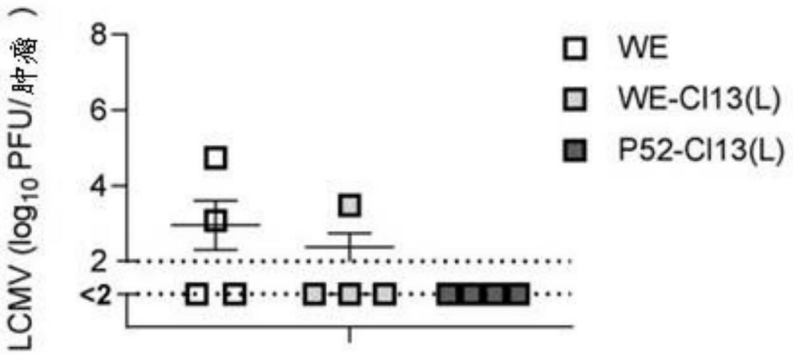

LCMV (log10 PFU/肿瘤)
8
6
4
2
<2
WE
WE-Cl13(L)
P52-Cl13(L)

图36

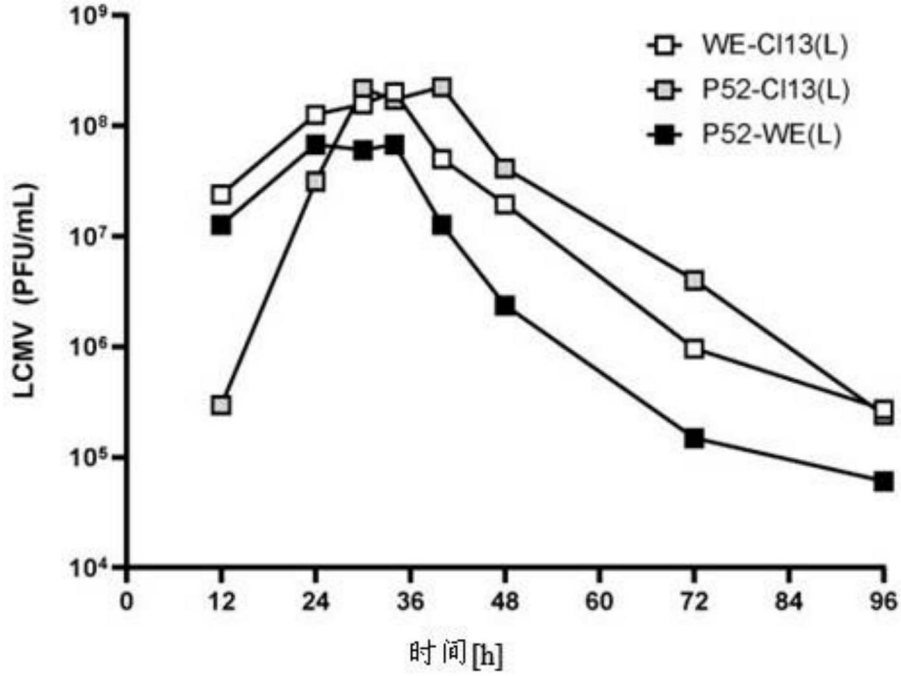

LCMV (PFU/mL)
10⁹
10⁸
10⁷
10⁶
10⁵
10⁴
0
12
24
36
48
60
72
84
96
时间[h]
WE-Cl13(L)
P52-Cl13(L)
P52-WE(L)

图37

A. 淋巴细胞性脉络丛脑膜炎病毒 (LCMV) 毒株 WE

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源: 1-3376 区段=S
LCMV WE S-区段

GCGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCCTTTAGGACAATTGGGTGCTGGATTCTATCCAATAAAAGGATGGGTCA
GATTGTGACAATGTTTGAGGCTTTGCCTCACATCATTGATGAGGTCATCAACATTGTCATTATTGTGCTCATTATAATCACGAGCA
TCAAAGCTGTGTACAATTTCGCCACCTGTGGGATATTAGCACTGGTCAGCTTCCTTTTTTTGGCTGGTAGGTCCTGTGGCATGTAC
GGCCTTAATGGTCCCGACATCTATAAAGGGGTTTACCAGTTCAAATCAGTGGAGTTTGATATGTCTCACTTAAATCTGACGATGCC
CAATGCGTGCTCAGCCAACAACTCTCATCACTACATCAGTATGGGAAGCTCTGGACTGGAGCTAACTTTCACTAACGACTCCATCC
TTAATCACAATTTTTGCAACTTAACCTCCGCTTTCAACAAAAAGACTTTTGACCATACACTCATGAGTATAGTCTCGAGTCTGCAC
CTCAGTATTAGAGGGAATTCCAACCACAAAGCAGTGTCTTGTGATTTTAACAATGGCATCACCATTCAATACAACTTGTCATTTTC
GGACCCACAGAGCGCTATAAGCCAGTGTAGGACTTTCAGAGGTAGAGTCTTGGACATGTTTAGAACTGCCTTTGGAGGAAAATACA
TGAGAAGTGGCTGGGGCTGGGCAGGTTCAGATGGCAAGACCACTTGGTGCAGCCAAACAAGCTATCAGTACCTAATCATACAAAAC
AGGACTTGGGAAAACCACTGTAGATATGCAGGCCCTTTTGGGATGTCTAGAATCCTCTTTGCTCAGGAAAAGACAAAGTTTCTCAC
TAGGAGACTTGCAGGCACATTCACCTGGACCCTGTCAGACTCCTCAGGAGTAGAAAATCCAGGTGGTTATTGCCTGACCAAATGGA
TGATCCTTGCTGCAGAGCTCAAATGTTTTGGGAATACAGCTGTTGCAAAATGTAATGTCAATCATGATGAAGAGTTCTGTGACATG
CTACGACTAATTGATTACAACAAGGCCGCCCTGAGTAAGTTCAAGCAAGATGTAGAGTCTGCCTTGCATGTATTCAAAACAACAGT
AAATTCTCTGATTTCCGATCAGCTGTTGATGAGGAATCATCTAAGAGATCTAATGGGGGTACCATACTGTAATTACTCAAAGTTCT
GGTATCTGGAACATGCTAAGACTGGTGAGACTAGTGTACCCAAGTGCTGGCTTGTCACTAATGGCTCCTACTTGAATGAGACCCAC
TTTAGTGATCAAATCGAACAAGAAGCAGATAACATGATCACAGAGATGTTGAGGAAGGACTACATAAAAAGACAAGGGAGTACTCC
TTTAGCCTTAATGGATCTTTTGATGTTTTCAACATCAGCATATCTAATCAGCATCTTTCTGCATCTTGTGAAGATACCAACACATA
GACACATAAAGGGCGGTTCATGTCCAAAGCCACACCGCTTGACCAACAAGGGGATCTGTAGTTGTGGTGCATTCAAGGTGCCTGGT
GTAAAAACTATCTGGAAAAGACGCTGATCAGCAGCGCCTCCCTGACTCTCCACCTCGAAAGAGGTGGAGAGTCAGGGAGGCCCAGT
GGGTCTTAGAGTGTCACAACATTGGGTCCTCTGAAGATTAAATCATGTGGCAGGATGTTGTGAACGGTTTTTAGATCAGGGAGTCT
TGCCTTGGAAGCACTCTCAAAAATGATGCAGTCCATGAGTGCACAGTGTGGGGTGATCTCTTTCTTCTTTTTGTCTCTCACTACCC
CAGTGTGCATTTTGCATAGCCAGCCATATTTGTCCCACACTTTATCTTCATATTCTCTTGAGGCCTCCTTGGTCATCTCAACATCA
ATGAGTTTTATGTCCCTTCTATTTTGTGAGTCCAGAAGCTTTCTGATGTCATCAGAACCTTGACAGCTCAAAACCATCCCTTGTGG
GAGAGCACCTATAACTGATGAGGTCAGCCCAGGCTGTGCATTGAAGAGATCAGCAAGATCCATGCCGTGTGAATACTTTGAGTCCT
GCTTGAATTGCTTCTGGTCCGTAGGTTCCCTGTAAAAATGTATGAATTGCCCATTTTGTGGTTGGAATATTGCTATCTCCACTGGA
TCATTGAACCTGCCCTCAATGTCAATCCATGTGGGAGCATTGGGATCAATCCCTCCCATCAAGTCTTTCAACAGCATTGTCTGACT
GTAACTCAAGCCCACCTGAGGTGGGCCTGCTGCTCCAGGCACTGGCCTAGATGAGTTGGCAACAAGTTTTTCATTTGTGAGATCAA
TTGTTGTGTTCTCCCATGCTCTCCCCACAACTGACGTTCTACAGGCTATGTATGGCCATCCTTCACCTGAAAGACAGACTTTATAA
AGGATGTTTTCATAGGGATTTCTATCTCCAACTTGATCTGAGACAAACATGTTGAGTTTCTTCTTGGCCCCGAGGACTGCTTTTAG
GAGATCCTCACTGTTGCTCGGTTTGATCAAGATAGATTCCAGCATGTTCCCTCCATCTAGCAGAGCTGCCCCCGCTTTCACAGCTG
CACCAAGACTGAAATTATAACCAGAGATATTGATACTAGATTGCTGTTCAGTAATGACCCCCAGAACTGGGTGTTTATCCTTTAGC
CTTTCAAGATCACTGAGATTCGGGTATTTGACTGTGTAAAGTAAGCCAAGGTCTGTGAGTGCCTGCACAACATCATTGAGTGGGGT
CTGTGACTGTTTTGCCATGCAAGCCATTGTCAGGCTTGGCATTGTGCCGAACTGATTGTTCAGAAGTGATGAGTCCTTCACATCCC
AAACCCTTACTACACCACTTGCACCCTGCTGAGGTCTTCTCATCCCAACCATTTGCAGTATTTGGGATCTTTGATCAAGTTGTTGT
GCTGTCAAATTTCCCATGTAGACTCCAGAAGCTTGAGGCCTCTCAGTTCTCATAATTTTGGCCTTCAGCTTCTCAAGATCAGCTGC
AAGGGTCATCAATTCCTCTGCACTAAGTCTTCCCACTTTCAGAACATTTTTCTTTGATGTAGACTTCAGATCAACAAGAGAATGCA
CAGTCTGGTTAAGACTCCTGAGTCTCTGCAAGTCTTTATCATCCCTCCTTTCCTTTCTCATGATCCTCTGAACGTTGCTGACTTCA
GAAAAGTCCAACCCATTTAGAAGACTGGTTGCGTCCTTGATGACGGCAGCCTTTACATCTGATGTAAAACTCTGCAACTCCCTCCT
CAACGCCTGTGTCCACTGAAAGCTTTTGACTTCTTTGGACAAAGACATTTTGTCACACAATGAATTTCCAAATAAAAGCGCAATTA
AATGCCTAGGATCCACTGTGCG
(SEQ ID NO: 1)

图38

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源：1-7236 区段=L
LCMV WE L-区段

GCGCACCGGGGATCCTAGGCGTTTAGTTGCGCTGCTTTATTGCACAGCTTCACTCTGCTAAACCATCAGGAACTGACCGATCATCA
GTCATGGGCCAAGGCAAGTCCAAAGAAGAAAGGGACACCAGCAATACAGGCAGAGCAGAGCTTTTGCCAGACACCACCTATCTTGG
TCCTCTAAATTGTAAATCATGTTGGCAGAAATTTGACAGCTTGGTTAGATGCCATGACCACTATCTTTGCAGACACTGTCTGAATC
TCCTGCTGTCAGTTTCCGACAGATGTCCTCTCTGTAAGTATCCACTGCCAACCAAACTGAAGGTGTCAACAGTCCCAAGCTCCCCA
CCTCCCTATGAGGAGTGACGCCCCAGACCTCGACACAACAGGCCACCCAACACAGAAAAACCACACACAAACCGGCACACACAGAC
ACAGCAACCAGCACAAAGCGCACGAAAACACACACACACACACACACACACCCTCACCCACGCGCCCCCCCGCACCGCCGGGGGGG
CGCCCCCCCCGGGGGGCAGCCCCCCGGGGGCCCGGGCAGGGCCCCGCGGAGATGCCGGCTAGTCGATCTCCTCGGCCACCCGCTCCG
CCAGCCAATCGTCACAGGATTTCCCCTTGAGTCTGAACCTGCCCCCAGTTGTCTCATACATTACAGTGTTCTTTGACCTGCTGAAG
CAGAGCCTACAATCTCTGAAGGTGAACCAATCTGGCACAAAAGATAATGGTGTCAGCATGACGGATCTGTCCATGCAGAGCTCCTG
AAGAACTGTACTTATTTCTGACTCCATCAAGTGCTCACCAGTTCTGAATCGGTGCAGGAGGAGGCTGCCGAGGACATCACCAATTT
TTCCACAGCCCTCGAGCTCTGCCAGAAAGACCCTCATGTCCTTTGTCTCCAATTTCACAGAGATATTCTGAACAAAGTTCCTCCCC
TCAAAGAGGGCACCCTTCCTTATGGTCAGAGGCACAGGTTCCCACTCAGGCCCTATCCTCTCAAAGTCAGTAGATTTGATCTCATT
CAGAATCCTTCTAGAACCTATTAGTTCAAGTTCTAGTGAATCACCAAGTGTCAAAGGGTCTTCCATGTAATCTTCAAACTCTTCAG
ACCTAATGTCAAAGACTCCATCATTCGCTTTAAAGATGGGGTCTGTCCTCAACAGATTGAGACACTCATCTAATAATCTCCTGTCA
ACCTCACCTTTGAAGAAATGAGAGCACGATAAGTAATCAGCTACACCTGGACTCTGTAATTGGCATTTAACCACAAAGATCAATGA
AAATTTCCTCAAGCAGTCAGTGTTGTTCTGGTTGTGTGTGAAATCCACTGTGATTGAGAACTCCAATATCCCCTCTGTGCTGCTGA
GCATGTAATCCCACAAATCTCTTAAAGATTTAAATGCTTTTGGATCTGTCAAACCCTGCTTAATTAACATAGCGGCATTACACACA
ACATCCCCCACACGATAAGAGAACCAACCAAAACCAAACTGCAAGTCATTCCTAAACATGGGCCTCTCTATTTTCTTGTTCACCAC
TTTCAAAATAAATGATTGGAAGGGTCCCAGTGCTTCAGCGCCATCTTCAGATGGCATCATGTCCTTATGGGGGAACCATGAAAAGT
TACCTAAGGTCCTAGCTGTTGCAACAAACTCTCGTACAAATGATTCGAAATACACTTGCTTCAAAAAGTTCTTGCAGACATCCCTT
GTGCTGACAACAAATTCATCAACTAAACTTGAGTCTGACCGTTGGTGAGAGTTGACGAGATCAGAAAACAGCACAGTGTAATGTTC
GTCCCTCTTCCATTTGACAACATGAGAAATGAGTGACAAAGACTCTGAGTTGATGTCAATCAGCACACAAAGGTCAAGGAATTTAA
TCCTGGGACTCCATCTCATATTTTTTGAGCTCACATCAGACATGAATGGGAGCAACTGATCCTCAAAGATTTTGGGGTACAGTCGC
CTCACAGATTGAATTACATGATTCAAACTCACTTTATCCTCTAGTAGTCTCGAACTCTCAGGTTTTCTTGCTACATAATCACATGG
ATTTAAGTGCCTAACAGCCGAATTACTCTCGTTCTTTCCTTTCACAGGTTCTGCTAAAACCCAAACACCCAGCTCAAAAGAGTTGC
TCAATGAGATGCAAATGTAGTCCCAGAGAAGGGGCCTCAAAAGGTTGATGTGGTCACGGTGAGCCTCTGGGTGTCTCTGCTTGTCG
CAAATGTACAACATCACACCATCTTGTTTGTGAACCCTTGTGACATGTTCATCCATGGTCAGATCTTCAAGCACCTTTCTGATATA
CATATTTTCCCTGTTTTTATTTCTCACACACCTACTTCCTAAAGTCTTACAGAGACCTATAAAGCCGGATGAGACACAACTCTGAA
AAGCTGATTTGTTGATTGCCTCTGACAACAGCTTCTGTGCACCTCTTGTGAACTTACTACAAAGCTTATTTTGGAGTGTTTTAATC
AATGAGGGGATCTTTTCCTCTTGAAAGGTCATTACTGATGGGTAAACCACTTTTTGTCTCAGAACCATCCTCAATGGGAACATTTC
ATTCAGATTCAACCAATTGATGCTTGCCAACTCATTAAGATCATCCTCAAGACCAAGAATCTCTCCCAATTGAAGGATGGCCTCTT
TCTTTTCCCTGTTGAAGAGGTCTAGAAAAAATTCCTCGTTACATTCACCGTTCTTGAGTTTGTGATGTAGTCTTCTTACAAGTTTT
CTCATGATCTTTGTTTCACTGGGACACAATTCTTCAATGAGTCTTTGGATTCTATAACCTCTAGAACCATCTAACCAATCCTTTAC
ATCAGTGTGAGTGTTTAACAAGAATGGATCTAAAGGGAAATTAGCATATTTCAAGAGATCCAGTGTCCTCCTCTGGATACAGTTTA
CTAAAAAAACTGGAACTCCATTTGCTATAGCTTGATCAGCAATCGTATCTATTGTCTCACAAAGTTGATGCGGTTCTTTACACTTA
ACATTGTGTAGTGCCGCAGACACAAATTTCGTGAGGAGAGGGACCTCCTCCCCCCACACATAAAATCTGGATTTGAATTCCGCTGC
AAACCGCCCAACCACACTTTTTGGACTGATGAACTTGTTCAACAAACCACTTAAGTGAGAGTGGAATTCCAGCAAGACAAGGACTT
CTTCTGGGTCACTATCAACTAAGTCACTCAATCTCTTGTCAAATAAAGTGATCTGATCATCACTTGATGTATAGGCTTCTGGCCTC
TCTCCAAAAATGACACCAATACAATAATTGATAAACCTTTCACTAATTAAACCGTAAAAATCAGAAGCATTGTGTAGGATCCCCTG
TCCCATGTCAATGAGACTAGATATGTGAGATGGCACCACCCCCATTTCAAAATACTCTCTAAAGATTCTCTCCGTAACAGTCGTTC
CTGACCCTTTGAGAAGCTTGAGTTTTGATTTAACATATGATTTCATCATTGCATTCACAACAGGGAAAGGGACTTCAACAAGTTTA
TGCATATGCCAAGTCAACAAGGTGCTAACATGATCTTTTCCAGAACGCACGTACTGATCATCACCCAGTTTGAGATTTTGGAGAAG
CATTAAGAATAGGAATGGGCACATCATTGGTCCCCATTTGCTGTGATCCATGCTGTAGTTTAACAACCCTTCTCTCACATTGATAG
TCATTGACAAGATTGCATTTTCAAACTCTTTGTCATTGTTTAAACAAGATCCTGAAAAGAAACTAGAAAAGGATTCAAAATAATCT
TCTACCAATCTTGTGAACATTTTTGTCCTCAAATCCCCAATGTAAAGCTCTCTATTTCCCCCAACCTGCTCTTTGTATGACAATGC
AAATTTTAGTCTCCCAGAGTCAGGGCCAACTGAAGTGTATGATGTTGGTGATTCTTCTGAGTAAAAACACAGATTCTTTAGAGCAG
CACTCATGCATTTTGTCAATGAAAGGGCCTTACTTAGAGATTCAGAATTGCTTTCCCTTTCACTAATTCTTACATCTTCTTCCAAT
TTGTCCCAGTCAAATTTAAAATTTAAGCTCTGCCTCTGCATGTGTCTGTACTTCCCTGAATACGCATTTGCATTCATCTGTAACAA
GATCATCTTCATACATGAGAACCAATCACCCTCTGAGAAGAACTTTCTACAGAGGTTTCTTGCCATCTCATCCAGACCACATTGTT
CTTTGACAGCTGATGTAAAATACAATGGTGACAGTTCTGTTGAACCTTCAACAGCCTCACAAATAAACCTCATGTCGTCATTGGTG
AGACAGGATGGATCAAAGTCCTCTACTAGATGAAATGAAATTTCTGATAAAATGACTTTCCTCAGATAAGCTCTTTTACCTGACAA
AATAATCTGAAGGTGGTGTAGTCCTTTTGTGTTCTTGAATTCTCCCTCCCCTTGCCCTTCATTAAGCCTAGTGCCTCTATTATACC
GTGTTATTGTGGAGCTGACCTTATCTTCTAAACTCCTGAAAAAACTTGTCTCCTCCTCCCCCTCGAAACACACATCTACCGGATCA
TCTTCCAATTTGTCTACTTCTGTTTTCCTGGAACCGATGACTAATCTAGAGACAAGCTTTGAGACCTTATATTCGTAATCTGAGTG
TCTCAGCTTATACTTTTGTTTCCTCATGAAGCCCTCTGTAATTTGGCTCACAGCACTAACAAGCAATTTGTTAAAATCATACTCCA
AAAGCCGTTCTCCATTCAGATGTTTATTGACAACCACACTTTTGTTGCTTGCGAGATCTAATGCTGTCGCACATCCAGAGTTGGTC
ATGGGGTCCAGATTGTTGAGCCTTTTCTCCCCTTTTAGAATTAAGGTGCCATTGTTGAATGAAGATACCATCATGCTAAAGATCTC
TAAATTAACACCAGGGGTTGAATGCTGACAATCAATATCTTTACCGGTGAACTTCTTCATTTGTTCATAAAAAACACATTCCTCTT
CGGGTGTGATTGTTTCCTTAGGGTTGACAAAGAAACCAAACTCACTCTTGGGCTCAAAGAACTTTTCAAAACATTTTATCTGATCT
GTCAATCTATCAGGGGTCTCCTTTGTGATCAAATGACACAGGTATGACACATTCAACATAAACTTGAATTTTGCACTCAATAACAC
CTTTTCACCAGTACCAAAAATTGTCCTAATCAAAAACCGAAGCAGCCTGTACACCACTTTCTCGGCAGGTGTGATTAGATCCTCCT
TCAACTTATCCATTAATGAGGTCGATGAAAAGTCTGAGACGATGGCCATCACTAAATACCTAATATTTTGAACCTGCTTTTGATTT

图38(续)

CTCTTTGTTGGGTTGGTGAGCATCAGTAGGATCAATGTCCTTAGTGCAGTCTCAATGTCAATAAGAGAATCTTTTAAGTCAGGGCA
TGACCTAATCCATGAAATCATTGTGTCTATCATGTTGTGCAACACCTCATCTGAAAAAATTGGTAAAAAGAACCTTTTTGGATCTG
CGTAAAAGGAAATCAAGTGACCATCCGGACCTTGTATGGAATAACACCTCGATGATTCTCCAGTTTTCTGATATAGTAGATGATAC
TCTTCGGAATCCAGTTTTATTATCTGGCAAAACACCTCTTTGCACTCCACCACTTGATATCTCACAGACCCCAGTTGGTTCTGTCT
CAACCTTGCAACTGAGCTTGTTTTCATGCTGTTTGTTAGAGCCAAACAAACAGATGACAGTTTTCTCAAACTCTGTAAACCCCTCA
ATTGCTCTATGTTAGGCTGGAAAGTGTAATCTTCAAATTTTGTGTAATGCATTACAGGATGAGTCCCGGCTCTCATAAAGTTCTCA
AATTCAGCAAATGGTATATGGCATTCTTGCACGAGGCATTCTGATAGTCCGTAATGCTCAAAACTAAGTCCCACTGTTGATAGGCA
TTTCTGGATTTTTGCTATGAACTCATTTATGGATACCCTAAAAAGCTCATCAAGAGATGCCTTTTTGTGCACTCTTGATTTTCTTC
TGTTCTTCAAAAGTCTCATGAATTCTTCTTTGGTACTTTGAAGGCTCACAAGCCTATCATTCACACTACTGTAGCAACAACCAACC
CAATGTTTATCATTTTCCAACCCTTTGGAAATTGACTGCTTAATAAGTGAAGAAAGACATAAGACATCTAAGTTCAGCAGCTGTCT
CCTTCTAGTGTTTAATAATTTTAAACTTTTCACCTTGTTCAACATAGAGAGTAGCCTTTCATACTCAGTGTTAGCATCGCTTCCTC
TCTCATGCCCATGGGTCTCTGCTGTAATGAACCTCATTAAGGGGCAGGATTCAACTGCCTCTTTGCTCAACATTAATATGTCATCA
TTATCAGTAAGGGTTTCATAAAGTTCAGAGAATTCCTTGATTAAGCCCCCAGGGCTGACCTTTTGGAAATTCCTTTTGAGTTTCCC
ATTTAACAGGTCCCTCCTAAACCTGCCAAAAAAGGAATTTATGCCAAAGACCACATCATCGCAACTCATGTTGGGGTTGACACCAT
CGTGGCACATTTTCATAATCTCATCGTTATGAAATGATCTTGCGTCTTTCAAAATTTTCATTGAGTCCATGCCGGAACGTTTGTCA
ACAGTGGTCTTAAGAGACTCACAGAGCCTGAAGTATTCAGACTCCTCAAAAACTTTCTCATCTTGACTAGAATACTCCAGGAGTTT
AAATAGGAGGTCTCTGAACTTAAAATTCACCCATTCTGGCATGAAACTGTTATCATAATCACAACGACCATCCACTATTGGAACCA
GTGTGATGCCTGCAACAGCAAGATCTTCTTTGATGCATGCTAGTTTGTTGGTGTCCTCAATGAACTTCTTTTCAAAACTAGCTGGT
GTGCTTCTAACAAAACATTCAAGAAGAATAAGGGAATTGTCAATCAACTTATAACCATCAGGGATGATGAGTGGCAGTCCTGGACA
CACAATCCCAGAGTCTATTAGGATTGTTTCAACAGATTTGTCATCGTGGTTGTGTATGCAACCACTTTTGTCTGCACTGTCTATCT
CTATACAGCGTGATAACAATTTGAGTCCCTCAATTAGCACCATTCTGGGTTCTCTTTGTCCCAGGAAGTTGAGTTTTTGCCTTGAC
AGCCTCTCGTCCTGTTCTATGTAATTTAGACACAACTCTCTCAAATCTGCAATAGTTTCATCCATTGCGCATCAAAAAGCCTAGGA
TCCTCGGTGCGC
(SEQ ID NO: 2)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源: 1-3376 区段=S
蛋白: 前糖蛋白多蛋白 GP 复合物
基因: GPC
LCMV WE GPC

ATGGGTCAGATTGTGACAATGTTTGAGGCTTTGCCTCACATCATTGATGAGGTCATCAACATTGTCATTATTGTGCTCATTATAAT
CACGAGCATCAAAGCTGTGTACAATTTCGCCACCTGTGGGATATTAGCACTGGTCAGCTTCCTTTTTTTGGCTGGTAGGTCCTGTG
GCATGTACGGCCTTAATGGTCCCGACATCTATAAAGGGGTTTACCAGTTCAAATCAGTGGAGTTTGATATGTCTCACTTAAATCTG
ACGATGCCCAATGCGTGCTCAGCCAACAACTCTCATCACTACATCAGTATGGGAAGCTCTGGACTGGAGCTAACTTTCACTAACGA
CTCCATCCTTAATCACAATTTTTGCAACTTAACCTCCGCTTTCAACAAAAAGACTTTTGACCATACACTCATGAGTATAGTCTCGA
GTCTGCACCTCAGTATTAGAGGGAATTCCAACCACAAAGCAGTGTCTTGTGATTTTAACAATGGCATCACCATTCAATACAACTTG
TCATTTTCGGACCCACAGAGCGCTATAAGCCAGTGTAGGACTTTCAGAGGTAGAGTCTTGGACATGTTTAGAACTGCCTTTGGAGG
AAAATACATGAGAAGTGGCTGGGGCTGGGCAGGTTCAGATGGCAAGACCACTTGGTGCAGCCAAACAAGCTATCAGTACCTAATCA
TACAAAACAGGACTTGGGAAAACCACTGTAGATATGCAGGCCCTTTTGGGATGTCTAGAATCCTCTTTGCTCAGGAAAAGACAAAG
TTTCTCACTAGGAGACTTGCAGGCACATTCACCTGGACCCTGTCAGACTCCTCAGGAGTAGAAAATCCAGGTGGTTATTGCCTGAC
CAAATGGATGATCCTTGCTGCAGAGCTCAAATGTTTTGGGAATACAGCTGTTGCAAAATGTAATGTCAATCATGATGAAGAGTTCT
GTGACATGCTACGACTAATTGATTACAACAAGGCCGCCCTGAGTAAGTTCAAGCAAGATGTAGAGTCTGCCTTGCATGTATTCAAA
ACAACAGTAAATTCTCTGATTTCCGATCAGCTGTTGATGAGGAATCATCTAAGAGATCTAATGGGGGTACCATACTGTAATTACTC
AAAGTTCTGGTATCTGGAACATGCTAAGACTGGTGAGACTAGTGTACCCAAGTGCTGGCTTGTCACTAATGGCTCCTACTTGAATG
AGACCCACTTTAGTGATCAAATCGAACAAGAAGCAGATAACATGATCACAGAGATGTTGAGGAAGGACTACATAAAAAGACAAGGG
AGTACTCCTTTAGCCTTAATGGATCTTTTGATGTTTTCAACATCAGCATATCTAATCAGCATCTTTCTGCATCTTGTGAAGATACC
AACACATAGACACATAAAGGGCGGTTCATGTCCAAAGCCACACCGCTTGACCAACAAGGGGATCTGTAGTTGTGGTGCATTCAAGG
TGCCTGGTGTAAAAACTATCTGGAAAAGACGCTGA
(SEQ ID NO: 3)

翻译=
LCMV WE GPC

MGQIVTMFEALPHIIDEVINIVIIVLIIITSIKAVYNFATCGILALVSFLFLAGRSCGMYGLNGPDIYKGVYQFKSVEFDMSHLNL
TMPNACSANNSHHYISMGSSGLELTFTNDSILNHNFCNLTSAFNKKTFDHTLMSIVSSLHLSIRGNSNHKAVSCDFNNGITIQYNL
SFSDPQSAISQCRTFRGRVLDMFRTAFGGKYMRSGWGWAGSDGKTTWCSQTSYQYLIIQNRTWENHCRYAGPFGMSRILFAQEKTK
FLTRRLAGTFTWTLSDSSGVENPGGYCLTKWMILAAELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSKFKQDVESALHVFK
TTVNSLISDQLLMRNHLRDLMGVPYCNYSKFWYLEHAKTGETSVPKCWLVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQG
STPLALMDLLMFSTSAYLISIFLHLVKIPTHRHIKGGSCPKPHRLTNKGICSCGAFKVPGVKTIWKRR
(SEQ ID NO: 4)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源: 1-3376 区段=S
蛋白: 核蛋白
基因: NP
LCMV WE NP

ATGTCTTTGTCCAAAGAAGTCAAAAGCTTTCAGTGGACACAGGCGTTGAGGAGGGAGTTGCAGAGTTTTACATCAGATGTAAAGGC
TGCCGTCATCAAGGACGCAACCAGTCTTCTAAATGGGTTGGACTTTTCTGAAGTCAGCAACGTTCAGAGGATCATGAGAAAGGAAA
GGAGGGATGATAAAGACTTGCAGAGACTCAGGAGTCTTAACCAGACTGTGCATTCTCTTGTTGATCTGAAGTCTACATCAAAGAAA
AATGTTCTGAAAGTGGGAAGACTTAGTGCAGAGGAATTGATGACCCTTGCAGCTGATCTTGAGAAGCTGAAGGCCAAAATTATGAG
AACTGAGAGGCCTCAAGCTTCTGGAGTCTACATGGGAAATTTGACAGCACAACAACTTGATCAAAGATCCCAAATACTGCAAATGG
TTGGGATGAGAAGACCTCAGCAGGGTGCAAGTGGTGTAGTAAGGGTTTGGGATGTGAAGGACTCATCACTTCTGAACAATCAGTTC
GGCACAATGCCAAGCCTGACAATGGCTTGCATGGCAAAACAGTCACAGACCCCACTCAATGATGTTGTGCAGGCACTCACAGACCT
TGGCTTACTTTACACAGTCAAATACCCGAATCTCAGTGATCTTGAAAGGCTAAAGGATAAACACCCAGTTCTGGGGGTCATTACTG
AACAGCAATCTAGTATCAATATCTCTGGTTATAATTTCAGTCTTGGTGCAGCTGTGAAAGCGGGGGCAGCTCTGCTAGATGGAGGG
AACATGCTGGAATCTATCTTGATCAAACCGAGCAACAGTGAGGATCTCCTAAAAGCAGTCCTCGGGGCCAAGAAGAAACTCAACAT
GTTTGTCTCAGATCAAGTTGGAGATAGAAATCCCTATGAAAACATCCTTTATAAAGTCTGTCTTTCAGGTGAAGGATGGCCATACA
TAGCCTGTAGAACGTCAGTTGTGGGGAGAGCATGGGAGAACACAACAATTGATCTCACAAATGAAAAACTTGTTGCCAACTCATCT
AGGCCAGTGCCTGGAGCAGCAGGCCCACCTCAGGTGGGCTTGAGTTACAGTCAGACAATGCTGTTGAAAGACTTGATGGGAGGGAT
TGATCCCAATGCTCCCACATGGATTGACATTGAGGGCAGGTTCAATGATCCAGTGGAGATAGCAATATTCCAACCACAAAATGGGC
AATTCATACATTTTTACAGGGAACCTACGGACCAGAAGCAATTCAAGCAGGACTCAAAGTATTCACACGGCATGGATCTTGCTGAT
CTCTTCAATGCACAGCCTGGGCTGACCTCATCAGTTATAGGTGCTCTCCCACAAGGGATGGTTTTGAGCTGTCAAGGTTCTGATGA
CATCAGAAAGCTTCTGGACTCACAAAATAGAAGGGACATAAAACTCATTGATGTTGAGATGACCAAGGAGGCCTCAAGAGAATATG
AAGATAAAGTGTGGGACAAATATGGCTGGCTATGCAAAATGCACACTGGGGTAGTGAGAGACAAAAAGAAGAAAGAGATCACCCCA
CACTGTGCACTCATGGACTGCATCATTTTTGAGAGTGCTTCCAAGGCAAGACTCCCTGATCTAAAAACCGTTCACAACATCCTGCC
ACATGATTTAATCTTCAGAGGACCCAATGTTGTGACACTCTAA
(SEQ ID NO: 5)

翻译=LCMV WE NP
MSLSKEVKSFQWTQALRRELQSFTSDVKAAVIKDATSLLNGLDFSEVSNVQRIMRKERRDDKDLQRLRSLNQTVHSLVDLKSTSKK
NVLKVGRLSAEELMTLAADLEKLKAKIMRTERPQASGVYMGNLTAQQLDQRSQILQMVGMRRPQQGASGVVRVWDVKDSSLLNNQF
GTMPSLTMACMAKQSQTPLNDVVQALTDLGLLYTVKYPNLSDLERLKDKHPVLGVITEQQSSINISGYNFSLGAAVKAGAALLDGG
NMLESILIKPSNSEDLLKAVLGAKKKLNMFVSDQVGDRNPYENILYKVCLSGEGWPYIACRTSVVGRAWENTTIDLTNEKLVANSS
RPVPGAAGPPQVGLSYSQTMLLKDLMGGIDPNAPTWIDIEGRFNDPVEIAIFQPQNGQFIHFYREPTDQKQFKQDSKYSHGMDLAD
LFNAQPGLTSSVIGALPQGMVLSCQGSDDIRKLLDSQNRRDIKLIDVEMTKEASREYEDKVWDKYGWLCKMHTGVVRDKKKKEITP
HCALMDCIIFESASKARLPDLKTVHNILPHDLIFRGPNVVTL
(SEQ ID NO: 6)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源: 1-7235 区段=L
蛋白: 环指蛋白 Z
基因: ZP
LCMV WE ZP

ATGGGCCAAGGCAAGTCCAAAGAAGAAAGGGACACCAGCAATACAGGCAGAGCAGAGCTTTTGCCAGACACCACCTATCTTGGTCC
TCTAAATTGTAAATCATGTTGGCAGAAATTTGACAGCTTGGTTAGATGCCATGACCACTATCTTTGCAGACACTGTCTGAATCTCC
TGCTGTCAGTTTCCGACAGATGTCCTCTCTGTAAGTATCCACTGCCAACCAAACTGAAGGTGTCAACAGTCCCAAGCTCCCCACCT
CCCTATGAGGAGTGA
(SEQ ID NO: 7)

翻译=LCMV WE ZP
MGQGKSKEERDTSNTGRAELLPDTTYLGPLNCKSCWQKFDSLVRCHDHYLCRHCLNLLLSVSDRCPLCKYPLPTKLKVSTVPSSPP
PYEE
(SEQ ID NO: 8)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 WE-DUE
来源: 1-7235 区段=L
蛋白: RNA 指导的 RNA 聚合酶 L
基因: LCMV WE LP

ATGGATGAAACTATTGCAGATTTGAGAGAGTTGTGTCTAAATTACATAGAACAGGACGAGAGGCTGTCAAGGCAAAAACTCAACTT
CCTGGGACAAAGAGAACCCAGAATGGTGCTAATTGAGGGACTCAAATTGTTATCACGCTGTATAGAGATAGACAGTGCAGACAAAA
GTGGTTGCATACACAACCACGATGACAAATCTGTTGAAACAATCCTAATAGACTCTGGGATTGTGTGTCCAGGACTGCCACTCATC
ATCCCTGATGGTTATAAGTTGATTGACAATTCCCTTATTCTTCTTGAATGTTTTGTTAGAAGCACACCAGCTAGTTTTGAAAAGAA
GTTCATTGAGGACACCAACAAACTAGCATGCATCAAAGAAGATCTTGCTGTTGCAGGCATCACACTGGTTCCAATAGTGGATGGTC
GTTGTGATTATGATAACAGTTTCATGCCAGAATGGGTGAATTTTAAGTTCAGAGACCTCCTATTTAAACTCCTGGAGTATTCTAGT
CAAGATGAGAAAGTTTTTGAGGAGTCTGAATACTTCAGGCTCTGTGAGTCTCTTAAGACCACTGTTGACAAACGTTCCGGCATGGA
CTCAATGAAAATTTTGAAAGACGCAAGATCATTTCATAACGATGAGATTATGAAAATGTGCCACGATGGTGTCAACCCCAACATGA
GTTGCGATGATGTGGTCTTTGGCATAAATTCCTTTTTTGGCAGGTTTAGGAGGGACCTGTTAAATGGGAAACTCAAAAGGAATTTC
CAAAAGGTCAGCCCTGGGGGCTTAATCAAGGAATTCTCTGAACTTTATGAAACCCTTACTGATAATGATGACATATTAATGTTGAG
CAAAGAGGCAGTTGAATCCTGCCCCTTAATGAGGTTCATTACAGCAGAGACCCATGGGCATGAGAGAGGAAGCGATGCTAACACTG
AGTATGAAAGGCTACTCTCTATGTTGAACAAGGTGAAAAGTTTAAAATTATTAAACACTAGAAGGAGACAGCTGCTGAACTTAGAT
GTCTTATGTCTTTCTTCACTTATTAAGCAGTCAATTTCCAAAGGGTTGGAAAATGATAAACATTGGGTTGGTTGTTGCTACAGTAG
TGTGAATGATAGGCTTGTGAGCCTTCAAAGTACCAAAGAAGAATTCATGAGACTTTTGAAGAACAGAAGAAAATCAAGAGTGCACA
AAAAGGCATCTCTTGATGAGCTTTTTAGGGTATCCATAAATGAGTTCATAGCAAAAATCCAGAAATGCCTATCAACAGTGGGACTT
AGTTTTGAGCATTACGGACTATCAGAATGCCTCGTGCAAGAATGCCATATACCATTTGCTGAATTTGAGAACTTTATGAGAGCCGG
GACTCATCCTGTAATGCATTACACAAAATTTGAAGATTACACTTTCCAGCCTAACATAGAGCAATTGAGGGGTTTACAGAGTTTGA
GAAAACTGTCATCTGTTTGTTTGGCTCTAACAAACAGCATGAAAACAAGCTCAGTTGCAAGGTTGAGACAGAACCAACTGGGGTCT
GTGAGATATCAAGTGGTGGAGTGCAAAGAGGTGTTTTGCCAGATAATAAAACTGGATTCCGAAGAGTATCATCTACTATATCAGAA
AACTGGAGAATCATCGAGGTGTTATTCCATACAAGGTCCGGATGGTCACTTGATTTCCTTTTACGCAGATCCAAAAAGGTTCTTTT
TACCAATTTTTTCAGATGAGGTGTTGCACAACATGATAGACACAATGATTTCATGGATTAGGTCATGCCCTGACTTAAAAGATTCT
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TATTAGGTATTTAGTGATGGCCATCGTCTCAGACTTTTCATCGACCTCATTAATGGATAAGTTGAAGGAGGATCTAATCACACCTG
CCGAGAAAGTGGTGTACAGGCTGCTTCGGTTTTTGATTAGGACAATTTTTGGTACTGGTGAAAAGGTGTTATTGAGTGCAAAATTC
AAGTTTATGTTGAATGTGTCATACCTGTGTCATTTGATCACAAAGGAGACCCCTGATAGATTGACAGATCAGATAAAATGTTTTGA
AAAGTTCTTTGAGCCCAAGAGTGAGTTTGGTTTCTTTGTCAACCCTAAGGAAACAATCACACCCGAAGAGGAATGTGTTTTTTATG
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AGCATTAGATCTCGCAAGCAACAAAAGTGTGGTTGTCAATAAACATCTGAATGGAGAACGGCTTTTGGAGTATGATTTTAACAAAT
TGCTTGTTAGTGCTGTGAGCCAAATTACAGAGGGCTTCATGAGGAAACAAAAGTATAAGCTGAGACACTCAGATTACGAATATAAG
GTCTCAAAGCTTGTCTCTAGATTAGTCATCGGTTCCAGGAAAACAGAAGTAGACAAATTGGAAGATGATCCGGTAGATGTGTGTTT
CGAGGGGGAGGAGGAGACAAGTTTTTTCAGGAGTTTAGAAGATAAGGTCAGCTCCACAATAACACGGTATAATAGAGGCACTAGGC
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GGTGATGATCAGTACGTGCGTTCTGGAAAAGATCATGTTAGCACCTTGTTGACTTGGCATATGCATAAACTTGTTGAAGTCCCTTT
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TCTAGAGGTTATAGAATCCAAAGACTCATTGAAGAATTGTGTCCCAGTGAAACAAAGATCATGAGAAAACTTGTAAGAAGACTACA
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GCTTTATAGGTCTCTGTAAGACTTTAGGAAGTAGGTGTGTGAGAAATAAAAACAGGGAAAATATGTATATCAGAAAGGTGCTTGAA
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图38(续)

TGAGGATCAGTTGCTCCCATTCATGTCTGATGTGAGCTCAAAAAATATGAGATGGAGTCCCAGGATTAAATTCCTTGACCTTTGTG
TGCTGATTGACATCAACTCAGAGTCTTTGTCACTCATTTCTCATGTTGTCAAATGGAAGAGGGACGAACATTACACTGTGCTGTTT
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AGGCCCATGTTTAGGAATGACTTGCAGTTTGGTTTTGGTTGGTTCTCTTATCGTGTGGGGGATGTTGTGTGTAATGCCGCTATGTT
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TGGAGTTCTCAATCACAGTGGATTTCACACACAACCAGAACAACACTGACTGCTTGAGGAAATTTTCATTGATCTTTGTGGTTAAA
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GTGTCTCAATCTGTTGAGGACAGACCCCATCTTTAAAGCGAATGATGGAGTCTTTGACATTAGGTCTGAAGAGTTTGAAGATTACA
TGGAAGACCCTTTGACACTTGGTGATTCACTAGAACTTGAACTAATAGGTTCTAGAAGGATTCTGAATGAGATCAAATCTACTGAC
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TATCTCTGTGAAATTGGAGACAAAGGACATGAGGGTCTTTCTGGCAGAGCTCGAGGGCTGTGGAAAAATTGGTGATGTCCTCGGCA
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TCCGTCATGCTGACACCATTATCTTTTGTGCCAGATTGGTTCACCTTCAGAGATTGTAGGCTCTGCTTCAGCAGGTCAAAGAACAC
TGTAATGTATGAGACAACTGGGGGCAGGTTCAGACTCAAGGGGAAATCCTGTGACGATTGGCTGGCGGAGCGGGTGGCCGAGGAGA
TCGACTAG
(SEQ ID NO: 9)

翻译=LCMV WE LP

MDETIADLRELCLNYIEQDERLSRQKLNFLGQREPRMVLIEGLKLLSRCIEIDSADKSGCIHNHDDKSVETILIDSGIVCPGLPLI
IPDGYKLIDNSLILLECFVRSTPASFEKKFIEDTNKLACIKEDLAVAGITLVPIVDGRCDYDNSFMPEWVNFKFRDLLFKLLEYSS
QDEKVFEESEYFRLCESLKTTVDKRSGMDSMKILKDARSFHNDEIMKMCHDGVNPNMSCDDVVFGINSFFGRFRRDLLNGKLKRNF
QKVSPGGLIKEFSELYETLTDNDDILMLSKEAVESCPLMRFITAETHGHERGSDANTEYERLLSMLNKVKSLKLLNTRRRQLLNLD
VLCLSSLIKQSISKGLENDKHWVGCCYSSVNDRLVSLQSTKEEFMRLLKNRRKSRVHKKASLDELFRVSINEFIAKIQKCLSTVGL
SFEHYGLSECLVQECHIPFAEFENFMRAGTHPVMHYTKFEDYTFQPNIEQLRGLQSLRKLSSVCLALTNSMKTSSVARLRQNQLGS
VRYQVVECKEVFCQIIKLDSEEYHLLYQKTGESSRCYSIQGPDGHLISFYADPKRFFLPIFSDEVLHNMIDTMISWIRSCPDLKDS
LIDIETALRTLILLMLTNPTKRNQKQVQNIRYLVMAIVSDFSSTSLMDKLKEDLITPAEKVVYRLLRFLIRTIFGTGEKVLLSAKF
KFMLNVSYLCHLITKETPDRLTDQIKCFEKFFEPKSEFGFFVNPKETITPEEECVFYEQMKKFTGKDIDCQHSTPGVNLEIFSMMV
SSFNNGTLILKGEKRLNNLDPMTNSGCATALDLASNKSVVVNKHLNGERLLEYDFNKLLVSAVSQITEGFMRKQKYKLRHSDYEYK
VSKLVSRLVIGSRKTEVDKLEDDPVDVCFEGEEETSFFRSLEDKVSSTITRYNRGTRLNEGQGEGEFKNTKGLHHLQIILSGKRAY
LRKVILSEISFHLVEDFDPSCLTNDDMRFICEAVEGSTELSPLYFTSAVKEQCGLDEMARNLCRKFFSEGDWFSCMKMILLQMNAN
AYSGKYRHMQRQSLNFKFDWDKLEEDVRISERESNSESLSKALSLTKCMSAALKNLCFYSEESPTSYTSVGPDSGRLKFALSYKEQ
VGGNRELYIGDLRTKMFTRLVEDYFESFSSFFSGSCLNNDKEFENAILSMTINVREGLLNYSMDHSKWGPMMCPFLFLMLLQNLKL
GDDQYVRSGKDHVSTLLTWHMHKLVEVPFPVVNAMMKSYVKSKLKLLKGSGTTVTERIFREYFEMGVVPSHISSLIDMGQGILHNA
SDFYGLISERFINYCIGVIFGERPEAYTSSDDQITLFDKRLSDLVDSDPEEVLVLLEFHSHLSGLLNKFISPKSVVGRFAAEFKSR
FYVWGEEVPLLTKFVSAALHNVKCKEPHQLCETIDTIADQAIANGVPVFLVNCIQRRTLDLLKYANFPLDPFLLNTHTDVKDWLDG
SRGYRIQRLIEELCPSETKIMRKLVRRLHHKLKNGECNEEFFLDLFNREKKEAILQLGEILGLEDDLNELASINWLNLNEMFPLRM
VLRQKVVYPSVMTFQEEKIPSLIKTLQNKLCSKFTRGAQKLLSEAINKSAFQSCVSSGFIGLCKTLGSRCVRNKNRENMYIRKVLE
DLTMDEHVTRVHKQDGVMLYICDKQRHPEAHRDHINLLRPLLWDYICISLSNSFELGVWVLAEPVKGKNESNSAVRHLNPCDYVAR
KPESSRLLEDKVSLNHVIQSVRRLYPKIFEDQLLPFMSDVSSKNMRWSPRIKFLDLCVLIDINSESLSLISHVVKWKRDEHYTVLF
SDLVNSHQRSDSSLVDEFVVSTRDVCKNFLKQVYFESFVREFVATARTLGNFSWFPHKDMMPSEDGAEALGPFQSFILKVVNKKIE
RPMFRNDLQFGFGWFSYRVGDVVCNAAMLIKQGLTDPKAFKSLRDLWDYMLSSTEGILEFSITVDFTHNQNNTDCLRKFSLIFVVK
CQLQSPGVADYLSCSHFFKGEVDRRLLDECLNLLRTDPIFKANDGVFDIRSEEFEDYMEDPLTLGDSLELELIGSRRILNEIKSTD
FERIGPEWEPVPLTIRKGALFEGRNFVQNISVKLETKDMRVFLAELEGCGKIGDVLGSLLLHRFRTGEHLMESEISTVLQELCMDR
SVMLTPLSFVPDWFTFRDCRLCFSRSKNTVMYETTGGRFRLKGKSCDDWLAERVAEEID
(SEQ ID NO: 10)

图38(续)

B. 淋巴细胞性脉络丛脑膜炎病毒 (LCMV)毒株 P52-WE

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-3376 区段=S
LCMV P52-WE (L) S-区段

GCGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCCTTTAGGACAATTGGGTGCTGGATTCTATCCAATAAAAGGATGGGTCA
GATTGTGACAATGTTTGAGGCTTTGCCTCACATCATTGATGAGGTCATCAACATTGTCATTATTGTGCTCATTATAATCACGAGCA
TCAAAGCTGTGTACAATTTCGCCACCTGTGGGATATTAGCACTGGTCAGCTTCCTTTTTTTGGCTGGTAGGTCCTGTGGCATGTAC
GGCCTTAATGGTCCCGACATCTATAAAGGGGTTTACCAGTTCAAATCAGTGGAGTTTGATATGTCTCACTTAAATCTGACGATGCC
CAATGCGTGCTCAGCCAACAACTCTCATCACTACATCAGTATGGGAAGCTCTGGACTGGAGCTAACTTTCACTAACGACTCCATCC
TTAATCACAATTTTTGCAACTTAACCTCCGCTTTCAACAAAAAGACTTTTGACCATACACTCATGAGTATAGTCTCGAGTCTGCAC
CTCAGTATTAGAGGGAATTCCAACCACAAAGCAGTGTCTTGTGATTTTAACAATGGCATCACCATTCAATACAACTTGTCATTTTC
GGACCCACAGAGCGCTATGAGCCAGTGTTGGACTTTCAGAGGTAGAGTCTTGGACATGTTTAGAACTGCCTTTGGAGGAAAATACA
TGAGAAGTGGCTGGGGCTGGGCAGGTTCAGATGGCAAGACCACTTGGTGCAGCCAAACAAGCTATCAGTACCTAATCATACAAAAC
AGGACTTGGGAAAACCACTGTAGATATGCAGGCCCTTTTGGGATGTCTAGAATCCTCTTTGCTCAGGAAAAGACAAAGTTTCTCAC
TAGGAGACTTGCAGGCACATTCACCTGGACCCTGTCAGACTCCTCAGGAGTAGAAAATCCAGGTGGTTATTGCCTGACCAAATGGA
TGATCCTTGCTGCAGAGCTCAAATGTTTTGGGAATACAGCTGTTGCAAAATGTAATGTCAATCATGATGAAGAGTTCTGTGACATG
CTACGACTAATTGATTACAACAAGGCCGCCCTGAGTAAGTTCAAGCAAGATGTAGAGTCTGCCTTGCATGTATTCAAAACAACAGT
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GGTATCTGGAACATGCTAAGACTGGTGAGACTAGTGTACCCAAGTGCTGGCTTGTCACTAATGGCTCCTACTTGAATGAGACCCAC
TTTAGTGATCAAATCGAACAAGAAGCAGATAACATGATCACAGAGATGTTGAGGAAGGACTACATAAAAAGACAAGGGAGTACTCC
TTTAGCCTTAATGGATCTTTTGATGTTTTCAACATCAGCATATCTAATCAGCATCTTTCTGCATCTTGTGAAGATACCAACACATA
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TGCCTTGGAAGCACTCTCAAAAATGATGCAGTCCATGAGTGCACAGTGTGGGGTGATCTCTTTCTTCTTTTTGTCTCTCACTACCC
CAGTGTGCATTTTGCATAGCCAGCCATATTTGTCCCACACTTTATCTTCATATTCTCTTGAGGCCTCCTTGGTCATCTCAACATCA
ATGAGTTTTATGTCCCTTCTATTTTGTGAGTCCAGAAGCTTTCTGATGTCATCAGAACCTTGACAGCTCAAAACCATCCCTTGTGG
GAGAGCACCTATAACTGATGAGGTCAGCCCAGGCTGTGCATTGAAGAGATCAGCAAGATCCATGCCGTGTGAATACTTTGAGTCCT
GCTTGAATTGCTTCTGGTCCGTAGGTTCCCTGTAAAAATGTATGAATTGCCCATTTTGTGGTTGGAATATTGCTATCTCCACTGGA
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TTGTTGTGTTCTCCCATGCTCTCCCCACAACTGACGTTCTACAGGCTATGTATGGCCATCCTTCACCTGAAAGACAGACTTTATAA
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GAGATCCTCACTGTTGCTCGGTTTGATCAAGATAGATTCCAGCATGTTCCCTCCATCTAGCAGAGCTGCCCCCGCTTTCACAGCTG
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AAACCCTTACTACACCACTTGCACCCTGCTGAGGTCTTCTCATCCCAACCATTTGCAGTATTTGGGATCTTTGATCAAGTTGTTGT
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AAGGGTCATCAATTCCTCTGCACTAAGTCTTCCCACTTTCAGAACATTTTTCTTTGATGTAGACTTCAGATCAACAAGAGAATGCA
CAGTCTGGTTAAGACTCCTGAGTCTCTGCAAGTCTTTATCATCCCTCCTTTCCTTTCTCATGATCCTCTGAACGTTGCTGACTTCA
GAAAAGTCCAACCCATTTAGAAGACTGGTTGCGTCCTTGATGACGGCAGCCTTTACATCTGATGTAAAACTCTGCAACTCCCTCCT
CAACGCCTGTGTCCACTGAAAGCTTTTGACTTCTTTGGACAAAGACATTTTGTCACACAATGAATTTCCAAATAAAAGCGCAATTA
AATGCCTAGGATCCACTGTGCG
(SEQ ID NO: 11)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-7236 区段=L
LCMV P52-WE (L) L-区段

GCGCACCGGGGATCCTAGGCGTTTAGTTGCGCTGCTTTATTGCACAGCTTCACTCTGCTAAACCATCAGGAACTGACCGATCATCA
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TCCTCTAAATTGTAAATCATGTTGGCAGAAATTTGACAGCTTGGTTAGATGCCATGACCACTATCTTTGCAGACACTGTCTGAATC
TCCTGCTGTCAGTTTCCGACAGATGTCCTCTCTGTAAGTATCCACTGCCAACCAAACTGAAGGTGTCAACAGTCCCAAGCTCCCCA
CCTCCCTATGAGGAGTGACGCCCCAGACCTCGACACAACAGGCCACCCAACACAGAAAAACCACACACAAACCGGCACACACAGAC
ACAGCAACCAGCACAAAGCGCACGAAAACACACACACACACACACACACCCTCACCCACGCGCCCCCCCGCACCGCCGGGGGGG
CGCCCCCCCGGGGGGCAGCCCCCCGGGGGCCCGGGCAGGGCCCCGCGGAGATGCCGGCTAGTCGATCTCCTCGGCCACCCGCTCCG
CCAGCCAATCGTCACAGGATTTCCCCTTGAGTCTGAACCTGCCCCCAGTTGTCTCATACATTACAGTGTTCTTTGACCTGCTGAAG
CAGAGCCTACAATCTCTGAAGGTGAACCAATCTGGCACAAAAGATAATGGTGTCAGCATGACGGATCTGTCCATGCAGAGCTCCTG
AAGAACTGTACTTATTTCTGACTCCATCAAGTGCTCACCAGTTCTGAATCGGTGCAGGAGGAGGCTGCCGAGGACATCACCAATTT
TTCCACAGCCCTCGAGCTCTGCCAGAAAGACCCTCATGTCCTTTGTCTCCAATTTCACAGAGATATTCTGAACAAAGTTCCTCCCC
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TTTCAAAATAAATGATTGGAAGGGTCCCAGTGCTTCAGCGCCATCTTCAGATGGCATCATGTCCTTATGGGGGAACCATGAAAAGT
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CTCACAGATTGAATTACATGATTCAAACTCACTTTATCCTCTAGTAGTCTCGAACTCTCAGGTTTTCTTGCTACATAATCACATGG
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CAAATGTACAACATCACACCATCTTGTTTGTGAACCCTTGTGACATGTTCATCCATGGTCAGATCTTCAAGCACCTTTCTGATATA
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TCCCATGTCAATGAGACTAGATATGTGAGATGGCACCACCCCCATTTCAAAATACTCTCTAAAGATTCTCTCCGTAACAGTCGTTC
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CTTTGACAGCTGATGTAAAATACAATGGTGACAGTTCTGTTGAACCTTCAACAGCCTCACAAATAAACCTCATGTCGTCATTGGTG
AGACAGGATGGATCAAAGTCCTCTACTAGATGAAATGAAATTTCTGATAAAATGACTTTCCTCAGATAAGCTCTTTTACCTGACAA
AATAATCTGAAGGTGGTGTAGTCCTTTTGTGTTCTTGAATTCTCCCTCCCCTTGCCCTTCATTAAGCCTAGTGCCTCTATTATACC
GTGTTATTGTGGAGCTGACCTTATCTTCTAAACTCCTGAAAAAACTTGTCTCCTCCTCCCCCTCGAAACACACATCTACCGGATCA
TCTTCCAATTTGTCTACTTCTGTTTTCCTGGAACCGATGACTAATCTAGAGACAAGCTTTGAGACCTTATATTCGTAATCTGAGTG
TCTCAGCTTATACTTTTGTTTCCTCATGAAGCCCTCTGTAATTTGGCTCACAGCACTAACAAGCAATTTGTTAAAATCATACTCCA
AAAGCCGTTCTCCATTCAGATGTTTATTGACAACCACACTTTTGTTGCTTGCGAGATCTAATGCTGTCGCACATCCAGAGTTGGTC
ATGGGGTCCAGATTGTTGAGCCTTTTCTCCCCTTTTAGAATTAAGGTGCCATTGTTGAATGAAGATACCATCATGCTAAAGATCTC
TAAATTAACACCAGGGGTTGAATGCTGACAATCAATATCTTTACCGGTGAACTTCTTCATTTGTTCATAAAAAACACATTCCTCTT
CGGGTGTGATTGTTTCCTTAGGGTTGACAAAGAAACCAAACTCACTCTTGGGCTCAAAGAACTTTTCAAAACATTTTATCTGATCT
GTCAATCTATCAGGGGTCTCCTTTGTGATCAAATGACACAGGTATGACACATTCAACATAAACTTGAATTTTGCACTCAATAACAC
CTTTTCACCAGTACCAAAAATTGTCCTAATCAAAAACCGAAGCAGCCTGTACACCACTTTCTCGGCAGGTGTGATTAGATCCTCCT
TCAACTTATCCATTAATGAGGTCGATGAAAAGTCTGAGACGATGGCCATCACTAAATACCTAATATTTTGAACCTGCTTTTGATTT

图38(续)

CTCTTTGTTGGGTTGGTGAGCATCAGTAGGATCAATGTCCTTAGTGCAGTCTCAATGTCAATAAGAGAATCTTTTAAGTCAGGGCA
TGACCTAATCCATGAAATCATTGTGTCTATCATGTTGTGCAACACCTCATCTGAAAAAATTGGTAAAAAGAACCTTTTTGGATCTG
CGTAAAAGGAAATCAAGTGACCATCCGGACCTTGTATGGAATAACACCTCGATGATTCTCCAGTTTTCTGATATAGTAGATGATAC
TCTTCGGAATCCAGTTTTATTATCTGGCAAAACACCTCTTTGCACTCCACCACTTGATATCTCACAGACCCCAGTTGGTTCTGTCT
CAACCTTGCAACTGAGCTTGTTTTCATGCTGTTTGTTAGAGCCAAACAAACAGATGACAGTTTTCTCAAACTCTGTAAACCCCTCA
ATTGCTCTATGTTAGGCTGGAAAGTGTAATCTTCAAATTTTGTGTAATGCATTACAGGATGAGTCCCGGCTCTCATAAAGTTCTCA
AATTCAGCAAATGGTATATGGCATTCTTGCACGAGGCATTCTGATAGTCCGTAATGCTCAAAACTAAGTCCCACTGTTGATAGGCA
TTTCTGGATTTTTGCTATGAACTCATTTATGGATACCCTAAAAAGCTCATCAAGAGATGCCTTTTTGTGCACTCTTGATTTTCTTC
TGTTCTTCAAAAGTCTCATGAATTCTTCTTTGGTACTTTGAAGGCTCACAAGCCTATCATTCACACTACTGTAGCAACAACCAACC
CAATGTTTATCATTTTCCAACCCTTTGGAAATTGACTGCTTAATAAGTGAAGAAAGACATAAGACATCTAAGTTCAGCAGCTGTCT
CCTTCTAGTGTTTAATAATTTTAAACTTTTCACCTTGTTCAACATAGAGAGTAGCCTTTCATACTCAGTGTTAGCATCGCTTCCTC
TCTCATGCCCATGGGTCTCTGCTGTAATGAACCTCATTAAGGGGCAGGATTCAACTGCCTCTTTGCTCAACATTAATATGTCATCA
TTATCAGTAAGGGTTTCATAAAGTTCAGAGAATTCCTTGATTAAGCCCCCAGGGCTGACCTTTTGGAAATTCCTTTTGAGTTTCCC
ATTTAACAGGTCCCTCCTAAACCTGCCAAAAAAGGAATTTATGCCAAAGACCACATCATCGCAACTCATGTTGGGGTTGACACCAT
CGTGGCACATTTTCATAATCTCATCGTTATGAAATGATCTTGCGTCTTTCAAAATTTTCATTGAGTCCATGCCGGAACGTTTGTCA
ACAGTGGTCTTAAGAGACTCACAGAGCCTGAAGTATTCAGACTCCTCAAAAACTTTCTCATCTTGACTAGAATACTCCAGGAGTTT
AAATAGGAGGTCTCTGAACTTAAAATTCACCCATTCTGGCATGAAACTGTTATCATAATCACAACGACCATCCACTATTGGAACCA
GTGTGATGCCTGCAACAGCAAGATCTTCTTTGATGCATGCTAGTTTGTTGGTGTCCTCAATGAACTTCTTTTCAAAACTAGCTGGT
GTGCTTCTAACAAAACATTCAAGAAGAATAAGGGAATTGTCAATCAACTTATAACCATCAGGGATGATGAGTGGCAGTCCTGGACA
CACAATCCCAGAGTCTATTAGGATTGTTTCAACAGATTTGTCATCGTGGTTGTGTATGCAACCACTTTTGTCTGCACTGTCTATCT
CTATACAGCGTGATAACAATTTGAGTCCCTCAATTAGCACCATTCTGGGTTCTCTTTGTCCCAGGAAGTTGAGTTTTTGCCTTGAC
AGCCTCTCGTCCTGTTCTATGTAATTTAGACACAACTCTCTCAAATCTGCAATAGTTTCATCCATTGCGCATCAAAAAGCCTAGGA
TCCTCGGTGCGC
(SEQ ID NO: 12)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-3376 区段=S
蛋白: 前糖蛋白多蛋白 GP 复合物
基因: GPC
LCMV P52-WE(L) GPC

ATGGGTCAGATTGTGACAATGTTTGAGGCTTTGCCTCACATCATTGATGAGGTCATCAACATTGTCATTATTGTGCTCATTATAAT
CACGAGCATCAAAGCTGTGTACAATTTCGCCACCTGTGGGATATTAGCACTGGTCAGCTTCCTTTTTTTGGCTGGTAGGTCCTGTG
GCATGTACGGCCTTAATGGTCCCGACATCTATAAAGGGGTTTACCAGTTCAAATCAGTGGAGTTTGATATGTCTCACTTAAATCTG
ACGATGCCCAATGCGTGCTCAGCCAACAACTCTCATCACTACATCAGTATGGGAAGCTCTGGACTGGAGCTAACTTTCACTAACGA
CTCCATCCTTAATCACAATTTTTGCAACTTAACCTCCGCTTTCAACAAAAAGACTTTTGACCATACACTCATGAGTATAGTCTCGA
GTCTGCACCTCAGTATTAGAGGGAATTCCAACCACAAAGCAGTGTCTTGTGATTTTAACAATGGCATCACCATTCAATACAACTTG
TCATTTTCGGACCCACAGAGCGCTATGAGCCAGTGTTGGACTTTCAGAGGTAGAGTCTTGGACATGTTTAGAACTGCCTTTGGAGG
AAAATACATGAGAAGTGGCTGGGGCTGGGCAGGTTCAGATGGCAAGACCACTTGGTGCAGCCAAACAAGCTATCAGTACCTAATCA
TACAAAACAGGACTTGGGAAAACCACTGTAGATATGCAGGCCCTTTTGGGATGTCTAGAATCCTCTTTGCTCAGGAAAAGACAAAG
TTTCTCACTAGGAGACTTGCAGGCACATTCACCTGGACCCTGTCAGACTCCTCAGGAGTAGAAAATCCAGGTGGTTATTGCCTGAC
CAAATGGATGATCCTTGCTGCAGAGCTCAAATGTTTTGGGAATACAGCTGTTGCAAAATGTAATGTCAATCATGATGAAGAGTTCT
GTGACATGCTACGACTAATTGATTACAACAAGGCCGCCCTGAGTAAGTTCAAGCAAGATGTAGAGTCTGCCTTGCATGTATTCAAA
ACAACAGTAAATTCTCTGATTTCCGATCAGCTGTTGATGAGGAATCATCTAAGAGATCTAATGGGGGTACCATACTGTAATTACTC
AAAGTTCTGGTATCTGGAACATGCTAAGACTGGTGAGACTAGTGTACCCAAGTGCTGGCTTGTCACTAATGGCTCCTACTTGAATG
AGACCCACTTTAGTGATCAAATCGAACAAGAAGCAGATAACATGATCACAGAGATGTTGAGGAAGGACTACATAAAAAGACAAGGG
AGTACTCCTTTAGCCTTAATGGATCTTTTGATGTTTTCAACATCAGCATATCTAATCAGCATCTTTCTGCATCTTGTGAAGATACC
AACACATAGACACATAAAGGGCGGTTCATGTCCAAAGCCACACCGCTTGACCAACAAGGGGATCTGTAGTTGTGGTGCATTCAAGG
TGCCTGGTGTAAAAACTATCTGGAAAAGACGCTGA
(SEQ ID NO: 13)

翻译=LCMV P52-WE (L) GPC

MGQIVTMFEALPHIIDEVINIVIIVLIIITSIKAVYNFATCGILALVSFLFLAGRSCGMYGLNGPDIYKGVYQFKSVEFDMSHLNL
TMPNACSANNSHHYISMGSSGLELTFTNDSILNHNFCNLTSAFNKKTFDHTLMSIVSSLHLSIRGNSNHKAVSCDFNNGITIQYNL
SFSDPQSAMSQCWTFRGRVLDMFRTAFGGKYMRSGWGWAGSDGKTTWCSQTSYQYLIIQNRTWENHCRYAGPFGMSRILFAQEKTK
FLTRRLAGTFTWTLSDSSGVENPGGYCLTKWMILAAELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSKFKQDVESALHVFK
TTVNSLISDQLLMRNHLRDLMGVPYCNYSKFWYLEHAKTGETSVPKCWLVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQG
STPLALMDLLMFSTSAYLISIFLHLVKIPTHRHIKGGSCPKPHRLTNKGICSCGAFKVPGVKTIWKRR
(SEQ ID NO: 14)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-3376 区段=S
蛋白: 核蛋白
基因: NP
LCMV P52-WE(L) NP

ATGTCTTTGTCCAAAGAAGTCAAAAGCTTTCAGTGGACACAGGCGTTGAGGAGGGAGTTGCAGAGTTTTACATCAGATGTAAAGGC
TGCCGTCATCAAGGACGCAACCAGTCTTCTAAATGGGTTGGACTTTTCTGAAGTCAGCAACGTTCAGAGGATCATGAGAAAGGAAA
GGAGGGATGATAAAGACTTGCAGAGACTCAGGAGTCTTAACCAGACTGTGCATTCTCTTGTTGATCTGAAGTCTACATCAAAGAAA
AATGTTCTGAAAGTGGGAAGACTTAGTGCAGAGGAATTGATGACCCTTGCAGCTGATCTTGAGAAGCTGAAGGCCAAAATTATGAG
AACTGAGAGGCCTCAAGCTTCTGGAGTCTACATGGGAAATTTGACAGCACAACAACTTGATCAAAGATCCCAAATACTGCAAATGG
TTGGGATGAGAAGACCTCAGCAGGGTGCAAGTGGTGTAGTAAGGGTTTGGGATGTGAAGGACTCATCACTTCTGAACAATCAGTTC
GGCACAATGCCAAGCCTGACAATGGCTTGCATGGCAAAACAGTCACAGACCCCACTCAATGATGTTGTGCAGGCACTCACAGACCT
TGGCTTACTTTACACAGTCAAATACCCGAATCTCAGTGATCTTGAAAGGCTAAAGGATAAACACCCAGTTCTGGGGGTCATTACTG
AACAGCAATCTAGTATCAATATCTCTGGTTATAATTTCAGTCTTGGTGCAGCTGTGAAAGCGGGGGCAGCTCTGCTAGATGGAGGG
AACATGCTGGAATCTATCTTGATCAAACCGAGCAACAGTGAGGATCTCCTAAAAGCAGTCCTCGGGGCCAAGAAGAAACTCAACAT
GTTTGTCTCAGATCAAGTTGGAGATAGAAATCCCTATGAAAACATCCTTTATAAAGTCTGTCTTTCAGGTGAAGGATGGCCATACA
TAGCCTGTAGAACGTCAGTTGTGGGGAGAGCATGGGAGAACACAACAATTGATCTCACAAATGAAAAACTTGTTGCCAACTCATCT
AGGCCAGTGCCTGGAGCAGCAGGCCCACCTCAGGTGGGCTTGAGTTACAGTCAGACAATGCTGTTGAAAGACTTGATGGGAGGGAT
TGATCCCAATGCTCCCACATGGATTGACATTGAGGGCAGGTTCAATGATCCAGTGGAGATAGCAATATTCCAACCACAAAATGGGC
AATTCATACATTTTTACAGGGAACCTACGGACCAGAAGCAATTCAAGCAGGACTCAAAGTATTCACACGGCATGGATCTTGCTGAT
CTCTTCAATGCACAGCCTGGGCTGACCTCATCAGTTATAGGTGCTCTCCCACAAGGGATGGTTTTGAGCTGTCAAGGTTCTGATGA
CATCAGAAAGCTTCTGGACTCACAAAATAGAAGGGACATAAAACTCATTGATGTTGAGATGACCAAGGAGGCCTCAAGAGAATATG
AAGATAAAGTGTGGGACAAATATGGCTGGCTATGCAAAATGCACACTGGGGTAGTGAGAGACAAAAAGAAGAAAGAGATCACCCCA
CACTGTGCACTCATGGACTGCATCATTTTTGAGAGTGCTTCCAAGGCAAGACTCCCTGATCTAAAAACCGTTCACAACATCCTGCC
ACATGATTTAATCTTCAGAGGACCCAATGTTGTGACACTCTAA
(SEQ ID NO: 15)

翻译=LCMV P52-WE (L) NP

MSLSKEVKSFQWTQALRRELQSFTSDVKAAVIKDATSLLNGLDFSEVSNVQRIMRKERRDDKDLQRLRSLNQTVHSLVDLKSTSKK
NVLKVGRLSAEELMTLAADLEKLKAKIMRTERPQASGVYMGNLTAQQLDQRSQILQMVGMRRPQQGASGVVRVWDVKDSSLLNNQF
GTMPSLTMACMAKQSQTPLNDVVQALTDLGLLYTVKYPNLSDLERLKDKHPVLGVITEQQSSINISGYNFSLGAAVKAGAALLDGG
NMLESILIKPSNSEDLLKAVLGAKKKLNMFVSDQVGDRNPYENILYKVCLSGEGWPYIACRTSVVGRAWENTTIDLTNEKLVANSS
RPVPGAAGPPQVGLSYSQTMLLKDLMGGIDPNAPTWIDIEGRFNDPVEIAIFQPQNGQFIHFYREPTDQKQFKQDSKYSHGMDLAD
LFNAQPGLTSSVIGALPQGMVLSCQGSDDIRKLLDSQNRRDIKLIDVEMTKEASREYEDKVWDKYGWLCKMHTGVVRDKKKKEITP
HCALMDCIIFESASKARLPDLKTVHNILPHDLIFRGPNVVTL
(SEQ ID NO: 16)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-7235 区段=L
蛋白: 环指蛋白 Z
基因: ZP
LCMV P52-WE(L) ZP

ATGGGCCAAGGCAAGTCCAAAGAAGAAAGGGACACCAGCAATACAGGCAGAGCAGAGCTTTTGCCAGACACCACCTATCTTGGTCC
TCTAAATTGTAAATCATGTTGGCAGAAATTTGACAGCTTGGTTAGATGCCATGACCACTATCTTTGCAGACACTGTCTGAATCTCC
TGCTGTCAGTTTCCGACAGATGTCCTCTCTGTAAGTATCCACTGCCAACCAAACTGAAGGTGTCAACAGTCCCAAGCTCCCCACCT
CCCTATGAGGAGTGA
(SEQ ID NO: 17)

翻译=LCMV P52-WE (L) ZP

MGQGKSKEERDTSNTGRAELLPDTTYLGPLNCKSCWQKFDSLVRCHDHYLCRHCLNLLLSVSDRCPLCKYPLPTKLKVSTVPSSPP
PYEE
(SEQ ID NO: 18)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 P52-WE (L)
来源: 1-7235 区段=L
蛋白: RNA 指导的 RNA 聚合酶 L
基因: LCMV P52-WE(L) LP

ATGGATGAAACTATTGCAGATTTGAGAGAGTTGTGTCTAAATTACATAGAACAGGACGAGAGGCTGTCAAGGCAAAAACTCAACTT
CCTGGGACAAAGAGAACCCAGAATGGTGCTAATTGAGGGACTCAAATTGTTATCACGCTGTATAGAGATAGACAGTGCAGACAAAA
GTGGTTGCATACACAACCACGATGACAAATCTGTTGAAACAATCCTAATAGACTCTGGGATTGTGTGTCCAGGACTGCCACTCATC
ATCCCTGATGGTTATAAGTTGATTGACAATTCCCTTATTCTTCTTGAATGTTTTGTTAGAAGCACACCAGCTAGTTTTGAAAAGAA
GTTCATTGAGGACACCAACAAACTAGCATGCATCAAAGAAGATCTTGCTGTTGCAGGCATCACACTGGTTCCAATAGTGGATGGTC
GTTGTGATTATGATAACAGTTTCATGCCAGAATGGGTGAATTTTAAGTTCAGAGACCTCCTATTTAAACTCCTGGAGTATTCTAGT
CAAGATGAGAAAGTTTTTGAGGAGTCTGAATACTTCAGGCTCTGTGAGTCTCTTAAGACCACTGTTGACAAACGTTCCGGCATGGA
CTCAATGAAAATTTTGAAAGACGCAAGATCATTTCATAACGATGAGATTATGAAAATGTGCCACGATGGTGTCAACCCCAACATGA
GTTGCGATGATGTGGTCTTTGGCATAAATTCCTTTTTTGGCAGGTTTAGGAGGGACCTGTTAAATGGGAAACTCAAAAGGAATTTC
CAAAAGGTCAGCCCTGGGGGCTTAATCAAGGAATTCTCTGAACTTTATGAAACCCTTACTGATAATGATGACATATTAATGTTGAG
CAAAGAGGCAGTTGAATCCTGCCCCTTAATGAGGTTCATTACAGCAGAGACCCATGGGCATGAGAGAGGAAGCGATGCTAACACTG
AGTATGAAAGGCTACTCTCTATGTTGAACAAGGTGAAAAGTTTAAAATTATTAAACACTAGAAGGAGACAGCTGCTGAACTTAGAT
GTCTTATGTCTTTCTTCACTTATTAAGCAGTCAATTTCCAAAGGGTTGGAAAATGATAAACATTGGGTTGGTTGTTGCTACAGTAG
TGTGAATGATAGGCTTGTGAGCCTTCAAAGTACCAAAGAAGAATTCATGAGACTTTTGAAGAACAGAAGAAAATCAAGAGTGCACA
AAAAGGCATCTCTTGATGAGCTTTTTAGGGTATCCATAAATGAGTTCATAGCAAAAATCCAGAAATGCCTATCAACAGTGGGACTT
AGTTTTGAGCATTACGGACTATCAGAATGCCTCGTGCAAGAATGCCATATACCATTTGCTGAATTTGAGAACTTTATGAGAGCCGG
GACTCATCCTGTAATGCATTACACAAAATTTGAAGATTACACTTTCCAGCCTAACATAGAGCAATTGAGGGGTTTACAGAGTTTGA
GAAAACTGTCATCTGTTTGTTTGGCTCTAACAAACAGCATGAAAACAAGCTCAGTTGCAAGGTTGAGACAGAACCAACTGGGGTCT
GTGAGATATCAAGTGGTGGAGTGCAAAGAGGTGTTTTGCCAGATAATAAAACTGGATTCCGAAGAGTATCATCTACTATATCAGAA
AACTGGAGAATCATCGAGGTGTTATTCCATACAAGGTCCGGATGGTCACTTGATTTCCTTTTACGCAGATCCAAAAAGGTTCTTTT
TACCAATTTTTTCAGATGAGGTGTTGCACAACATGATAGACACAATGATTTCATGGATTAGGTCATGCCCTGACTTAAAAGATTCT
CTTATTGACATTGAGACTGCACTAAGGACATTGATCCTACTGATGCTCACCAACCCAACAAAGAGAAATCAAAAGCAGGTTCAAAA
TATTAGGTATTTAGTGATGGCCATCGTCTCAGACTTTTCATCGACCTCATTAATGGATAAGTTGAAGGAGGATCTAATCACACCTG
CCGAGAAAGTGGTGTACAGGCTGCTTCGGTTTTTGATTAGGACAATTTTTGGTACTGGTGAAAAGGTGTTATTGAGTGCAAAATTC
AAGTTTATGTTGAATGTGTCATACCTGTGTCATTTGATCACAAAGGAGACCCCTGATAGATTGACAGATCAGATAAAATGTTTTGA
AAAGTTCTTTGAGCCCAAGAGTGAGTTTGGTTTCTTTGTCAACCCTAAGGAAACAATCACACCCGAAGAGGAATGTGTTTTTTATG
AACAAATGAAGAAGTTCACCGGTAAAGATATTGATTGTCAGCATTCAACCCCTGGTGTTAATTTAGAGATCTTTAGCATGATGGTA
TCTTCATTCAACAATGGCACCTTAATTCTAAAAGGGGAGAAAAGGCTCAACAATCTGGACCCCATGACCAACTCTGGATGTGCGAC
AGCATTAGATCTCGCAAGCAACAAAAGTGTGGTTGTCAATAAACATCTGAATGGAGAACGGCTTTTGGAGTATGATTTTAACAAAT
TGCTTGTTAGTGCTGTGAGCCAAATTACAGAGGGCTTCATGAGGAAACAAAAGTATAAGCTGAGACACTCAGATTACGAATATAAG
GTCTCAAAGCTTGTCTCTAGATTAGTCATCGGTTCCAGGAAAACAGAAGTAGACAAATTGGAAGATGATCCGGTAGATGTGTGTTT
CGAGGGGGAGGAGGAGACAAGTTTTTTCAGGAGTTTAGAAGATAAGGTCAGCTCCACAATAACACGGTATAATAGAGGCACTAGGC
TTAATGAAGGGCAAGGGGAGGGAGAATTCAAGAACACAAAAGGACTACACCACCTTCAGATTATTTTGTCAGGTAAAAGAGCTTAT
CTGAGGAAAGTCATTTTATCAGAAATTTCATTTCATCTAGTAGAGGACTTTGATCCATCCTGTCTCACCAATGACGACATGAGGTT
TATTTGTGAGGCTGTTGAAGGTTCAACAGAACTGTCACCATTGTATTTTACATCAGCTGTCAAAGAACAATGTGGTCTGGATGAGA
TGGCAAGAAACCTCTGTAGAAAGTTCTTCTCAGAGGGTGATTGGTTCTCATGTATGAAGATGATCTTGTTACAGATGAATGCAAAT
GCGTATTCAGGGAAGTACAGACACATGCAGAGGCAGAGCTTAAATTTTAAATTTGACTGGGACAAATTGGAAGAAGATGTAAGAAT
TAGTGAAAGGGAAAGCAATTCTGAATCTCTAAGTAAGGCCCTTTCATTGACAAAATGCATGAGTGCTGCTCTAAAGAATCTGTGTT
TTTACTCAGAAGAATCACCAACATCATACACTTCAGTTGGCCCTGACTCTGGGAGACTAAAATTTGCATTGTCATACAAAGAGCAG
GTTGGGGGAAATAGAGAGCTTTACATTGGGGATTTGAGGACAAAAATGTTCACAAGATTGGTAGAAGATTATTTTGAATCCTTTTC
TAGTTTCTTTTCAGGATCTTGTTTAAACAATGACAAAGAGTTTGAAAATGCAATCTTGTCAATGACTATCAATGTGAGAGAAGGGT
TGTTAAACTACAGCATGGATCACAGCAAATGGGGACCAATGATGTGCCCATTCCTATTCTTAATGCTTCTCCAAAATCTCAAACTG
GGTGATGATCAGTACGTGCGTTCTGGAAAAGATCATGTTAGCACCTTGTTGACTTGGCATATGCATAAACTTGTTGAAGTCCCTTT
CCCTGTTGTGAATGCAATGATGAAATCATATGTTAAATCAAAACTCAAGCTTCTCAAAGGGTCAGGAACGACTGTTACGGAGAGAA
TCTTTAGAGAGTATTTTGAAATGGGGGTGGTGCCATCTCACATATCTAGTCTCATTGACATGGGACAGGGGATCCTACACAATGCT
TCTGATTTTTACGGTTTAATTAGTGAAAGGTTTATCAATTATTGTATTGGTGTCATTTTTGGAGAGAGGCCAGAAGCCTATACATC
AAGTGATGATCAGATCACTTTATTTGACAAGAGATTGAGTGACTTAGTTGATAGTGACCCAGAAGAAGTCCTTGTCTTGCTGGAAT
TCCACTCTCACTTAAGTGGTTTGTTGAACAAGTTCATCAGTCCAAAAAGTGTGGTTGGGCGGTTTGCAGCGGAATTCAAATCCAGA
TTTTATGTGTGGGGGGAGGAGGTCCCTCTCCTCACGAAATTTGTGTCTGCGGCACTACACAATGTTAAGTGTAAAGAACCGCATCA
ACTTTGTGAGACAATAGATACGATTGCTGATCAAGCTATAGCAAATGGAGTTCCAGTTTTTTTAGTAAACTGTATCCAGAGGAGGA
CACTGGATCTCTTGAAATATGCTAATTTCCCTTTAGATCCATTCTTGTTAAACACTCACACTGATGTAAAGGATTGGTTAGATGGT
TCTAGAGGTTATAGAATCCAAAGACTCATTGAAGAATTGTGTCCCAGTGAAACAAAGATCATGAGAAAACTTGTAAGAAGACTACA
TCACAAACTCAAGAACGGTGAATGTAACGAGGAATTTTTTCTAGACCTCTTCAACAGGGAAAAGAAAGAGGCCATCCTTCAATTGG
GAGAGATTCTTGGTCTTGAGGATGATCTTAATGAGTTGGCAAGCATCAATTGGTTGAATCTGAATGAAATGTTCCCATTGAGGATG
GTTCTGAGACAAAAAGTGGTTTACCCATCAGTAATGACCTTTCAAGAGGAAAAGATCCCCTCATTGATTAAAACACTCCAAAATAA
GCTTTGTAGTAAGTTCACAAGAGGTGCACAGAAGCTGTTGTCAGAGGCAATCAACAAATCAGCTTTTCAGAGTTGTGTCTCATCCG
GCTTTATAGGTCTCTGTAAGACTTTAGGAAGTAGGTGTGTGAGAAATAAAAACAGGGAAAATATGTATATCAGAAAGGTGCTTGAA
GATCTGACCATGGATGAACATGTCACAAGGGTTCACAAACAAGATGGTGTGATGTTGTACATTTGCGACAAGCAGAGACACCCAGA
GGCTCACCGTGACCACATCAACCTTTTGAGGCCCCTTCTCTGGGACTACATTTGCATCTCATTGAGCAACTCTTTTGAGCTGGGTG
TTTGGGTTTTAGCAGAACCTGTGAAAGGAAAGAACGAGAGTAATTCGGCTGTTAGGCACTTAAATCCATGTGATTATGTAGCAAGA
AAACCTGAGAGTTCGAGACTACTAGAGGATAAAGTGAGTTTGAATCATGTAATTCAATCTGTGAGGCGACTGTACCCCAAAATCTT

图38(续)

TGAGGATCAGTTGCTCCCATTCATGTCTGATGTGAGCTCAAAAAATATGAGATGGAGTCCCAGGATTAAATTCCTTGACCTTTGTG
TGCTGATTGACATCAACTCAGAGTCTTTGTCACTCATTTCTCATGTTGTCAAATGGAAGAGGGACGAACATTACACTGTGCTGTTT
TCTGATCTCGTCAACTCTCACCAACGGTCAGACTCAAGTTTAGTTGATGAATTTGTTGTCAGCACAAGGGATGTCTGCAAGAACTT
TTTGAAGCAAGTGTATTTCGAATCATTTGTACGAGAGTTTGTTGCAACAGCTAGGACCTTAGGTAACTTTTCATGGTTCCCCCATA
AGGACATGATGCCATCTGAAGATGGCGCTGAAGCACTGGGACCCTTCCAATCATTTATTTTGAAAGTGGTGAACAAGAAAATAGAG
AGGCCCATGTTTAGGAATGACTTGCAGTTTGGTTTTGGTTGGTTCTCTTATCGTGTGGGGGATGTTGTGTGTAATGCCGCTATGTT
AATTAAGCAGGGTTTGACAGATCCAAAAGCATTTAAATCTTTAAGAGATTTGTGGGATTACATGCTCAGCAGCACAGAGGGGATAT
TGGAGTTCTCAATCACAGTGGATTTCACACACAACCAGAACAACACTGACTGCTTGAGGAAATTTTCATTGATCTTTGTGGTTAAA
TGCCAATTACAGAGTCCAGGTGTAGCTGATTACTTATCGTGCTCTCATTTCTTCAAAGGTGAGGTTGACAGGAGATTATTAGATGA
GTGTCTCAATCTGTTGAGGACAGACCCCATCTTTAAAGCGAATGATGGAGTCTTTGACATTAGGTCTGAAGAGTTTGAAGATTACA
TGGAAGACCCTTTGACACTTGGTGATTCACTAGAACTTGAACTAATAGGTTCTAGAAGGATTCTGAATGAGATCAAATCTACTGAC
TTTGAGAGGATAGGGCCTGAGTGGGAACCTGTGCCTCTGACCATAAGGAAGGGTGCCCTCTTTGAGGGGAGGAACTTTGTTCAGAA
TATCTCTGTGAAATTGGAGACAAAGGACATGAGGGTCTTTCTGGCAGAGCTCGAGGGCTGTGGAAAAATTGGTGATGTCCTCGGCA
GCCTCCTCCTGCACCGATTCAGAACTGGTGAGCACTTGATGGAGTCAGAAATAAGTACAGTTCTTCAGGAGCTCTGCATGGACAGA
TCCGTCATGCTGACACCATTATCTTTTGTGCCAGATTGGTTCACCTTCAGAGATTGTAGGCTCTGCTTCAGCAGGTCAAAGAACAC
TGTAATGTATGAGACAACTGGGGGCAGGTTCAGACTCAAGGGGAAATCCTGTGACGATTGGCTGGCGGAGCGGGTGGCCGAGGAGA
TCGACTAG
(SEQ ID NO: 19)

翻译=LCMV P52-WE (L) LP

MDETIADLRELCLNYIEQDERLSRQKLNFLGQREPRMVLIEGLKLLSRCIEIDSADKSGCIHNHDDKSVETILIDSGIVCPGLPLI
IPDGYKLIDNSLILLECFVRSTPASFEKKFIEDTNKLACIKEDLAVAGITLVPIVDGRCDYDNSFMPEWVNFKFRDLLFKLLEYSS
QDEKVFEESEYFRLCESLKTTVDKRSGMDSMKILKDARSFHNDEIMKMCHDGVNPNMSCDDVVFGINSFFGRFRRDLLNGKLKRNF
QKVSPGGLIKEFSELYETLTDNDDILMLSKEAVESCPLMRFITAETHGHERGSDANTEYERLLSMLNKVKSLKLLNTRRRQLLNLD
VLCLSSLIKQSISKGLENDKHWVGCCYSSVNDRLVSLQSTKEEFMRLLKNRRKSRVHKKASLDELFRVSINEFIAKIQKCLSTVGL
SFEHYGLSECLVQECHIPFAEFENFMRAGTHPVMHYTKFEDYTFQPNIEQLRGLQSLRKLSSVCLALTNSMKTSSVARLRQNQLGS
VRYQVVECKEVFCQIIKLDSEEYHLLYQKTGESSRCYSIQGPDGHLISFYADPKRFFLPIFSDEVLHNMIDTMISWIRSCPDLKDS
LIDIETALRTLILLMLTNPTKRNQKQVQNIRYLVMAIVSDFSSTSLMDKLKEDLITPAEKVVYRLLRFLIRTIFGTGEKVLLSAKF
KFMLNVSYLCHLITKETPDRLTDQIKCFEKFFEPKSEFGFFVNPKETITPEEECVFYEQMKKFTGKDIDCQHSTPGVNLEIFSMMV
SSFNNGTLILKGEKRLNNLDPMTNSGCATALDLASNKSVVVNKHLNGERLLEYDFNKLLVSAVSQITEGFMRKQKYKLRHSDYEYK
VSKLVSRLVIGSRKTEVDKLEDDPVDVCFEGEEETSFFRSLEDKVSSTITRYNRGTRLNEGQGEGEFKNTKGLHHLQIILSGKRAY
LRKVILSEISFHLVEDFDPSCLTNDDMRFICEAVEGSTELSPLYFTSAVKEQCGLDEMARNLCRKFFSEGDWFSCMKMILLQMNAN
AYSGKYRHMQRQSLNFKFDWDKLEEDVRISERESNSESLSKALSLTKCMSAALKNLCFYSEESPTSYTSVGPDSGRLKFALSYKEQ
VGGNRELYIGDLRTKMFTRLVEDYFESFSSFFSGSCLNNDKEFENAILSMTINVREGLLNYSMDHSKWGPMMCPFLFLMLLQNLKL
GDDQYVRSGKDHVSTLLTWHMHKLVEVPFPVVNAMMKSYVKSKLKLLKGSGTTVTERIFREYFEMGVVPSHISSLIDMGQGILHNA
SDFYGLISERFINYCIGVIFGERPEAYTSSDDQITLFDKRLSDLVDSDPEEVLVLLEFHSHLSGLLNKFISPKSVVGRFAAEFKSR
FYVWGEEVPLLTKFVSAALHNVKCKEPHQLCETIDTIADQAIANGVPVFLVNCIQRRTLDLLKYANFPLDPFLLNTHTDVKDWLDG
SRGYRIQRLIEELCPSETKIMRKLVRRLHHKLKNGECNEEFFLDLFNREKKEAILQLGEILGLEDDLNELASINWLNLNEMFPLRM
VLRQKVVYPSVMTFQEEKIPSLIKTLQNKLCSKFTRGAQKLLSEAINKSAFQSCVSSGFIGLCKTLGSRCVRNKNRENMYIRKVLE
DLTMDEHVTRVHKQDGVMLYICDKQRHPEAHRDHINLLRPLLWDYICISLSNSFELGVWVLAEPVKGKNESNSAVRHLNPCDYVAR
KPESSRLLEDKVSLNHVIQSVRRLYPKIFEDQLLPFMSDVSSKNMRWSPRIKFLDLCVLIDINSESLSLISHVVKWKRDEHYTVLF
SDLVNSHQRSDSSLVDEFVVSTRDVCKNFLKQVYFESFVREFVATARTLGNFSWFPHKDMMPSEDGAEALGPFQSFILKVVNKKIE
RPMFRNDLQFGFGWFSYRVGDVVCNAAMLIKQGLTDPKAFKSLRDLWDYMLSSTEGILEFSITVDFTHNQNNTDCLRKFSLIFVVK
CQLQSPGVADYLSCSHFFKGEVDRRLLDECLNLLRTDPIFKANDGVFDIRSEEFEDYMEDPLTLGDSLELELIGSRRILNEIKSTD
FERIGPEWEPVPLTIRKGALFEGRNFVQNISVKLETKDMRVFLAELEGCGKIGDVLGSLLLHRFRTGEHLMESEISTVLQELCMDR
SVMLTPLSFVPDWFTFRDCRLCFSRSKNTVMYETTGGRFRLKGKSCDDWLAERVAEEID
(SEQ ID NO: 20)

图38(续)

C. 淋巴细胞性脉络丛脑膜炎病毒 (LCMV)毒株 Armstrong 53b

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源: 1-3376 区段=S
LCMV Armstrong S-区段

CGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCCTCTAGATCAACTGGGTGTCAGGCCCTATCCTACAGAAGGATGGGTCAG
ATTGTGACAATGTTTGAGGCTCTGCCTCACATCATCGATGAGGTGATCAACATTGTCATTATTGTGCTTATCGTGATCACGGGTAT
CAAGGCTGTCTACAATTTTGCCACCTGTGGGATATTCGCATTGATCAGTTTCCTACTTCTGGCTGGCAGGTCCTGTGGCATGTACG
GTCTTAAGGGACCCGACATTTACAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATATGTCACATCTGAACCTGACCATGCCC
AACGCATGTTCAGCCAACAACTCCCACCATTACATCAGTATGGGGACTTCTGGACTAGAATTGACCTTCACCAATGATTCCATCAT
CAGTCACAACTTTTGCAATCTGACCTCTGCCTTCAATAAAAAGACCTTTGACCACACACTCATGAGTATAGTTTCGAGCCTACACC
TCAGTATCAGAGGGAACTCCAACTATAAGGCAGTATCCTGCGACTTCAACAATGGCATAACCATCCAATACAACTTGACATTCTCA
AATGCACAAAGTGCTCAGAGCCAGTGTAGAACCTTCAGAGGTAGAGTCCTAGATATGTTTAGAACTGCCTTCGGGGGGAAATACAT
GAGGAGTGGCTGGGGCTGGACAGGCTCAGATGGCAAGACCACCTGGTGTAGCCAGACGAGTTACCAATACCTGATTATACAAAATA
GAACCTGGGAAAACCACTGCACATATGCAGGTCCTTTTGGGATGTCCAGGATTCTCCTTTCCCAAGAGAAGACTAAGTTCTTCACT
AGGAGACTAGCGGGCACATTCACCTGGACTTTGTCAGACTCTTCAGGGGTGGAGAATCCAGGTGGTTATTGCCTGACCAAATGGAT
GATTCTTGCTGCAGAGCTTAAGTGTTTCGGGAACACAGCAGTTGCGAAATGCAATGTAAATCATGATGAAGAATTCTGTGACATGC
TGCGACTAATTGACTACAACAAGGCTGCTTTGAGTAAGTTCAAAGAGGACGTAGAATCTGCCTTGCACTTATTCAAAACAACAGTG
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GTACCTAGAACATGCAAAGACCGGCGAAACTAGTGTCCCCAAGTGCTGGCTTGTCACCAATGGTTCTTACTTAAATGAGACCCACT
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TAAAAACCGTCTGGAAAAGACGCTGAAGAACAGCGCCTCCCTGACTCTCCACCTCGAAAGAGGTGGAGAGTCAGGGAGGCCCAGAG
GGTCTTAGAGTGTCACAACATTTGGGCCTCTAAAAATTAGGTCATGTGGCAGAATGTTGTGAACAGTTTTCAGATCTGGGAGCCTT
GCTTTGGAGGCGCTTTCAAAAATGATGCAGTCCATGAGTGCACAGTGCGGGGTGATCTCTTTCTTCTTTTTGTCCCTTACTATTCC
AGTATGCATCTTACACAACCAGCCATATTTGTCCCACACTTTGTCTTCATACTCCCTCGAAGCTTCCCTGGTCATTTCAACATCGA
TAAGCTTAATGTCCTTCCTATTCTGTGAGTCCAGAAGCTTTCTGATGTCATCGGAGCCTTGACAGCTTAGAACCATCCCCTGCGGA
AGAGCACCTATAACTGACGAGGTCAACCCGGGTTGCGCATTGAAGAGGTCGGCAAGATCCATGCCGTGTGAGTACTTGGAATCTTG
CTTGAATTGTTTTTGATCAACGGGTTCCCTGTAAAAGTGTATGAACTGCCCGTTCTGTGGTTGGAAAATTGCTATTTCCACTGGAT
CATTAAATCTACCCTCAATGTCAATCCATGTAGGAGCGTTGGGGTCAATTCCTCCCATGAGGTCTTTTAAAAGCATTGTCTGGCTG
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TGTTGTGTTTTCCCATGCTCTCCCCACAATCGATGTTCTACAAGCTATGTATGGCCATCCTTCACCTGAAAGGCAAACTTTATAGA
GGATGTTTTCATAAGGGTTCCTGTCCCCAACTTGGTCTGAAACAAACATGTTGAGTTTTCTCTTGGCCCCGAGAACTGCCTTCAAG
AGGTCCTCGCTGTTGCTTGGCTTGATCAAAATTGACTCTAACATGTTACCCCCATCCAACAGGGCTGCCCCTGCCTTCACGGCAGC
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TGTGACTGTTTGGCCATACAAGCCATAGTTAGACTTGGCATTGTGCCAAATTGATTGTTCAAAAGTGATGAGTCTTTCACATCCCA
AACTCTTACCACACCACTTGCACCCTGCTGAGGCTTTCTCATCCCAACTATCTGTAGGATCTGAGATCTTTGGTCTAGTTGCTGTG
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AGAGACATCAGTTCTTCTGCACTGAGCCTCCCCACTTTCAAAACATTCTTCTTTGATGTTGACTTTAAATCCACAAGAGAATGTAC
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AGAAGTCCAACCCATTCAGAAGGTTGGTTGCATCCTTAATGACAGCAGCCTTCACATCTGATGTGAAGCTCTGCAATTCTCTTCTC
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AATGCCTAGGATCCACTGTGCG
(SEQ ID NO: 21)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源：1-7228 区段=L
LCMV Armstrong L-区段

CGCACCGGGGATCCTAGGCGTTTAGTTGCGCTGTTTGGTTGCACAACTTTCTTCGTGAGGCTGTCAGAAGTGGACCTGGCTGATAG
CGATGGGTCAAGGCAAGTCCAGAGAGGAGAAAGGCACCAATAGTACAAACAGGGCCGAAATCCTACCAGATACCACCTATCTTGGC
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TCTGCTGTCAGTATCCGACAGGTGTCCTCTTTGTAAATATCCATTACCAACCAGATTGAAGATATCAACAGCCCCAAGCTCTCCAC
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CACAGCACCCAACACAGAACACGCACACACACACACACACACCCACACGCACGCGCCCCCACCACCGGGGGGCGCCCCCCCCCG
GGGGGCGGCCCCCCGGGAGCCCGGGCGGAGCCCCACGGAGATGCCCATCAGTCGATGTCCTCGGCCACCGACCCGCCCAGCCAATC
GTCGCAGGACCTCCCCTTGAGTCTAAACCTGCCCCCCACTGTTTCATACATCAAAGTGCTCCTAGATTTGCTAAAACAAAGTCTGC
AATCCTTAAAGGCGAACCAGTCTGGCAAAAGCGACAGTGGAATCAGCAGAATAGATCTGTCTATACATAGTTCCTGGAGGATTACA
CTTATCTCTGAACCCAACAAATGTTCACCAGTTCTGAATCGATGCAGGAAGAGGTTCCCAAGGACATCACTAATCTTTTCATAGCC
CTCAAGTCCTGCTAGAAAGACTTTCATGTCCTTGGTCTCCAGCTTCACAATGATATTTTGGACAAGGTTTCTTCCTTCAAAAAGGG
CACCCATCTTTACAGTCAGTGGCACAGGCTCCCACTCAGGTCCAACTCTCTCAAAGTCAATAGATCTAATCCCATCCAGTATTCTT
TTGGAGCCCAACAACTCAAGCTCAAGAGAATCACCAAGTATCAAGGGATCTTCCATGTAATCCTCAAACTCTTCAGATCTGATATC
AAAGACACCATCGTTCACCTTGAAGACAGAGTCTGTCCTCAGTAAGTGGAGGCATTCATCCAACATTCTTCTATCTATCTCACCCT
TAAAGAGGTGAGAGCATGATAAAAGTTCAGCCACACCTGGATTCTGTAATTGGCACCTAACCAAGAATATCAATGAAAATTTCCTT
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AATGATTGAAAGGGGCCCAGTGCCTCAGCACCATCTTCAGATGGCATCATTTCTTTATGAGGGAACCATGAAAAATTGCCTAATGT
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CTAGGCTGTTTAGCTTCTTCTCTCCTTTGAAAATTAAAGTGCCGTTGTTAAATGAAGACACCATTAGGCTAAAGGCTTCCAGATTA
ACACCTGGAGTTGTATGCTGACAGTCAATTTCTTTACTAGTGAATCTCTTCATTTGCTCATAGAACACACATTCTTCCTCAGGAGT
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TGTCAGGGGTCTCCTTTGTGATCAAATGACACAGGTATGACACATTCAACATAAATTTAAATTTTGCACTCAACAACACCTTCTCA
CCAGTACCAAAAATAGTTTTTATTAGGAATCTAAGCAGCTTATACACCACCTTCTCAGCAGGTGTGATCAGATCCTCCCTCAACTT
ATCCATTAATGATGTAGATGAGAAATCTGACACTATTGCCATCACCAAATATCTGACACTCTGTACCTGCTTTTGATTTCTCTTTG

图38(续)

TTGGGTTGGTGAGCATTAGCAACAATAGGGTCCTCAGTGCAACCTCAATGTCGGTGAGACAGTCTTTCAAATCAGGACATGATCTA
ATCCATGAAATCATGATGTCTATCATATTGTATAAGACCTCATCTGAAAAAATTGGTAAAAAGAACCTTTTAGGATCTGCATAGAA
GGAAATTAAATGACCATCCGGGCCTTGTATGGAGTAGCACCTTGAAGATTCTCCAGTCTTCTGGTATAATAGGTGGTATTCTTCAG
AGTCCAGTTTTATTACTTGGCAAAACACTTCTTTGCATTCTACCACTTGATATCTCACAGACCCTATTTGATTTTGCCTTAGTCTA
GCAACTGAGCTAGTTTTCATACTGTTTGTTAAGGCCAGACAAACAGATGATAATCTTCTCAGGCTCTGTATGTTCTTCAGCTGCTC
TGTGCTGGGTTGGAAATTGTAATCTTCAAACTTCGTATAATACATTATCGGGTGAGCTCCAATTTTCATAAAGTTCTCAAATTCAG
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ATTTTTGCAATGAACTCACTAATAGACGCCCTAAACAATTCCTCAAAAGACACCTTTCTAAACACCTTTGACTTTTTTCTATTCCT
CAAAAGTCTAATGAACTCCTCTTTAGTGCTGTGAAAGCTTACCAGCCTATCATTCACACTACTATAGCAACAACCCACCCAGTGTT
TATCATTTTTTAACCCTTTGAATTTCGACTGTTTTATCAATGAGGAAAGACACAAAACATCCAGATTTAACAACTGTCTCCTTCTA
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CAAGGTTTTCATAGAGCTCAGAGAATTCCTTGATCAAGCCTTCAGGGTTTACTTTCTGAAAGTTTCTCTTTAATTTCCCACTTTCT
AAATCTCTTCTAAACCTGCTGAAAAGAGAGTTTATTCCAAAAACCACATCATCACAGCTCATGTTGGGGTTGATGCCTTCGTGGCA
CATCCTCATAATTTCATCATTATGAGTTGACCTCGCATCTTTCAGAATTTTCATAGAGTCCATACCGGAGCGCTTGTCGATAGTAG
TCTTCAGGGACTCACAGAGTCTAAAATATTCAGACTCTTCAAAGACTTTCTCATTTTGGTTAGAATACTCCAAAAGTTTGAATAAA
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CCAGACTCCACCAAAATTGTTTCCACAGACTTATCGTCGTGGTTGTGTGTGCAGCCACTCTTGTCTGCACTGTCTATTTCAATGCA
GCGTGACAGCAACTTGAGTCCCTCAATCAGAACCATTCTGGGTTCCCTTTGTCCCAGAAAGTTGAGTTTCTGCCTTGACAACCTCT
CATCCTGTTCTATATAGTTTAAACATAACTCTCTCAATTCTGAGATGATTTCATCCATTGCGCATCAAAAAGCCTAGGATCCTCGG
TGCG
(SEQ ID NO: 22)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源：1-3376 区段=S
蛋白：前糖蛋白多蛋白 GP 复合物
基因：GPC
LCMV Armstrong GPC

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ATGGGTCAGATTGTGACAATGTTTGAGGCTCTGCCTCACATCATCGATGAGGTGATCAACATTGTCATTATTGTGCTTATCGTGAT
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GCATGTACGGTCTTAAGGGACCCGACATTTACAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATATGTCACATCTGAACCTG
ACCATGCCCAACGCATGTTCAGCCAACAACTCCCACCATTACATCAGTATGGGGACTTCTGGACTAGAATTGACCTTCACCAATGA
TTCCATCATCAGTCACAACTTTTGCAATCTGACCTCTGCCTTCAATAAAAAGACCTTTGACCACACACTCATGAGTATAGTTTCGA
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TACAAAATAGAACCTGGGAAAACCACTGCACATATGCAGGTCCTTTTGGGATGTCCAGGATTCTCCTTTCCCAAGAGAAGACTAAG
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CAAATGGATGATTCTTGCTGCAGAGCTTAAGTGTTTCGGGAACACAGCAGTTGCGAAATGCAATGTAAATCATGATGAAGAATTCT
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AGACCCACTTCAGTGATCAAATCGAACAGGAAGCCGATAACATGATTACAGAGATGTTGAGGAAGGATTACATAAAGAGGCAGGGG
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TGCCTGGTGTAAAAACCGTCTGGAAAAGACGCTGA
(SEQ ID NO: 23)
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翻译=LCMV Armstrong GPC

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MGQIVTMFEALPHIIDEVINIVIIVLIVITGIKAVYNFATCGIFALISFLLLAGRSCGMYGLKGPDIYKGVYQFKSVEFDMSHLNL
TMPNACSANNSHHYISMGTSGLELTFTNDSIISHNFCNLTSAFNKKTFDHTLMSIVSSLHLSIRGNSNYKAVSCDFNNGITIQYNL
TFSNAQSAQSQCRTFRGRVLDMFRTAFGGKYMRSGWGWTGSDGKTTWCSQTSYQYLIIQNRTWENHCTYAGPFGMSRILLSQEKTK
FFTRRLAGTFTWTLSDSSGVENPGGYCLTKWMILAAELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSKFKEDVESALHLFK
TTVNSLISDQLLMRNHLRDLMGVPYCNYSKFWYLEHAKTGETSVPKCWLVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQG
STPLALMDLLMFSTSAYLVSIFLHLVKIPTHRHIKGGSCPKPHRLTNKGICSCGAFKVPGVKTVWKRR
(SEQ ID NO: 24)
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图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源: 1-3376 区段=S
蛋白: 核蛋白
基因: NP
LCMV Armstrong NP

ATGTCCTTGTCTAAGGAAGTTAAGAGCTTCCAATGGACGCAAGCATTGAGAAGAGAATTGCAGAGCTTCACATCAGATGTGAAGGC
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AGAGAGATGACAAAGACCTACAGAGACTCAGAAGTCTCAACCAGACTGTACATTCTCTTGTGGATTTAAAGTCAACATCAAAGAAG
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ACATGACCTAATTTTTAGAGGCCCAAATGTTGTGACACTCTAA
(SEQ ID NO: 25)

翻译=LCMV Armstrong NP

MSLSKEVKSFQWTQALRRELQSFTSDVKAAVIKDATNLLNGLDFSEVSNVQRIMRKEKRDDKDLQRLRSLNQTVHSLVDLKSTSKK
NVLKVGRLSAEELMSLAADLEKLKAKIMRSERPQASGVYMGNLTTQQLDQRSQILQIVGMRKPQQGASGVVRVWDVKDSSLLNNQF
GTMPSLTMACMAKQSQTPLNDVVQALTDLGLLYTVKYPNLNDLERLKDKHPVLGVITEQQSSINISGYNFSLGAAVKAGAALLDGG
NMLESILIKPSNSEDLLKAVLGAKRKLNMFVSDQVGDRNPYENILYKVCLSGEGWPYIACRTSIVGRAWENTTIDLTSEKPAVNSP
RPAPGAAGPPQVGLSYSQTMLLKDLMGGIDPNAPTWIDIEGRFNDPVEIAIFQPQNGQFIHFYREPVDQKQFKQDSKYSHGMDLAD
LFNAQPGLTSSVIGALPQGMVLSCQGSDDIRKLLDSQNRKDIKLIDVEMTREASREYEDKVWDKYGWLCKMHTGIVRDKKKKEITP
HCALMDCIIFESASKARLPDLKTVHNILPHDLIFRGPNVVTL
(SEQ ID NO: 26)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源: 1-7228 区段=L
蛋白: 环指蛋白 Z
基因: ZP
LCMV Armstrong ZP

ATGGGTCAAGGCAAGTCCAGAGAGGAGAAAGGCACCAATAGTACAAACAGGGCCGAAATCCTACCAGATACCACCTATCTTGGCCC
TTTAAGCTGCAAATCTTGCTGGCAGAAATTTGACAGCTTGGTAAGATGCCATGACCACTACCTTTGCAGGCACTGTTTAAACCTTC
TGCTGTCAGTATCCGACAGGTGTCCTCTTTGTAAATATCCATTACCAACCAGATTGAAGATATCAACAGCCCCAAGCTCTCCACCT
CCCTACGAAGAGTAA
(SEQ ID NO: 27)

翻译=LCMV Armstrong ZP

MGQGKSREEKGTNSTNRAEILPDTTYLGPLSCKSCWQKFDSLVRCHDHYLCRHCLNLLLSVSDRCPLCKYPLPTRLKISTAPSSPP
PYEE
(SEQ ID NO: 28)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株 Armstrong 53b
来源：1-7228 区段=L
蛋白：RNA 指导的 RNA 聚合酶 L
基因：LP
LCMV Armstrong LP

ATGGATGAAATCATCTCAGAATTGAGAGAGTTATGTTTAAACTATATAGAACAGGATGAGAGGTTGTCAAGGCAGAAACTCAACTT
TCTGGGACAAAGGGAACCCAGAATGGTTCTGATTGAGGGACTCAAGTTGCTGTCACGCTGCATTGAAATAGACAGTGCAGACAAGA
GTGGCTGCACACACAACCACGACGATAAGTCTGTGGAAACAATTTTGGTGGAGTCTGGAATTGTATGCCCAGGACTACCACTTATC
ATTCCTGATGGTTACAAGCTGATAGACAATTCTCTCATTCTTCTTGAGTGTTTTGTTAGGAGCACTCCAGCCAGTTTTGAGAAGAA
ATTTATAGAGGACACTAACAAATTGGCATGCATCAGGGAAGACCTTGCTGTTGCGGGTGTCACATTAGTTCCAATAGTAGATGGTC
GTTGTGATTATGATAATAGTTTTATGCCAGAGTGGGCAAACTTCAAATTTAGAGACCTTTTATTCAAACTTTTGGAGTATTCTAAC
CAAAATGAGAAAGTCTTTGAAGAGTCTGAATATTTTAGACTCTGTGAGTCCCTGAAGACTACTATCGACAAGCGCTCCGGTATGGA
CTCTATGAAAATTCTGAAAGATGCGAGGTCAACTCATAATGATGAAATTATGAGGATGTGCCACGAAGGCATCAACCCCAACATGA
GCTGTGATGATGTGGTTTTTGGAATAAACTCTCTTTTCAGCAGGTTTAGAAGAGATTTAGAAAGTGGGAAATTAAAGAGAAACTTT
CAGAAAGTAAACCCTGAAGGCTTGATCAAGGAATTCTCTGAGCTCTATGAAAACCTTGCTGATAGTGATGATATCTTAACATTAAG
CAGGGAGGCAGTGGAATCCTGTCCTTTGATGAGATTCATAACTGCAGAGACCCATGGGCACGAAAGGGGAAGTGAGACTAGCACTG
AATATGAGAGGCTCCTCTCTATGTTAAACAAAGTCAAGAGTTTGAAACTGTTGAATACTAGAAGGAGACAGTTGTTAAATCTGGAT
GTTTTGTGTCTTTCCTCATTGATAAAACAGTCGAAATTCAAAGGGTTAAAAAATGATAAACACTGGGTGGGTTGTTGCTATAGTAG
TGTGAATGATAGGCTGGTAAGCTTTCACAGCACTAAAGAGGAGTTCATTAGACTTTTGAGGAATAGAAAAAAGTCAAAGGTGTTTA
GAAAGGTGTCTTTTGAGGAATTGTTTAGGGCGTCTATTAGTGAGTTCATTGCAAAAATTCAAAAATGCCTGTTAGTGGTGGGACTG
AGTTTCGAGCATTACGGACTGTCTGAACACCTTGAGCAAGAATGCCACATACCATTCACTGAATTTGAGAACTTTATGAAAATTGG
AGCTCACCCGATAATGTATTATACGAAGTTTGAAGATTACAATTTCCAACCCAGCACAGAGCAGCTGAAGAACATACAGAGCCTGA
GAAGATTATCATCTGTTTGTCTGGCCTTAACAAACAGTATGAAAACTAGCTCAGTTGCTAGACTAAGGCAAAATCAAATAGGGTCT
GTGAGATATCAAGTGGTAGAATGCAAAGAAGTGTTTTGCCAAGTAATAAAACTGGACTCTGAAGAATACCACCTATTATACCAGAA
GACTGGAGAATCTTCAAGGTGCTACTCCATACAAGGCCCGGATGGTCATTTAATTTCCTTCTATGCAGATCCTAAAAGGTTCTTTT
TACCAATTTTTTCAGATGAGGTCTTATACAATATGATAGACATCATGATTTCATGGATTAGATCATGTCCTGATTTGAAAGACTGT
CTCACCGACATTGAGGTTGCACTGAGGACCCTATTGTTGCTAATGCTCACCAACCCAACAAAGAGAAATCAAAAGCAGGTACAGAG
TGTCAGATATTTGGTGATGGCAATAGTGTCAGATTTCTCATCTACATCATTAATGGATAAGTTGAGGGAGGATCTGATCACACCTG
CTGAGAAGGTGGTGTATAAGCTGCTTAGATTCCTAATAAAAACTATTTTTGGTACTGGTGAGAAGGTGTTGTTGAGTGCAAAATTT
AAATTTATGTTGAATGTGTCATACCTGTGTCATTTGATCACAAAGGAGACCCCTGACAGGCTAACAGATCAGATAAAATGTTTTGA
AAAGTTCTTTGAGCCCAAAAGTCAATTTGGTTTTTTTGTCAACCCCAAGGAAGCAATCACTCCTGAGGAAGAATGTGTGTTCTATG
AGCAAATGAAGAGATTCACTAGTAAAGAAATTGACTGTCAGCATACAACTCCAGGTGTTAATCTGGAAGCCTTTAGCCTAATGGTG
TCTTCATTTAACAACGGCACTTTAATTTTCAAAGGAGAGAAGAAGCTAAACAGCCTAGATCCCATGACTAACTCTGGATGTGCGAC
AGCATTAGATCTTGCTAGTAACAAAAGTGTGGTGGTTAATAAGCATCTAAATGGAGAACGACTTCTGGAATATGACTTTAACAAAT
TGCTTGTTAGTGCTGTGAGTCAAATTACGGAGAGTTTCGTAAGAAAACAAAAGTATAAGTTGAGCCACTCAGACTATGAATATAAA
GTTTCCAAGTTAGTCTCTAGATTGGTCATCGGTTCCAAGGGAGAAGAGACAGGGAGATCGGAAGACAACCTGGCAGAAATATGTTT
TGATGGAGAAGAAGAGACAAGCTTCTTCAAAAGTCTCGAAGAAAAGGTCAACACCACAATAGCACGGTACAGAAGAGGTAGGAGGG
CCAATGACAAAGGAGATGGAGAAAAACTTACAAATACAAAAGGACTACATCATTTACAGCTTATTCTAACAGGGAAGATGGCTCAC
TTAAGAAAAGTTATCTTGTCAGAAATATCTTTCCATTTAGTAGAAGACTTTGACCCATCATGTCTAACCAATGATGACATGAAATT
TATCTGTGAGGCTGTTGAGGGTTCCACAGAGCTGTCACCTTTGTATTTCACCTCAGTCATTAAAGATCAGTGTGGCCTCGATGAGA
TGGCAAAAAACCTTTGTAGAAAGTTCTTTTCTGAGAATGATTGGTTTTCTTGCATGAAGATGATTCTGTTGCAAATGAATGCAAAT
GCGTACTCAGGGAAATACAGGCATATGCAAAGGCAAGGCTTGAATTTCAAATTTGACTGGGACAAACTGGAAGAAGACGTGAGAAT
CAGTGAGAGGGAAAGTAATTCTGAGTCCCTTAGTAAAGCTCTGTCGTTGACAAAATGTATGAGTGCTGCTTTGAAAAATCTGTGCT
TCTACTCAGAAGAATCACCAACATCATACACCTCAGTAGGTCCTGACTCTGGAAGGCTGAAATTTGCACTATCTTATAAAGAGCAG
GTTGGGGGAAATAGAGAACTCTATATTGGAGATTTGAGGACAAAAATGTTCACAAGGTTAATAGAAGATTATTTTGAGTCTTTTTC
AAGTTTCTTTTCAGGCTCCTGTTTAAACAATGATAAGGAATTTGAAAATGCAATCTTGTCAATGACTATCAATGTGCGGGAAGGGT
TCTTAAACTATAGTATGGATCACAGCAAATGGGGACCAATGATGTGCCCATTTTTGTTCTTAATGTTTCTACAAAATCTCAAACTA
GGTGATGACCAGTATGTGCGTTCCGGGAAAGATCATGTTAGCACTTTGTTAACTTGGCACATGCATAAGCTTGTCGAGGTCCCCTT
TCCTGTTGTGAATGCAATGATGAAATCATATGTCAAGTCGAAGCTAAAACTTCTCAGGGGTTCAGAAACAACTGTTACTGAGAGAA
TTTTCAGACAATATTTTGAAATGGGGATAGTGCCATCCCATATATCCAGCCTTATTGATATGGGGCAGGGAATCTTGCATAATGCT
TCTGACTTCTATGGTTTGCTTAGCGAGAGGTTCATCAACTACTGCATTGGTGTTATCTTTGGCGAAAGACCAGAGGCTTACACATC
AAGTGATGATCAGATCACTTTATTTGATAGGAGGCTGAGTGACCTGGTTGTAAGTGATCCGGAGGAAGTCCTTGTCCTGTTGGAAT
TCCAATCTCATCTGAGCGGCTTGTTAAACAAATTTATCAGCCCAAAAAGTGTGGCTGGGAGGTTCGCTGCAGAATTTAAATCTAGA
TTCTATGTATGGGGGGAGGAAGTCCCTCTTCTCACAAAGTTTGTATCTGCAGCGCTACACAATGTCAAGTGTAAAGAGCCACATCA
ACTTTGTGAAACAATAGATACAATTGCAGATCAAGCCATCGCAAATGGCGTCCCAGTCTCCCTAGTTAATAGTATCCAAAGGAGAA
CACTGGACCTCCTAAAGTATGCCAATTTCCCTTTGGATCCATTTCTACTGAATACCAACACTGATGTGAAAGATTGGCTGGATGGT
TCTAGAGGTTACAGAATACAAAGACTCATTGAGGAACTGTGTCCTAATGAAACAAAGGTTGTAAGAAAGCTTGTAAGGAAACTGCA
TCATAAGCTCAAAAATGGTGAATTTAATGAAGAATTTTTCTTAGACCTATTTAACAGAGATAAAAAGGAGGCCATTCTTCAATTGG
GAGACCTCCTCGGTCTTGAAGAAGATCTGAATCAGTTAGCAGATGTTAACTGGTTGAATTTGAATGAAATGTTCCCATTAAGGATG
GTTTTAAGACAAAAGGTGGTTTATCCATCAGTGATGACTTTCCAAGAGGAAAGAATCCCATCATTGATCAAGACACTCCAGAACAA
ACTTTGTAGTAAATTCACAAGGGGTGCACAGAAGCTGCTGTCAGAAGCAATCAACAAGTCAGCTTTCCAGAGTTGTATCTCATCTG
GCTTTATAGGCCTTTGCAAAACTCTAGGAAGCAGGTGTGTGAGAAACAAAAATAGGGAAAATCTGTATATCAAAAAGCTGCTTGAG
GATCTAACCACAGATGATCATGTGACAAGAGTTTGCAATCGGGATGGTATAACGCTGTACATTTGTGACAAACAGTCTCATCCAGA
AGCCCACCGTGATCATATATGCCTTTTAAGGCCTCTTCTTTGGGACTACATTTGTATTTCATTGAGCAACTCTTTTGAGTTGGGTG
TTTGGGTCCTAGCAGAACCGACCAAAGGGAAGAATAACAGTGAGAACCTAACTCTTAAGCACTTAAACCCATGTGATTATGTAGCA

图38(续)

AGAAAGCCTGAGAGCTCAAGGCTACTGGAGGACAAAGTGAATTTGAACCAAGTGATTCAATCTGTGAGGCGGTTATATCCCAAGAT
CTTTGAGGATCAGCTTCTTCCATTTATGTCTGACATGAGCTCAAAAAACATGAGGTGGAGTCCCAGAATTAAATTCCTTGACCTCT
GTGTTTTAATTGATATTAACTCAGAATCCTTGTCACTCATTTCTCATGTTGTTAAGTGGAAAAGGGATGAACATTACACTGTTCTG
TTTTCTGACCTTGCCAATTCTCATCAGCGATCTGACTCCAGTCTGGTTGATGAATTTGTTGTTAGCACGAGGGATGTCTGCAAGAA
CTTCTTAAAACAGGTGTATTTTGAATCATTTGTTCGAGAATTTGTTGCAACAACCAGGACATTAGGCAATTTTTCATGGTTCCCTC
ATAAAGAAATGATGCCATCTGAAGATGGTGCTGAGGCACTGGGCCCCTTTCAATCATTTGTCTCAAAGGTGGTGAACAAAAATGTG
GAGAGGCCTATGTTTAGGAATGATTTGCAGTTTGGTTTTGGGTGGTTCTCTTACCGAATGGGAGATGTTGTGTGTAATGCTGCCAT
GTTGATTAGGCAGGGCCTGACAAACCCAAAGGCATTTAAATCCTTAAAGGATCTGTGGGACTACATGCTCAACTACACAAAAGGGG
TATTGGAGTTTTCAATTTCAGTGGACTTTACGCACAATCAGAATAATACTGACTGTTTAAGGAAATTTTCATTGATATTCTTGGTT
AGGTGCCAATTACAGAATCCAGGTGTGGCTGAACTTTTATCATGCTCTCACCTCTTTAAGGGTGAGATAGATAGAAGAATGTTGGA
TGAATGCCTCCACTTACTGAGGACAGACTCTGTCTTCAAGGTGAACGATGGTGTCTTTGATATCAGATCTGAAGAGTTTGAGGATT
ACATGGAAGATCCCTTGATACTTGGTGATTCTCTTGAGCTTGAGTTGTTGGGCTCCAAAAGAATACTGGATGGGATTAGATCTATT
GACTTTGAGAGAGTTGGACCTGAGTGGGAGCCTGTGCCACTGACTGTAAAGATGGGTGCCCTTTTTGAAGGAAGAAACCTTGTCCA
AAATATCATTGTGAAGCTGGAGACCAAGGACATGAAAGTCTTTCTAGCAGGACTTGAGGGCTATGAAAAGATTAGTGATGTCCTTG
GGAACCTCTTCCTGCATCGATTCAGAACTGGTGAACATTTGTTGGGTTCAGAGATAAGTGTAATCCTCCAGGAACTATGTATAGAC
AGATCTATTCTGCTGATTCCACTGTCGCTTTTGCCAGACTGGTTCGCCTTTAAGGATTGCAGACTTTGTTTTAGCAAATCTAGGAG
CACTTTGATGTATGAAACAGTGGGGGGCAGGTTTAGACTCAAGGGGAGGTCCTGCGACGATTGGCTGGGCGGGTCGGTGGCCGAGG
ACATCGACTGA
(SEQ ID NO: 29)

翻译=LCMV Armstrong LP

MDEIISELRELCLNYIEQDERLSRQKLNFLGQREPRMVLIEGLKLLSRCIEIDSADKSGCTHNHDDKSVETILVESGIVCPGLPLI
IPDGYKLIDNSLILLECFVRSTPASFEKKFIEDTNKLACIREDLAVAGVTLVPIVDGRCDYDNSFMPEWANFKFRDLLFKLLEYSN
QNEKVFEESEYFRLCESLKTTIDKRSGMDSMKILKDARSTHNDEIMRMCHEGINPNMSCDDVVFGINSLFSRFRRDLESGKLKRNF
QKVNPEGLIKEFSELYENLADSDDILTLSREAVESCPLMRFITAETHGHERGSETSTEYERLLSMLNKVKSLKLLNTRRRQLLNLD
VLCLSSLIKQSKFKGLKNDKHWVGCCYSSVNDRLVSFHSTKEEFIRLLRNRKKSKVFRKVSFEELFRASISEFIAKIQKCLLVVGL
SFEHYGLSEHLEQECHIPFTEFENFMKIGAHPIMYYTKFEDYNFQPSTEQLKNIQSLRRLSSVCLALTNSMKTSSVARLRQNQIGS
VRYQVVECKEVFCQVIKLDSEEYHLLYQKTGESSRCYSIQGPDGHLISFYADPKRFFLPIFSDEVLYNMIDIMISWIRSCPDLKDC
LTDIEVALRTLLLLMLTNPTKRNQKQVQSVRYLVMAIVSDFSSTSLMDKLREDLITPAEKVVYKLLRFLIKTIFGTGEKVLLSAKF
KFMLNVSYLCHLITKETPDRLTDQIKCFEKFFEPKSQFGFFVNPKEAITPEEECVFYEQMKRFTSKEIDCQHTTPGVNLEAFSLMV
SSFNNGTLIFKGEKKLNSLDPMTNSGCATALDLASNKSVVVNKHLNGERLLEYDFNKLLVSAVSQITESFVRKQKYKLSHSDYEYK
VSKLVSRLVIGSKGEETGRSEDNLAEICFDGEEETSFFKSLEEKVNTTIARYRRGRRANDKGDGEKLTNTKGLHHLQLILTGKMAH
LRKVILSEISFHLVEDFDPSCLTNDDMKFICEAVEGSTELSPLYFTSVIKDQCGLDEMAKNLCRKFFSENDWFSCMKMILLQMNAN
AYSGKYRHMQRQGLNFKFDWDKLEEDVRISERESNSESLSKALSLTKCMSAALKNLCFYSEESPTSYTSVGPDSGRLKFALSYKEQ
VGGNRELYIGDLRTKMFTRLIEDYFESFSSFFSGSCLNNDKEFENAILSMTINVREGFLNYSMDHSKWGPMMCPFLFLMFLQNLKL
GDDQYVRSGKDHVSTLLTWHMHKLVEVPFPVVNAMMKSYVKSKLKLLRGSETTVTERIFRQYFEMGIVPSHISSLIDMGQGILHNA
SDFYGLLSERFINYCIGVIFGERPEAYTSSDDQITLFDRRLSDLVVSDPEEVLVLLEFQSHLSGLLNKFISPKSVAGRFAAEFKSR
FYVWGEEVPLLTKFVSAALHNVKCKEPHQLCETIDTIADQAIANGVPVSLVNSIQRRTLDLLKYANFPLDPFLLNTNTDVKDWLDG
SRGYRIQRLIEELCPNETKVVRKLVRKLHHKLKNGEFNEEFFLDLFNRDKKEAILQLGDLLGLEEDLNQLADVNWLNLNEMFPLRM
VLRQKVVYPSVMTFQEERIPSLIKTLQNKLCSKFTRGAQKLLSEAINKSAFQSCISSGFIGLCKTLGSRCVRNKNRENLYIKKLLE
DLTTDDHVTRVCNRDGITLYICDKQSHPEAHRDHICLLRPLLWDYICISLSNSFELGVWVLAEPTKGKNNSENLTLKHLNPCDYVA
RKPESSRLLEDKVNLNQVIQSVRRLYPKIFEDQLLPFMSDMSSKNMRWSPRIKFLDLCVLIDINSESLSLISHVVKWKRDEHYTVL
FSDLANSHQRSDSSLVDEFVVSTRDVCKNFLKQVYFESFVREFVATTRTLGNFSWFPHKEMMPSEDGAEALGPFQSFVSKVVNKNV
ERPMFRNDLQFGFGWFSYRMGDVVCNAAMLIRQGLTNPKAFKSLKDLWDYMLNYTKGVLEFSISVDFTHNQNNTDCLRKFSLIFLV
RCQLQNPGVAELLSCSHLFKGEIDRRMLDECLHLLRTDSVFKVNDGVFDIRSEEFEDYMEDPLILGDSLELELLGSKRILDGIRSI
DFERVGPEWEPVPLTVKMGALFEGRNLVQNIIVKLETKDMKVFLAGLEGYEKISDVLGNLFLHRFRTGEHLLGSEISVILQELCID
RSILLIPLSLLPDWFAFKDCRLCFSKSRSTLMYETVGGRFRLKGRSCDDWLGGSVAEDID
(SEQ ID NO: 30)

图38(续)

D. 淋巴细胞性脉络丛脑膜炎病毒 (LCMV)毒株克隆 13

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源: 1-3377 区段=S
LCMV 克隆 13 S-区段

GCGCACCGGGGATCCTAGGCTTTTTGGATTGCGCTTTCCTCTAGATCAACTGGGTGTCAGGCCCTATCCTACAGAAGGATGGGTCA
GATTGTGACAATGTTTGAGGCTCTGCCTCACATCATCGATGAGGTGATCAACATTGTCATTATTGTGCTTATCGTGATCACGGGTA
TCAAGGCTGTCTACAATTTTGCCACCTGTGGGATATTCGCATTGATCAGTTTCCTACTTCTGGCTGGCAGGTCCTGTGGCATGTAC
GGTCTTAAGGGACCCGACATTTACAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATATGTCACATCTGAACCTGACCATGCC
CAACGCATGTTCAGCCAACAACTCCCACCATTACATCAGTATGGGGACTTCTGGACTAGAATTGACCTTCACCAATGATTCCATCA
TCAGTCACAACTTTTGCAATCTGACCTCTGCCTTCAACAAAAAGACCTTTGACCACACACTCATGAGTATAGTTTCGAGCCTACAC
CTCAGTATCAGAGGGAACTCCAACTATAAGGCAGTATCCTGCGACTTCAACAATGGCATAACCATCCAATACAACTTGACATTCTC
AGATGCACAAAGTGCTCAGAGCCAGTGTAGAACCTTCAGAGGTAGAGTCCTAGATATGTTTAGAACTGCCTTCGGGGGGAAATACA
TGAGGAGTGGCTGGGGCTGGACAGGCTCAGATGGCAAGACCACCTGGTGTAGCCAGACGAGTTACCAATACCTGATTATACAAAAT
AGAACCTGGGAAAACCACTGCACATATGCAGGTCCTTTTGGGATGTCCAGGATTCTCCTTTCCCAAGAGAAGACTAAGTTCCTCAC
TAGGAGACTAGCGGGCACATTCACCTGGACTTTGTCAGACTCTTCAGGGGTGGAGAATCCAGGTGGTTATTGCCTGACCAAATGGA
TGATTCTTGCTGCAGAGCTTAAGTGTTTCGGGAACACAGCAGTTGCGAAATGCAATGTAAATCATGATGAAGAATTCTGTGACATG
CTGCGACTAATTGACTACAACAAGGCTGCTTTGAGTAAGTTCAAAGAGGACGTAGAATCTGCCTTGCACTTATTCAAAACAACAGT
GAATTCTTTGATTTCAGATCAACTACTGATGAGGAACCACTTGAGAGATCTGATGGGGGTGCCATATTGCAATTACTCAAAGTTTT
GGTACCTAGAACATGCAAAGACCGGCGAAACTAGTGTCCCCAAGTGCTGGCTTGTCACCAATGGTTCTTACTTAAATGAGACCCAC
TTCAGTGACCAAATCGAACAGGAAGCCGATAACATGATTACAGAGATGTTGAGGAAGGATTACATAAAGAGGCAGGGGAGTACCCC
CCTAGCATTGATGGACCTTCTGATGTTTTCCACATCTGCATATCTAGTCAGCATCTTCCTGCACCTTGTCAAAATACCAACACACA
GGCACATAAAAGGTGGCTCATGTCCAAAGCCACACCGATTAACCAACAAAGGAATTTGTAGTTGTGGTGCATTTAAGGTGCCTGGT
GTAAAAACCGTCTGGAAAAGACGCTGAAGAACAGCGCCTCCCTGACTCTCCACCTCGAAAGAGGTGGAGAGTCAGGGAGGCCCAGA
GGGTCTTAGAGTGTCACAACATTTGGGCCTCTAAAAATTAGGTCATGTGGCAGAATGTTGTGAACAGTTTTCAGATCTGGGAGCCT
TGCTTTGGAGGCGCTTTCAAAAATGATGCAGTCCATGAGTGCACAGTGCGGGGTGATCTCTTTCTTCTTTTTGTCCCTTACTATTC
CAGTATGCATCTTACACAACCAGCCATATTTGTCCCACACTTTGTCTTCATACTCCCTCGAAGCTTCCCTGGTCATTTCAACATCG
ATAAGCTTAATGTCCTTCCTATTCTGTGAGTCCAGAAGCTTTCTGATGTCATCGGAGCCTTGACAGCTTAGAACCATCCCCTGCGG
AAGAGCACCTATAACTGACGAGGTCAACCCGGGTTGCGCATTGAAGAGGTCGGCAAGATCCATGCCGTGTGAGTACTTGGAATCTT
GCTTGAATTGTTTTTGATCAACGGGTTCCCTGTAAAAGTGTATGAACTGCCCGTTCTGTGGTTGGAAAATTGCTATTTCCACTGGA
TCATTAAATCTACCCTCAATGTCAATCCATGTAGGAGCGTTGGGGTCAATTCCTCCCATGAGGTCTTTTAAAAGCATTGTCTGGCT
GTAGCTTAAGCCCACCTGAGGTGGACCTGCTGCTCCAGGCGCTGGCCTGGGTGAATTGACTGCAGGTTTCTCGCTTGTGAGATCAA
TTGTTGTGTTTTCCCATGCTCTCCCCACAATCGATGTTCTACAAGCTATGTATGGCCATCCTTCACCTGAAAGGCAAACTTTATAG
AGGATGTTTTCATAAGGGTTCCTGTCCCCAACTTGGTCTGAAACAAACATGTTGAGTTTTCTCTTGGCCCCGAGAACTGCCTTCAA
GAGGTCCTCGCTGTTGCTTGGCTTGATCAAAATTGACTCTAACATGTTACCCCCATCCAACAGGGCTGCCCCTGCCTTCACGGCAG
CACCAAGACTAAAGTTATAGCCAGAAATGTTGATGCTGGACTGCTGTTCAGTGATGACCCCCAGAACTGGGTGCTTGTCTTTCAGC
CTTTCAAGATCATTAAGATTTGGATACTTGACTGTGTAAAGCAAGCCAAGGTCTGTGAGCGCTTGTACAACGTCATTGAGCGGAGT
CTGTGACTGTTTGGCCATACAAGCCATAGTTAGACTTGGCATTGTGCCAAATTGATTGTTCAAAAGTGATGAGTCTTTCACATCCC
AAACTCTTACCACACCACTTGCACCCTGCTGAGGCTTTCTCATCCCAACTATCTGTAGGATCTGAGATCTTTGGTCTAGTTGCTGT
GTTGTTAAGTTCCCCATATATACCCCTGAAGCCTGGGGCCTTTCAGACCTCATGATCTTGGCCTTCAGCTTCTCAAGGTCAGCCGC
AAGAGACATCAGTTCTTCTGCACTGAGCCTCCCCACTTTCAAAACATTCTTCTTTGATGTTGACTTTAAATCCACAAGAGAATGTA
CAGTCTGGTTGAGACTTCTGAGTCTCTGTAGGTCTTTGTCATCTCTCTTTTCCTTCCTCATGATCCTCTGAACATTGCTGACCTCA
GAGAAGTCCAACCCATTCAGAAGGTTGGTTGCATCCTTAATGACAGCAGCCTTCACATCTGATGTGAAGCTCTGCAATTCTCTTCT
CAATGCTTGCGTCCATTGGAAGCTCTTAACTTCCTTAGACAAGGACATCTTGTTGCTCAATGGTTTCTCAAGACAAATGCGCAATC
AAATGCCTAGGATCCACTGTGCG
(SEQ ID NO: 31)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源: 1-7229 区段=L
LCMV 克隆 13 L-区段

GCGCACCGGGGATCCTAGGCGTTTAGTTGCGCTGTTTGGTTGCACAACTTTCTTCGTGAGGCTGTCAGAAGTGGACCTGGCTGATA
GCGATGGGTCAAGGCAAGTCCAGAGAGGAGAAAGGCACCAATAGTACAAACAGGGCCGAAATCCTACCAGATACCACCTATCTTGG
CCCTTTAAGCTGCAAATCTTGCTGGCAGAAATTTGACAGCTTGGTAAGATGCCATGACCACTACCTTTGCAGGCACTGTTTAAACC
TTCTGCTGTCAGTATCCGACAGGTGTCCTCTTTGTAAATATCCATTACCAACCAGATTGAAGATATCAACAGCCCCAAGCTCTCCA
CCTCCCTACGAAGAGTAACACCGTCCGGCCCCGGCCCCGACAAACAGCCCAGCACAAGGGAACCGCACGTCACCCAACGCACACAG
ACACAGCACCCAACACAGAACACGCACACACACACACACACACCCACACGCACGCGCCCCCACCACCGGGGGGCGCCCCCCCCC
GGGGGGCGGCCCCCCGGGAGCCCGGGCGGAGCCCCACGGAGATGCCCATCAGTCGATGTCCTCGGCCACCGACCCGCCCAGCCAAT
CGTCGCAGGACCTCCCCTTGAGTCTAAACCTGCCCCCCACTGTTTCATACATCAAAGTGCTCCTAGATTTGCTAAAACAAAGTCTG
CAATCCTTAAAGGCGAACCAGTCTGGCAAAAGCGACAGTGGAATCAGCAGAATAGATCTGTCTATACATAGTTCCTGGAGGATTAC
ACTTATCTCTGAACCCAACAAATGTTCACCAGTTCTGAATCGATGCAGGAAGAGGTTCCCAAGGACATCACTAATCTTTTCATAGC
CCTCAAGTCCTGCTAGAAAGACTTTCATGTCCTTGGTCTCCAGCTTCACAATGATATTTTGGACAAGGTTTCTTCCTTCAAAAAGG
GCACCCATCTTTACAGTCAGTGGCACAGGCTCCCACTCAGGTCCAACTCTCTCAAAGTCAATAGATCTAATCCCATCCAGTATTCT
TTTGGAGCCCAACAACTCAAGCTCAAGAGAATCACCAAGTATCAAGGGATCTTCCATGTAATCCTCAAACTCTTCAGATCTGATAT
CAAAGACACCATCGTTCACCTTGAAGACAGAGTCTGTCCTCAGTAAGTGGAGGCATTCATCCAACATTCTTCTATCTATCTCACCC
TTAAAGAGGTGAGAGCATGATAAAAGTTCAGCCACACCTGGATTCTGTAATTGGCACCTAACCAAGAATATCAATGAAAATTTCCT
TAAACAGTCAGTATTATTCTGATTGTGCGTAAAGTCCACTGAAATTGAAAACTCCAATACCCCTTTTGTGTAGTTGAGCATGTAGT
CCCACAGATCCTTTAAGGATTTAAATGCCTTTGGGTTTGTCAGGCCCTGCCTAATCAACATGGCAGCATTACACACAACATCTCCC
ATTCGGTAAGAGAACCACCCAAAACCAAACTGCAAATCATTCCTAAACATAGGCCTCTCCACATTTTTGTTCACCACCTTTGAGAC
AAATGATTGAAAGGGGCCCAGTGCCTCAGCACCATCTTCAGATGGCATCATTTCTTTATGAGGGAACCATGAAAAATTGCCTAATG
TCCTGGTTGTTGCAACAAATTCTCGAACAAATGATTCAAAATACACCTGTTTTAAGAAGTTCTTGCAGACATCCCTCGTGCTAACA
ACAAATTCATCAACCAGACTGGAGTCAGATCGCTGATGAGAATTGGCAAGGTCAGAAAACAGAACAGTGTAATGTTCATCCCTTTT
CCACTTAACAACATGAGAAATGAGTGACAAGGATTCTGAGTTAATATCAATTAAAACACAGAGGTCAAGGAATTTAATTCTGGGAC
TCCACCTCATGTTTTTTGAGCTCATGTCAGACATAAATGGAAGAAGCTGATCCTCAAAGATCTTGGGATATAGCCGCCTCACAGAT
TGAATCACTTGGTTCAAATTCACTTTGTCCTCCAGTAGCCTTGAGCTCTCAGGCTTTCTTGCTACATAATCACATGGGTTTAAGTG
CTTAAGAGTTAGGTTCTCACTGTTATTCTTCCCTTTGGTCGGTTCTGCTAGGACCCAAACACCCAACTCAAAAGAGTTGCTCAATG
AAATACAAATGTAGTCCCAAAGAAGAGGCCTTAAAAGGCATATATGATCACGGTGGGCTTCTGGATGAGACTGTTTGTCACAAATG
TACAGCGTTATACCATCCCGATTGCAAACTCTTGTCACATGATCATCTGTGGTTAGATCCTCAAGCAGCTTTTTGATATACAGATT
TTCCCTATTTTTGTTTCTCACACACCTGCTTCCTAGAGTTTTGCAAAGGCCTATAAAGCCAGATGAGATACAACTCTGGAAAGCTG
ACTTGTTGATTGCTTCTGACAGCAGCTTCTGTGCACCCCTTGTGAATTTACTACAAAGTTTGTTCTGGAGTGTCTTGATCAATGAT
GGGATTCTTTCCTCTTGGAAAGTCATCACTGATGGATAAACCACCTTTTGTCTTAAAACCATCCTTAATGGGAACATTTCATTCAA
ATTCAACCAGTTAACATCTGCTAACTGATTCAGATCTTCTTCAAGACCGAGGAGGTCTCCCAATTGAAGAATGGCCTCCTTTTTAT
CTCTGTTAAATAGGTCTAAGAAAAATTCTTCATTAAATTCACCATTTTTGAGCTTATGATGCAGTTTCCTTACAAGCTTTCTTACA
ACCTTTGTTTCATTAGGACACAGTTCCTCAATGAGTCTTTGTATTCTGTAACCTCTAGAACCATCCAGCCAATCTTTCACATCAGT
GTTGGTATTCAGTAGAAATGGATCCAAAGGGAAATTGGCATACTTTAGGAGGTCCAGTGTTCTCCTTTGGATACTATTAACTAGGG
AGACTGGGACGCCATTTGCGATGGCTTGATCTGCAATTGTATCTATTGTTTCACAAAGTTGATGTGGCTCTTTACACTTGACATTG
TGTAGCGCTGCAGATACAAACTTTGTGAGAAGAGGGACTTCCTCCCCCCATACATAGAATCTAGATTTAAATTCTGCAGCGAACCT
CCCAGCCACACTTTTTGGGCTGATAAATTTGTTTAACAAGCCGCTCAGATGAGATTGGAATTCCAACAGGACAAGGACTTCCTCCG
GATCACTTACAACCAGGTCACTCAGCCTCCTATCAAATAAAGTGATCTGATCATCACTTGATGTGTAAGCCTCTGGTCTTTCGCCA
AAGATAACACCAATGCAGTAGTTGATGAACCTCTCGCTAAGCAAACCATAGAAGTCAGAAGCATTATGCAAGATTCCCTGCCCCAT
ATCAATAAGGCTGGATATATGGGATGGCACTATCCCCATTTCAAAATATTGTCTGAAAATTCTCTCAGTAACAGTTGTTTCTGAAC
CCCTGAGAAGTTTTAGCTTCGACTTGACATATGATTTCATCATTGCATTCACAACAGGAAAGGGGACCTCGACAAGCTTATGCATG
TGCCAAGTTAACAAAGTGCTAACATGATCTTTCCCGGAACGCACATACTGGTCATCACCTAGTTTGAGATTTTGTAGAAACATTAA
GAACAAAAATGGGCACATCATTGGTCCCCATTTGCTGTGATCCATACTATAGTTTAAGAACCCTTCCCGCACATTGATAGTCATTG
ACAAGATTGCATTTTCAAATTCCTTATCATTGTTTAAACAGGAGCCTGAAAAGAAACTTGAAAAAGACTCAAAATAATCTTCTATT
AACCTTGTGAACATTTTTGTCCTCAAATCTCCAATATAGAGTTCTCTATTTCCCCCAACCTGCTCTTTATAAGATAGTGCAAATTT
CAGCCTTCCAGAGTCAGGACCTACTGAGGTGTATGATGTTGGTGATTCTTCTGAGTAGAAGCACAGATTTTTCAAAGCAGCACTCA
TACATTGTGTCAACGACAGAGCTTTACTAAGGGACTCAGAATTACTTTCCCTCTCACTGATTCTCACGTCTTCTTCCAGTTTGTCC
CAGTCAAATTTGAAATTCAAGCCTTGCCTTTGCATATGCCTGTATTTCCCTGAGTACGCATTTGCATTCATTTGCAACAGAATCAT
CTTCATGCAAGAAAACCAATCATTCTCAGAAAAGAACTTTCTACAAAGGTTTTTTGCCATCTCATCGAGGCCACACTGATCTTTAA
TGACTGAGGTGAAATACAAAGGTGACAGCTCTGTGGAACCCTCAACAGCCTCACAGATAAATTTCATGTCATCATTGGTTAGACAT
GATGGGTCAAAGTCTTCTACTAAATGGAAAGATATTTCTGACAAGATAACTTTTCTTAAGTGAGCCATCTTCCCTGTTAGAATAAG
CTGTAAATGATGTAGTCCTTTTGTATTTGTAAGTTTTTCTCCATCTCCTTTGTCATTGGCCCTCCTACCTCTTCTGTACCGTGCTA
TTGTGGTGTTGACCTTTTCTTCGAGACTTTTGAAGAAGCTTGTCTCTTCTTCTCCATCAAAACATATTTCTGCCAGGTTGTCTTCC
GATCTCCCTGTCTCTTCTCCCTTGGAACCGATGACCAATCTAGAGACTAACTTGGAAACTTTATATTCATAGTCTGAGTGGCTCAA
CTTATACTTTTGTTTTCTTACGAAACTCTCCGTAATTTGACTCACAGCACTAACAAGCAATTTGTTAAAGTCATATTCCAGAAGTC
GTTCTCCATTTAGATGCTTATTAACCACCACACTTTTGTTACTAGCAAGATCTAATGCTGTCGCACATCCAGAGTTAGTCATGGGA
TCTAGGCTGTTTAGCTTCTTCTCTCCTTTGAAAATTAAAGTGCCGTTGTTAAATGAAGACACCATTAGGCTAAAGGCTTCCAGATT
AACACCTGGAGTTGTATGCTGACAGTCAATTTCTTTACTAGTGAATCTCTTCATTTGCTCATAGAACACACATTCTTCCTCAGGAG
TGATTGCTTCCTTGGGGTTGACAAAAAAACCAAATTGACTTTTGGGCTCAAAGAACTTTTCAAAACATTTTATCTGATCTGTTAGC
CTGTCAGGGGTCTCCTTTGTGATCAAATGACACAGGTATGACACATTCAACATAAATTTAAATTTTGCACTCAACAACACCTTCTC
ACCAGTACCAAAAATAGTTTTTATTAGGAATCTAAGCAGCTTATACACCACCTTCTCAGCAGGTGTGATCAGATCCTCCCTCAACT
TATCCATTAATGATGTAGATGAAAAATCTGACACTATTGCCATCACCAAATATCTGACACTCTGTACCTGCTTTTGATTTCTCTTT

图38(续)

GTTGGGTTGGTGAGCATTAGCAACAATAGGGTCCTCAGTGCAACCTCAATGTCGGTGAGACAGTCTTTCAAATCAGGACATGATCT
AATCCATGAAATCATGATGTCTATCATATTGTATAAGACCTCATCTGAAAAAATTGGTAAAAAGAACCTTTTAGGATCTGCATAGA
AGGAAATTAAATGACCATCCGGGCCTTGTATGGAGTAGCACCTTGAAGATTCTCCAGTCTTCTGGTATAATAGGTGGTATTCTTCA
GAGTCCAGTTTTATTACTTGGCAAAACACTTCTTTGCATTCTACCACTTGATATCTCACAGACCCTATTTGATTTTGCCTTAGTCT
AGCAACTGAGCTAGTTTTCATACTGTTTGTTAAGGCCAGACAAACAGATGATAATCTTCTCAGGCTCTGTATGTTCTTCAGCTGCT
CTGTGCTGGGTTGGAAATTGTAATCTTCAAACTTCGTATAATACATTATCGGGTGAGCTCCAATTTTCATAAAGTTCTCAAATTCA
GTGAATGGTATGTGGCATTCTTGCTCAAGGTGTTCAGACAGTCCGTAATGCTCGAAACTCAGTCCCACCACTAACAGGCATTTTTG
AATTTTTGCAATGAACTCACTAATAGATGCCCTAAACAATTCCTCAAAAGACACCTTTCTAAACACCTTTGACTTTTTTCTATTCC
TCAAAAGTCTAATGAACTCCTCTTTAGTGCTGTGAAAGCTTACCAGCCTATCATTCACACTACTATAGCAACAACCCACCCAGTGT
TTATCATTTTTTAACCCTTTGAATTTCGACTGTTTTATCAATGAGGAAAGACACAAAACATCCAGATTTAACAACTGTCTCCTTCT
AGTATTCAACAGTTTCAAACTCTTGACTTTGTTTAACATAGAGAGGAGCCTCTCATATTCAGTGCTAGTCTCACTTCCCCTTTCGT
GCCCATGGGTCTCTGCAGTTATGAATCTCATCAAAGGACAGGATTCGACTGCCTCCCTGCTTAATGTTAAGATATCATCACTATCA
GCAAGGTTTTCATAGAGCTCAGAGAATTCCTTGATCAAGCCTTCAGGGTTTACTTTCTGAAAGTTTCTCTTTAATTTCCCACTTTC
TAAATCTCTTCTAAACCTGCTGAAAAGAGAGTTTATTCCAAAAACCACATCATCACAGCTCATGTTGGGGTTGATGCCTTCGTGGC
ACATCCTCATAATTTCATCATTGTGAGTTGACCTCGCATCTTTCAGAATTTTCATAGAGTCCATACCGGAGCGCTTGTCGATAGTA
GTCTTCAGGGACTCACAGAGTCTAAAATATTCAGACTCTTCAAAGACTTTCTCATTTTGGTTAGAATACTCCAAAAGTTTGAATAA
AAGGTCTCTAAATTTGAAGTTTGCCCACTCTGGCATAAAACTATTATCATAATCACAACGACCATCTACTATTGGAACTAATGTGA
CACCCGCAACAGCAAGGTCTTCCCTGATGCATGCCAATTTGTTAGTGTCCTCTATAAATTTCTTCTCAAAACTGGCTGGAGTGCTC
CTAACAAAACACTCAAGAAGAATGAGAGAATTGTCTATCAGCTTGTAACCATCAGGAATGATAAGTGGTAGTCCTGGGCATACAAT
TCCAGACTCCACCAAAATTGTTTCCACAGACTTATCGTCGTGGTTGTGTGTGCAGCCACTCTTGTCTGCACTGTCTATTTCAATGC
AGCGTGACAGCAACTTGAGTCCCTCAATCAGAACCATTCTGGGTTCCCTTTGTCCCAGAAAGTTGAGTTTCTGCCTTGACAACCTC
TCATCCTGTTCTATATAGTTTAAACATAACTCTCTCAATTCTGAGATGATTTCATCCATTGCGCATCAAAAAGCCTAGGATCCTCG
GTGCG
(SEQ ID NO: 32)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源: 1-3377 区段=S
蛋白: 前糖蛋白多蛋白 GP 复合物
基因: GPC
LCMV 克隆 13 GPC

ATGGGTCAGATTGTGACAATGTTTGAGGCTCTGCCTCACATCATCGATGAGGTGATCAACATTGTCATTATTGTGCTTATCGTGAT
CACGGGTATCAAGGCTGTCTACAATTTTGCCACCTGTGGGATATTCGCATTGATCAGTTTCCTACTTCTGGCTGGCAGGTCCTGTG
GCATGTACGGTCTTAAGGGACCCGACATTTACAAAGGAGTTTACCAATTTAAGTCAGTGGAGTTTGATATGTCACATCTGAACCTG
ACCATGCCCAACGCATGTTCAGCCAACAACTCCCACCATTACATCAGTATGGGGACTTCTGGACTAGAATTGACCTTCACCAATGA
TTCCATCATCAGTCACAACTTTTGCAATCTGACCTCTGCCTTCAACAAAAAGACCTTTGACCACACACTCATGAGTATAGTTTCGA
GCCTACACCTCAGTATCAGAGGGAACTCCAACTATAAGGCAGTATCCTGCGACTTCAACAATGGCATAACCATCCAATACAACTTG
ACATTCTCAGATGCACAAAGTGCTCAGAGCCAGTGTAGAACCTTCAGAGGTAGAGTCCTAGATATGTTTAGAACTGCCTTCGGGGG
GAAATACATGAGGAGTGGCTGGGGCTGGACAGGCTCAGATGGCAAGACCACCTGGTGTAGCCAGACGAGTTACCAATACCTGATTA
TACAAAATAGAACCTGGGAAAACCACTGCACATATGCAGGTCCTTTTGGGATGTCCAGGATTCTCCTTTCCCAAGAGAAGACTAAG
TTCCTCACTAGGAGACTAGCGGGCACATTCACCTGGACTTTGTCAGACTCTTCAGGGGTGGAGAATCCAGGTGGTTATTGCCTGAC
CAAATGGATGATTCTTGCTGCAGAGCTTAAGTGTTTCGGGAACACAGCAGTTGCGAAATGCAATGTAAATCATGATGAAGAATTCT
GTGACATGCTGCGACTAATTGACTACAACAAGGCTGCTTTGAGTAAGTTCAAAGAGGACGTAGAATCTGCCTTGCACTTATTCAAA
ACAACAGTGAATTCTTTGATTTCAGATCAACTACTGATGAGGAACCACTTGAGAGATCTGATGGGGGTGCCATATTGCAATTACTC
AAAGTTTTGGTACCTAGAACATGCAAAGACCGGCGAAACTAGTGTCCCCAAGTGCTGGCTTGTCACCAATGGTTCTTACTTAAATG
AGACCCACTTCAGTGACCAAATCGAACAGGAAGCCGATAACATGATTACAGAGATGTTGAGGAAGGATTACATAAAGAGGCAGGGG
AGTACCCCCCTAGCATTGATGGACCTTCTGATGTTTTCCACATCTGCATATCTAGTCAGCATCTTCCTGCACCTTGTCAAAATACC
AACACACAGGCACATAAAAGGTGGCTCATGTCCAAAGCCACACCGATTAACCAACAAAGGAATTTGTAGTTGTGGTGCATTTAAGG
TGCCTGGTGTAAAAACCGTCTGGAAAAGACGCTGA
(SEQ ID NO: 33)

翻译=LCMV 克隆 13 GPC

MGQIVTMFEALPHIIDEVINIVIIVLIVITGIKAVYNFATCGIFALISFLLLAGRSCGMYGLKGPDIYKGVYQFKSVEFDMSHLNL
TMPNACSANNSHHYISMGTSGLELTFTNDSIISHNFCNLTSAFNKKTFDHTLMSIVSSLHLSIRGNSNYKAVSCDFNNGITIQYNL
TFSDAQSAQSQCRTFRGRVLDMFRTAFGGKYMRSGWGWTGSDGKTTWCSQTSYQYLIIQNRTWENHCTYAGPFGMSRILLSQEKTK
FLTRRLAGTFTWTLSDSSGVENPGGYCLTKWMILAAELKCFGNTAVAKCNVNHDEEFCDMLRLIDYNKAALSKFKEDVESALHLFK
TTVNSLISDQLLMRNHLRDLMGVPYCNYSKFWYLEHAKTGETSVPKCWLVTNGSYLNETHFSDQIEQEADNMITEMLRKDYIKRQG
STPLALMDLLMFSTSAYLVSIFLHLVKIPTHRHIKGGSCPKPHRLTNKGICSCGAFKVPGVKTVWKRR
(SEQ ID NO: 34)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源: 1-3377 区段=S
蛋白: 核蛋白
基因: NP
LCMV 克隆 13 NP

ATGTCCTTGTCTAAGGAAGTTAAGAGCTTCCAATGGACGCAAGCATTGAGAAGAGAATTGCAGAGCTTCACATCAGATGTGAAGGC
TGCTGTCATTAAGGATGCAACCAACCTTCTGAATGGGTTGGACTTCTCTGAGGTCAGCAATGTTCAGAGGATCATGAGGAAGGAAA
AGAGAGATGACAAAGACCTACAGAGACTCAGAAGTCTCAACCAGACTGTACATTCTCTTGTGGATTTAAAGTCAACATCAAAGAAG
AATGTTTTGAAAGTGGGGAGGCTCAGTGCAGAAGAACTGATGTCTCTTGCGGCTGACCTTGAGAAGCTGAAGGCCAAGATCATGAG
GTCTGAAAGGCCCCAGGCTTCAGGGGTATATATGGGGAACTTAACAACACAGCAACTAGACCAAAGATCTCAGATCCTACAGATAG
TTGGGATGAGAAAGCCTCAGCAGGGTGCAAGTGGTGTGGTAAGAGTTTGGGATGTGAAAGACTCATCACTTTTGAACAATCAATTT
GGCACAATGCCAAGTCTAACTATGGCTTGTATGGCCAAACAGTCACAGACTCCGCTCAATGACGTTGTACAAGCGCTCACAGACCT
TGGCTTGCTTTACACAGTCAAGTATCCAAATCTTAATGATCTTGAAAGGCTGAAAGACAAGCACCCAGTTCTGGGGGTCATCACTG
AACAGCAGTCCAGCATCAACATTTCTGGCTATAACTTTAGTCTTGGTGCTGCCGTGAAGGCAGGGGCAGCCCTGTTGGATGGGGGT
AACATGTTAGAGTCAATTTTGATCAAGCCAAGCAACAGCGAGGACCTCTTGAAGGCAGTTCTCGGGGCCAAGAGAAAACTCAACAT
GTTTGTTTCAGACCAAGTTGGGGACAGGAACCCTTATGAAAACATCCTCTATAAAGTTTGCCTTTCAGGTGAAGGATGGCCATACA
TAGCTTGTAGAACATCGATTGTGGGGAGAGCATGGGAAAACACAACAATTGATCTCACAAGCGAGAAACCTGCAGTCAATTCACCC
AGGCCAGCGCCTGGAGCAGCAGGTCCACCTCAGGTGGGCTTAAGCTACAGCCAGACAATGCTTTTAAAAGACCTCATGGGAGGAAT
TGACCCCAACGCTCCTACATGGATTGACATTGAGGGTAGATTTAATGATCCAGTGGAAATAGCAATTTTCCAACCACAGAACGGGC
AGTTCATACACTTTTACAGGGAACCCGTTGATCAAAAACAATTCAAGCAAGATTCCAAGTACTCACACGGCATGGATCTTGCCGAC
CTCTTCAATGCGCAACCCGGGTTGACCTCGTCAGTTATAGGTGCTCTTCCGCAGGGGATGGTTCTAAGCTGTCAAGGCTCCGATGA
CATCAGAAAGCTTCTGGACTCACAGAATAGGAAGGACATTAAGCTTATCGATGTTGAAATGACCAGGGAAGCTTCGAGGGAGTATG
AAGACAAAGTGTGGGACAAATATGGCTGGTTGTGTAAGATGCATACTGGAATAGTAAGGGACAAAAAGAAGAAAGAGATCACCCCG
CACTGTGCACTCATGGACTGCATCATTTTTGAAAGCGCCTCCAAAGCAAGGCTCCCAGATCTGAAAACTGTTCACAACATTCTGCC
ACATGACCTAATTTTTAGAGGCCCAAATGTTGTGACACTCTAA
(SEQ ID NO: 35)

翻译=LCMV Armstrong NP

MSLSKEVKSFQWTQALRRELQSFTSDVKAAVIKDATNLLNGLDFSEVSNVQRIMRKEKRDDKDLQRLRSLNQTVHSLVDLKSTSKK
NVLKVGRLSAEELMSLAADLEKLKAKIMRSERPQASGVYMGNLTTQQLDQRSQILQIVGMRKPQQGASGVVRVWDVKDSSLLNNQF
GTMPSLTMACMAKQSQTPLNDVVQALTDLGLLYTVKYPNLNDLERLKDKHPVLGVITEQQSSINISGYNFSLGAAVKAGAALLDGG
NMLESILIKPSNSEDLLKAVLGAKRKLNMFVSDQVGDRNPYENILYKVCLSGEGWPYIACRTSIVGRAWENTTIDLTSEKPAVNSP
RPAPGAAGPPQVGLSYSQTMLLKDLMGGIDPNAPTWIDIEGRFNDPVEIAIFQPQNGQFIHFYREPVDQKQFKQDSKYSHGMDLAD
LFNAQPGLTSSVIGALPQGMVLSCQGSDDIRKLLDSQNRKDIKLIDVEMTREASREYEDKVWDKYGWLCKMHTGIVRDKKKKEITP
HCALMDCIIFESASKARLPDLKTVHNILPHDLIFRGPNVVTL
(SEQ ID NO: 36)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源: 1-7229 区段=L
蛋白: 环指蛋白 Z
基因: ZP
LCMV 克隆 13 ZP

ATGGGTCAAGGCAAGTCCAGAGAGGAGAAAGGCACCAATAGTACAAACAGGGCCGAAATCCTACCAGATACCACCTATCTTGGCCC
TTTAAGCTGCAAATCTTGCTGGCAGAAATTTGACAGCTTGGTAAGATGCCATGACCACTACCTTTGCAGGCACTGTTTAAACCTTC
TGCTGTCAGTATCCGACAGGTGTCCTCTTTGTAAATATCCATTACCAACCAGATTGAAGATATCAACAGCCCCAAGCTCTCCACCT
CCCTACGAAGAGTAA
(SEQ ID NO: 37)

翻译=LCMV 克隆 13 ZP

MGQGKSREEKGTNSTNRAEILPDTTYLGPLSCKSCWQKFDSLVRCHDHYLCRHCLNLLLSVSDRCPLCKYPLPTRLKISTAPSSPP
PYEE
(SEQ ID NO: 38)

图38(续)

淋巴细胞性脉络丛脑膜炎病毒(LCMV)毒株克隆 13
来源：1-7229 区段=L
蛋白：RNA 指导的 RNA 聚合酶 L
基因：LP
LCMV 克隆 13 LP

ATGGATGAAATCATCTCAGAATTGAGAGAGTTATGTTTAAACTATATAGAACAGGATGAGAGGTTGTCAAGGCAGAAACTCAACTT
TCTGGGACAAAGGGAACCCAGAATGGTTCTGATTGAGGGACTCAAGTTGCTGTCACGCTGCATTGAAATAGACAGTGCAGACAAGA
GTGGCTGCACACACAACCACGACGATAAGTCTGTGGAAACAATTTTGGTGGAGTCTGGAATTGTATGCCCAGGACTACCACTTATC
ATTCCTGATGGTTACAAGCTGATAGACAATTCTCTCATTCTTCTTGAGTGTTTTGTTAGGAGCACTCCAGCCAGTTTTGAGAAGAA
ATTTATAGAGGACACTAACAAATTGGCATGCATCAGGGAAGACCTTGCTGTTGCGGGTGTCACATTAGTTCCAATAGTAGATGGTC
GTTGTGATTATGATAATAGTTTTATGCCAGAGTGGGCAAACTTCAAATTTAGAGACCTTTTATTCAAACTTTTGGAGTATTCTAAC
CAAAATGAGAAAGTCTTTGAAGAGTCTGAATATTTTAGACTCTGTGAGTCCCTGAAGACTACTATCGACAAGCGCTCCGGTATGGA
CTCTATGAAAATTCTGAAAGATGCGAGGTCAACTCACAATGATGAAATTATGAGGATGTGCCACGAAGGCATCAACCCCAACATGA
GCTGTGATGATGTGGTTTTTGGAATAAACTCTCTTTTCAGCAGGTTTAGAAGAGATTTAGAAAGTGGGAAATTAAAGAGAAACTTT
CAGAAAGTAAACCCTGAAGGCTTGATCAAGGAATTCTCTGAGCTCTATGAAAACCTTGCTGATAGTGATGATATCTTAACATTAAG
CAGGGAGGCAGTCGAATCCTGTCCTTTGATGAGATTCATAACTGCAGAGACCCATGGGCACGAAAGGGGAAGTGAGACTAGCACTG
AATATGAGAGGCTCCTCTCTATGTTAAACAAAGTCAAGAGTTTGAAACTGTTGAATACTAGAAGGAGACAGTTGTTAAATCTGGAT
GTTTTGTGTCTTTCCTCATTGATAAAACAGTCGAAATTCAAAGGGTTAAAAAATGATAAACACTGGGTGGGTTGTTGCTATAGTAG
TGTGAATGATAGGCTGGTAAGCTTTCACAGCACTAAAGAGGAGTTCATTAGACTTTTGAGGAATAGAAAAAAGTCAAAGGTGTTTA
GAAAGGTGTCTTTTGAGGAATTGTTTAGGGCATCTATTAGTGAGTTCATTGCAAAAATTCAAAAATGCCTGTTAGTGGTGGGACTG
AGTTTCGAGCATTACGGACTGTCTGAACACCTTGAGCAAGAATGCCACATACCATTCACTGAATTTGAGAACTTTATGAAAATTGG
AGCTCACCCGATAATGTATTATACGAAGTTTGAAGATTACAATTTCCAACCCAGCACAGAGCAGCTGAAGAACATACAGAGCCTGA
GAAGATTATCATCTGTTTGTCTGGCCTTAACAAACAGTATGAAAACTAGCTCAGTTGCTAGACTAAGGCAAAATCAAATAGGGTCT
GTGAGATATCAAGTGGTAGAATGCAAAGAAGTGTTTTGCCAAGTAATAAAACTGGACTCTGAAGAATACCACCTATTATACCAGAA
GACTGGAGAATCTTCAAGGTGCTACTCCATACAAGGCCCGGATGGTCATTTAATTTCCTTCTATGCAGATCCTAAAAGGTTCTTTT
TACCAATTTTTTCAGATGAGGTCTTATACAATATGATAGACATCATGATTTCATGGATTAGATCATGTCCTGATTTGAAAGACTGT
CTCACCGACATTGAGGTTGCACTGAGGACCCTATTGTTGCTAATGCTCACCAACCCAACAAAGAGAAATCAAAAGCAGGTACAGAG
TGTCAGATATTTGGTGATGGCAATAGTGTCAGATTTTTCATCTACATCATTAATGGATAAGTTGAGGGAGGATCTGATCACACCTG
CTGAGAAGGTGGTGTATAAGCTGCTTAGATTCCTAATAAAAACTATTTTTGGTACTGGTGAGAAGGTGTTGTTGAGTGCAAAATTT
AAATTTATGTTGAATGTGTCATACCTGTGTCATTTGATCACAAAGGAGACCCCTGACAGGCTAACAGATCAGATAAAATGTTTTGA
AAAGTTCTTTGAGCCCAAAAGTCAATTTGGTTTTTTTGTCAACCCCAAGGAAGCAATCACTCCTGAGGAAGAATGTGTGTTCTATG
AGCAAATGAAGAGATTCACTAGTAAAGAAATTGACTGTCAGCATACAACTCCAGGTGTTAATCTGGAAGCCTTTAGCCTAATGGTG
TCTTCATTTAACAACGGCACTTTAATTTTCAAAGGAGAGAAGAAGCTAAACAGCCTAGATCCCATGACTAACTCTGGATGTGCGAC
AGCATTAGATCTTGCTAGTAACAAAAGTGTGGTGGTTAATAAGCATCTAAATGGAGAACGACTTCTGGAATATGACTTTAACAAAT
TGCTTGTTAGTGCTGTGAGTCAAATTACGGAGAGTTTCGTAAGAAAACAAAAGTATAAGTTGAGCCACTCAGACTATGAATATAAA
GTTTCCAAGTTAGTCTCTAGATTGGTCATCGGTTCCAAGGGAGAAGAGACAGGGAGATCGGAAGACAACCTGGCAGAAATATGTTT
TGATGGAGAAGAAGAGACAAGCTTCTTCAAAAGTCTCGAAGAAAAGGTCAACACCACAATAGCACGGTACAGAAGAGGTAGGAGGG
CCAATGACAAAGGAGATGGAGAAAAACTTACAAATACAAAAGGACTACATCATTTACAGCTTATTCTAACAGGGAAGATGGCTCAC
TTAAGAAAAGTTATCTTGTCAGAAATATCTTTCCATTTAGTAGAAGACTTTGACCCATCATGTCTAACCAATGATGACATGAAATT
TATCTGTGAGGCTGTTGAGGGTTCCACAGAGCTGTCACCTTTGTATTTCACCTCAGTCATTAAAGATCAGTGTGGCCTCGATGAGA
TGGCAAAAAACCTTTGTAGAAAGTTCTTTTCTGAGAATGATTGGTTTTCTTGCATGAAGATGATTCTGTTGCAAATGAATGCAAAT
GCGTACTCAGGGAAATACAGGCATATGCAAAGGCAAGGCTTGAATTTCAAATTTGACTGGGACAAACTGGAAGAAGACGTGAGAAT
CAGTGAGAGGGAAAGTAATTCTGAGTCCCTTAGTAAAGCTCTGTCGTTGACACAATGTATGAGTGCTGCTTTGAAAAATCTGTGCT
TCTACTCAGAAGAATCACCAACATCATACACCTCAGTAGGTCCTGACTCTGGAAGGCTGAAATTTGCACTATCTTATAAAGAGCAG
GTTGGGGGAAATAGAGAACTCTATATTGGAGATTTGAGGACAAAAATGTTCACAAGGTTAATAGAAGATTATTTTGAGTCTTTTTC
AAGTTTCTTTTCAGGCTCCTGTTTAAACAATGATAAGGAATTTGAAAATGCAATCTTGTCAATGACTATCAATGTGCGGGAAGGGT
TCTTAAACTATAGTATGGATCACAGCAAATGGGGACCAATGATGTGCCCATTTTTGTTCTTAATGTTTCTACAAAATCTCAAACTA
GGTGATGACCAGTATGTGCGTTCCGGGAAAGATCATGTTAGCACTTTGTTAACTTGGCACATGCATAAGCTTGTCGAGGTCCCCTT
TCCTGTTGTGAATGCAATGATGAAATCATATGTCAAGTCGAAGCTAAAACTTCTCAGGGGTTCAGAAACAACTGTTACTGAGAGAA
TTTTCAGACAATATTTTGAAATGGGGATAGTGCCATCCCATATATCCAGCCTTATTGATATGGGGCAGGGAATCTTGCATAATGCT
TCTGACTTCTATGGTTTGCTTAGCGAGAGGTTCATCAACTACTGCATTGGTGTTATCTTTGGCGAAAGACCAGAGGCTTACACATC
AAGTGATGATCAGATCACTTTATTTGATAGGAGGCTGAGTGACCTGGTTGTAAGTGATCCGGAGGAAGTCCTTGTCCTGTTGGAAT
TCCAATCTCATCTGAGCGGCTTGTTAAACAAATTTATCAGCCCAAAAAGTGTGGCTGGGAGGTTCGCTGCAGAATTTAAATCTAGA
TTCTATGTATGGGGGGAGGAAGTCCCTCTTCTCACAAAGTTTGTATCTGCAGCGCTACACAATGTCAAGTGTAAAGAGCCACATCA
ACTTTGTGAAACAATAGATACAATTGCAGATCAAGCCATCGCAAATGGCGTCCCAGTCTCCCTAGTTAATAGTATCCAAAGGAGAA
CACTGGACCTCCTAAAGTATGCCAATTTCCCTTTGGATCCATTTCTACTGAATACCAACACTGATGTGAAAGATTGGCTGGATGGT
TCTAGAGGTTACAGAATACAAAGACTCATTGAGGAACTGTGTCCTAATGAAACAAAGGTTGTAAGAAAGCTTGTAAGGAAACTGCA
TCATAAGCTCAAAAATGGTGAATTTAATGAAGAATTTTTCTTAGACCTATTTAACAGAGATAAAAAGGAGGCCATTCTTCAATTGG
GAGACCTCCTCGGTCTTGAAGAAGATCTGAATCAGTTAGCAGATGTTAACTGGTTGAATTTGAATGAAATGTTCCCATTAAGGATG
GTTTTAAGACAAAAGGTGGTTTATCCATCAGTGATGACTTTCCAAGAGGAAAGAATCCCATCATTGATCAAGACACTCCAGAACAA
ACTTTGTAGTAAATTCACAAGGGGTGCACAGAAGCTGCTGTCAGAAGCAATCAACAAGTCAGCTTTCCAGAGTTGTATCTCATCTG
GCTTTATAGGCCTTTGCAAAACTCTAGGAAGCAGGTGTGTGAGAAACAAAAATAGGGAAAATCTGTATATCAAAAAGCTGCTTGAG
GATCTAACCACAGATGATCATGTGACAAGAGTTTGCAATCGGGATGGTATAACGCTGTACATTTGTGACAAACAGTCTCATCCAGA
AGCCCACCGTGATCATATATGCCTTTTAAGGCCTCTTCTTTGGGACTACATTTGTATTTCATTGAGCAACTCTTTTGAGTTGGGTG
TTTGGGTCCTAGCAGAACCGACCAAAGGGAAGAATAACAGTGAGAACCTAACTCTTAAGCACTTAAACCCATGTGATTATGTAGCA

图38(续)

AGAAAGCCTGAGAGCTCAAGGCTACTGGAGGACAAAGTGAATTTGAACCAAGTGATTCAATCTGTGAGGCGGCTATATCCCAAGAT
CTTTGAGGATCAGCTTCTTCCATTTATGTCTGACATGAGCTCAAAAAACATGAGGTGGAGTCCCAGAATTAAATTCCTTGACCTCT
GTGTTTTAATTGATATTAACTCAGAATCCTTGTCACTCATTTCTCATGTTGTTAAGTGGAAAAGGGATGAACATTACACTGTTCTG
TTTTCTGACCTTGCCAATTCTCATCAGCGATCTGACTCCAGTCTGGTTGATGAATTTGTTGTTAGCACGAGGGATGTCTGCAAGAA
CTTCTTAAAACAGGTGTATTTTGAATCATTTGTTCGAGAATTTGTTGCAACAACCAGGACATTAGGCAATTTTTCATGGTTCCCTC
ATAAAGAAATGATGCCATCTGAAGATGGTGCTGAGGCACTGGGCCCCTTTCAATCATTTGTCTCAAAGGTGGTGAACAAAAATGTG
GAGAGGCCTATGTTTAGGAATGATTTGCAGTTTGGTTTTGGGTGGTTCTCTTACCGAATGGGAGATGTTGTGTGTAATGCTGCCAT
GTTGATTAGGCAGGGCCTGACAAACCCAAAGGCATTTAAATCCTTAAAGGATCTGTGGGACTACATGCTCAACTACACAAAGGGGG
TATTGGAGTTTTCAATTTCAGTGGACTTTACGCACAATCAGAATAATACTGACTGTTTAAGGAAATTTTCATTGATATTCTTGGTT
AGGTGCCAATTACAGAATCCAGGTGTGGCTGAACTTTTATCATGCTCTCACCTCTTTAAGGGTGAGATAGATAGAAGAATGTTGGA
TGAATGCCTCCACTTACTGAGGACAGACTCTGTCTTCAAGGTGAACGATGGTGTCTTTGATATCAGATCTGAAGAGTTTGAGGATT
ACATGGAAGATCCCTTGATACTTGGTGATTCTCTTGAGCTTGAGTTGTTGGGCTCCAAAAGAATACTGGATGGGATTAGATCTATT
GACTTTGAGAGAGTTGGACCTGAGTGGGAGCCTGTGCCACTGACTGTAAAGATGGGTGCCCTTTTTGAAGGAAGAAACCTTGTCCA
AAATATCATTGTGAAGCTGGAGACCAAGGACATGAAAGTCTTTCTAGCAGGACTTGAGGGCTATGAAAAGATTAGTGATGTCCTTG
GGAACCTCTTCCTGCATCGATTCAGAACTGGTGAACATTTGTTGGGTTCAGAGATAAGTGTAATCCTCCAGGAACTATGTATAGAC
AGATCTATTCTGCTGATTCCACTGTCGCTTTTGCCAGACTGGTTCGCCTTTAAGGATTGCAGACTTTGTTTTAGCAAATCTAGGAG
CACTTTGATGTATGAAACAGTGGGGGGCAGGTTTAGACTCAAGGGGAGGTCCTGCGACGATTGGCTGGGCGGGTCGGTGGCCGAGG
ACATCGACTGA
(SEQ ID NO: 39)

翻译=LCMV 克隆 13 LP

MDEIISELRELCLNYIEQDERLSRQKLNFLGQREPRMVLIEGLKLLSRCIEIDSADKSGCTHNHDDKSVETILVESGIVCPGLPLI
IPDGYKLIDNSLILLECFVRSTPASFEKKFIEDTNKLACIREDLAVAGVTLVPIVDGRCDYDNSFMPEWANFKFRDLLFKLLEYSN
QNEKVFEESEYFRLCESLKTTIDKRSGMDSMKILKDARSTHNDEIMRMCHEGINPNMSCDDVVFGINSLFSRFRRDLESGKLKRNF
QKVNPEGLIKEFSELYENLADSDDILTLSREAVESCPLMRFITAETHGHERGSETSTEYERLLSMLNKVKSLKLLNTRRRQLLNLD
VLCLSSLIKQSKFKGLKNDKHWVGCCYSSVNDRLVSFHSTKEEFIRLLRNRKKSKVFRKVSFEELFRASISEFIAKIQKCLLVVGL
SFEHYGLSEHLEQECHIPFTEFENFMKIGAHPIMYYTKFEDYNFQPSTEQLKNIQSLRRLSSVCLALTNSMKTSSVARLRQNQIGS
VRYQVVECKEVFCQVIKLDSEEYHLLYQKTGESSRCYSIQGPDGHLISFYADPKRFFLPIFSDEVLYNMIDIMISWIRSCPDLKDC
LTDIEVALRTLLLLMLTNPTKRNQKQVQSVRYLVMAIVSDFSSTSLMDKLREDLITPAEKVVYKLLRFLIKTIFGTGEKVLLSAKF
KFMLNVSYLCHLITKETPDRLTDQIKCFEKFFEPKSQFGFFVNPKEAITPEEECVFYEQMKRFTSKEIDCQHTTPGVNLEAFSLMV
SSFNNGTLIFKGEKKLNSLDPMTNSGCATALDLASNKSVVVNKHLNGERLLEYDFNKLLVSAVSQITESFVRKQKYKLSHSDYEYK
VSKLVSRLVIGSKGEETGRSEDNLAEICFDGEEETSFFKSLEEKVNTTIARYRRGRRANDKGDGEKLTNTKGLHHLQLILTGKMAH
LRKVILSEISFHLVEDFDPSCLTNDDMKFICEAVEGSTELSPLYFTSVIKDQCGLDEMAKNLCRKFFSENDWFSCMKMILLQMNAN
AYSGKYRHMQRQGLNFKFDWDKLEEDVRISERESNSESLSKALSLTQCMSAALKNLCFYSEESPTSYTSVGPDSGRLKFALSYKEQ
VGGNRELYIGDLRTKMFTRLIEDYFESFSSFFSGSCLNNDKEFENAILSMTINVREGFLNYSMDHSKWGPMMCPFLFLMFLQNLKL
GDDQYVRSGKDHVSTLLTWHMHKLVEVPFPVVNAMMKSYVKSKLKLLRGSETTVTERIFRQYFEMGIVPSHISSLIDMGQGILHNA
SDFYGLLSERFINYCIGVIFGERPEAYTSSDDQITLFDRRLSDLVVSDPEEVLVLLEFQSHLSGLLNKFISPKSVAGRFAAEFKSR
FYVWGEEVPLLTKFVSAALHNVKCKEPHQLCETIDTIADQAIANGVPVSLVNSIQRRTLDLLKYANFPLDPFLLNTNTDVKDWLDG
SRGYRIQRLIEELCPNETKVVRKLVRKLHHKLKNGEFNEEFFLDLFNRDKKEAILQLGDLLGLEEDLNQLADVNWLNLNEMFPLRM
VLRQKVVYPSVMTFQEERIPSLIKTLQNKLCSKFTRGAQKLLSEAINKSAFQSCISSGFIGLCKTLGSRCVRNKNRENLYIKKLLE
DLTTDDHVTRVCNRDGITLYICDKQSHPEAHRDHICLLRPLLWDYICISLSNSFELGVWVLAEPTKGKNNSENLTLKHLNPCDYVA
RKPESSRLLEDKVNLNQVIQSVRRLYPKIFEDQLLPFMSDMSSKNMRWSPRIKFLDLCVLIDINSESLSLISHVVKWKRDEHYTVL
FSDLANSHQRSDSSLVDEFVVSTRDVCKNFLKQVYFESFVREFVATTRTLGNFSWFPHKEMMPSEDGAEALGPFQSFVSKVVNKNV
ERPMFRNDLQFGFGWFSYRMGDVVCNAAMLIRQGLTNPKAFKSLKDLWDYMLNYTKGVLEFSISVDFTHNQNNTDCLRKFSLIFLV
RCQLQNPGVAELLSCSHLFKGEIDRRMLDECLHLLRTDSVFKVNDGVFDIRSEEFEDYMEDPLILGDSLELELLGSKRILDGIRSI
DFERVGPEWEPVPLTVKMGALFEGRNLVQNIIVKLETKDMKVFLAGLEGYEKISDVLGNLFLHRFRTGEHLLGSEISVILQELCID
RSILLIPLSLLPDWFAFKDCRLCFSKSRSTLMYETVGGRFRLKGRSCDDWLGGSVAEDID
(SEQ ID NO: 40)

图38(续)