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(54)发明名称

拮抗性CD40单克隆抗体及其用途

(57)摘要

本申请提供结合CD40的抗体，包括人源化抗体。该等抗体结合CD40且不显示CD40激动剂活性。该等抗体可包含经修饰IgG1Fc域，且显示未成熟树突状细胞的最低活化。提供包含抗体的组合物，用于治疗涉及CD40活性的疾病的方法，及在制备用于治疗涉及CD40活性的疾病的药物中的用途。

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1.一种分离的抗体或其抗原结合部分,其与人类CD40特异性结合,其中所述抗体包括包含重链可变区的第一多肽部分,及包含轻链可变区的第二多肽部分,其中:

所述重链可变区包括:由SEQ ID NO:1组成的CDR1,由SEQ ID NO:2组成的CDR2,和由SEQ ID NO:3组成的CDR3;且

所述轻链可变区包括:由SEQ ID NO:7组成的CDR1,由SEQ ID NO:8组成的CDR2,及由SEQ ID NO:9组成的CDR3。

2.如权利要求1的分离的抗体或其抗原结合部分,其中所述抗体或其抗原结合部分拮抗CD40活性。

3.如权利要求1的分离的抗体或其抗原结合部分,其中所述重链可变区由SEQ ID NO:4的氨基酸序列组成,且所述轻链可变区由SEQ ID NO:10的氨基酸序列组成。

4.如权利要求1的分离的抗体或其抗原结合部分,其中所述第一多肽部分包含人类重链恒定区;且所述第二多肽部分包含人类轻链恒定区。

5.如权利要求4的分离的抗体或其抗原结合部分,其中所述人类重链恒定区为人类IgG1 Fc域,其包含Kabat位置238的突变,所述突变降低与Fc-γ-受体(FcγR)的结合,其中脯氨酸238(P238)被取代为赖氨酸,且其中所述抗体或其抗原结合部分具有降低的FcγR结合。

6.如权利要求5的分离的抗体或其抗原结合部分,其中所述Fc域包含选自以下的氨基酸序列:SEQ ID NO:22、SEQ ID NO:23、SEQ ID NO:24、SEQ ID NO:25、SEQ ID NO:26、SEQ ID NO:27、SEQ ID NO:28或SEQ ID NO:29。

7.如权利要求5的分离的抗体或其抗原结合部分,其中所述人类IgG1 Fc域包含SEQ ID NO:22或SEQ ID NO:23的氨基酸序列。

8.如权利要求1的分离的抗体或其抗原结合部分,其中

所述第一多肽部分由选自由SEQ ID NO:5、SEQ ID NO:6、SEQ ID NO:30及SEQ ID NO:31组成的组的氨基酸序列组成;

且

所述第二多肽部分由SEQ ID NO:11的氨基酸序列组成。

9.如权利要求1的分离的抗体或其抗原结合部分,其中

所述第一多肽部分由SEQ ID NO:5的氨基酸序列组成;

且

所述第二多肽部分由SEQ ID NO:11的氨基酸序列组成。

10.如权利要求1的分离的抗体或其抗原结合部分,其中所述分离的抗体或其抗原结合部分为经人源化的。

11.如权利要求1的分离的抗体或其抗原结合部分,其中所述抗原结合部分为scFv-Fc。

12.如权利要求1的抗体或其抗原结合部分,其中所述抗体或其抗原结合部分为与治疗剂连接。

13.如权利要求1的抗体或其抗原结合部分,其中所述抗体或其抗原结合部分为与具有不同于所述抗体或其抗原结合部分的结合特异性的第二功能部分连接。

14.如权利要求1的抗体或其抗原结合部分,其进一步包含额外部分。

15.如权利要求1的抗体或其抗原结合部分,其中所述重链可变区由SEQ ID NO:4的氨

基酸序列组成，且所述轻链可变区由SEQ ID NO:16的氨基酸序列组成。

16.一种药物组合物，其包含:a)如权利要求1的抗体或其抗原结合部分;和b)药学上可接受的载体。

17.如权利要求1的抗体或其抗原结合部分在制备用于治疗或预防受试者的免疫反应的药物中的用途。

18.如权利要求1的抗体或其抗原结合部分在制备用于治疗或预防受试者的自体免疫或发炎性疾病的药物中的用途。

19.如权利要求18的用途，其中所述抗体或其抗原结合部分为与免疫抑制剂、免疫调节剂及/或抗炎剂一起给予。

20.如权利要求19的用途，其中所述免疫抑制剂、免疫调节剂及/或抗炎剂为CTLA4突变体分子L104EA29Y-Ig(贝拉希普(belatacept))。

21.如权利要求18的用途，其中所述受试者患有选自由以下组成的组的疾病:艾迪生氏病(Addison's disease)、过敏、过敏性反应、僵直性脊椎炎、哮喘、动脉粥样硬化、异位性过敏、耳部自体免疫疾病、眼部自体免疫疾病、自体免疫性肝炎、自体免疫性腮腺炎、支气管哮喘、冠心病、克罗恩病(Crohn'sdisease)、糖尿病、附睾炎、肾小球肾炎、格雷夫斯病(Graves'disease)、格林兰-巴雷症候群(Guillain-Barre syndrome)、桥本病(Hashimoto's disease)、溶血性贫血、特发性血小板减少性紫癜、发炎性肠病、对重组药物的免疫反应、狼疮性肾炎、系统性红斑狼疮、多发性硬化症、重症肌无力、天疱疮、牛皮癣、风湿热、类风湿关节炎、结节病、硬皮病、休格连氏症候群(Sjogren'ssyndrome)、脊椎关节炎、甲状腺炎、移植排斥、血管炎及溃疡性结肠炎。

22.如权利要求18的用途，其中所述受试者患有休格连氏症候群。

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[0001] 相关申请的交叉引用

[0002] 本申请要求2018年11月19日提交的美国临时申请第62/769,514号的优先权,该临时申请以全文引用的方式并入本文。

[0003] 序列表

[0004] 本申请包含序列表,该序列表已经以ASCII格式电子提交且以全文引用的方式并入本文。该ASCII副本创建于2019年11月13日,名为200896-0015-00-WO-592417_SL.txt且大小为170,111字节。

技术领域

[0005] 本申请提供结合CD40的抗体。该等抗体多肽结合CD40且不显示CD40激动剂活性。该等抗体可包含经修饰IgG1 Fc域,且显示未成熟树突状细胞的最低活化。提供包含抗体的组合物,用于治疗涉及CD40活性的疾病的方法,及在制备用于治疗涉及CD40活性的疾病的药物中的用途。

背景技术

[0006] CD40为属于肿瘤坏死因子(TNF)受体超家族的共刺激分子,其存在于抗原呈递细胞(APC)上,包括树突状细胞、B细胞及巨噬细胞。当CD40结合T_H细胞上的其配位体CD154(CD40L)时,APC被活化。CD40介导的APC活化涉及多种免疫反应,包括细胞因子产生,共刺激分子(例如CD86)的上调,及增强的抗原呈递及B细胞增殖。CD40还可由内皮细胞、平滑肌细胞、成纤维细胞及上皮细胞表达。

[0007] CD40活化还涉及与例如自体免疫、移植排斥或过敏反应有关的各种非所欲的T细胞反应。控制非所欲的T细胞反应的一种策略为用拮抗性抗体靶向CD40。例如,原名为Chiron 1212的单克隆抗体HCD122(鲁卡木单抗(Lucatumumab))目前在临床试验中用于治疗某些CD40介导的发炎性疾病。参见"Study of HCD122(Lucatumumab)and Bendamustine Combination Therapy in $CD40^+$Rituximab-Refractory Follicular Lymphoma",Clinical Trials Feeds,网址为超文本传输协议:clinicaltrialsfeeds.org/clinical-trials/show/NCT01275209(最新更新于2011年1月11日)。然而,单克隆抗体可显示激动剂活性。例如,抗CD40抗体Chi220的可用性受到其弱刺激潜力的限制。参见Adams等人,"Development of a chimeric anti-CD40 monoclonal antibody that synergizes with LEA29Y to prolong islet allograft survival",J.Immunol.174:542-50(2005)。

发明内容

[0008] 在第一实例中,本申请提供与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分,及包含轻链可变区的第二多肽部分,其中:

[0009] 该重链可变区包含以下之一:(i)包含SYWMH(SEQ ID NO:1)的CDR1,包含

QINPTTGRSQYNEKFKT(SEQ ID NO:2)的CDR2,包含WGLQPFAY(SEQ ID NO:3)的CDR3;及(ii)包含SYWMH(SEQ ID NO:1)的CDR1,包含QINPSQGRSQYNEKFKT(SEQ ID NO:12)的CDR2,包含WGLQPFAY(SEQ ID NO:3)的CDR3;及

[0010] 该轻链可变区包括包含KASQDVSTAVA(SEQ ID NO:7)的CDR1,包含SASYRYT(SEQ ID NO:8)的CDR2,及包含QQHYSTPWT(SEQ ID NO:9)的CDR3。

[0011] 本申请进一步提供了与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分及包含轻链可变区的第二多肽部分,其中:

[0012] 该重链可变区包含以下之一:(i)由SYWMH(SEQ ID NO:1)组成的CDR1,由QINPTTGRSQYNEKFKT(SEQ ID NO:2)组成的CDR2,由WGLQPFAY(SEQ ID NO:3)组成的CDR3;(ii)由SYWMH(SEQ ID NO:1)组成的CDR1,由QINPSQGRSQYNEKFKT(SEQ ID NO:12)组成的CDR2,由WGLQPFAY(SEQ ID NO:3)组成的CDR3;及

[0013] 该轻链可变区包含由KASQDVSTAVA(SEQ ID NO:7)组成的CDR1,由SASYRYT(SEQ ID NO:8)组成的CDR2及由QQHYSTPWT(SEQ ID NO:9)组成的CDR3。

[0014] 本申请进一步提供与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分,及包含轻链可变区的第二多肽部分,其中:

[0015] 该重链可变区包含由SYWMH(SEQ ID NO:1)组成的CDR1,由QINPTTGRSQYNEKFKT(SEQ ID NO:2)组成的CDR2,由WGLQPFAY(SEQ ID NO:3)组成的CDR3;及

[0016] 该轻链可变区包含由KASQDVSTAVA(SEQ ID NO:7)组成的CDR1,由SASYRYT(SEQ ID NO:8)组成的CDR2,及由QQHYSTPWT(SEQ ID NO:9)组成的CDR3。

[0017] 本申请进一步提供与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分及包含轻链可变区的第二多肽部分,其中:

[0018] 该重链可变区包含QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS(SEQ ID NO:4)的氨基酸序列,

[0019] 及该轻链可变区包含DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIK(SEQ ID NO:10)的氨基酸序列。

[0020] 本申请进一步提供与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分,及包含轻链可变区的第二多肽部分,其中

[0021] 该重链可变区包含以下氨基酸序列:

[0022] QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS(SEQ ID NO:13),

[0023] 及该轻链可变区包含以下氨基酸序列:

[0024] EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIK(SEQ ID NO:16)。

[0025] 本申请进一步提供与人类CD40特异性结合的分离的抗体或其抗原结合部分,其中该抗体包括包含重链可变区的第一多肽部分,及包含轻链可变区的第二多肽部分,其中该重链可变区包含以下氨基酸序列:

[0026] QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQYNEKFKTRV

TITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS(SEQ ID NO:4)，

[0027] 及该轻链可变区包含以下氨基酸序列：

[0028] EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSGSGSG TEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIK(SEQ ID NO:16)。

[0029] 在某些实施例中，分离的抗体或其抗原结合部分包括包含人类重链恒定区的第一多肽部分；及包含人类轻链恒定区的第二多肽部分。本申请所述的分离的抗体或其抗原结合部分可包含人类IgG1 Fc域，该域包含(1)Kabat位置238的突变，该突变降低与Fc-γ-受体(FcγR)的结合，其中脯氨酸238(P238)经突变为选自由赖氨酸、丝氨酸、丙氨酸、精氨酸及色氨酸组成的组的残基中的一个，及其中该抗体或其抗原结合部分具有降低的FcγR结合；或(2)取代在Kabat位置297的丙氨酸。

[0030] 本申请所述的分离的抗体或其抗原结合部分可包含人类IgG1 Fc域，该人类IgG1 Fc域在Kabat位置238包含突变，该突变降低与Fc-γ受体(FcγR)的结合，其中脯氨酸238(P238)经突变为选自由赖氨酸、丝氨酸、丙氨酸、精氨酸及色氨酸组成的组的残基中的一个，及其中该抗体或抗原结合部分具有降低的FcγR结合。在某些实施例中，P238经突变为赖氨酸。

[0031] 本申请所述的分离的抗体或其抗原结合部分可包括包含选自以下的氨基酸序列的Fc域：

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPG (SEQ ID NO: 22 ;IgG1-P238K (-C-端 Lys)),

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO: 23;IgG1-P238K),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK
THTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
[0032] KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 24;CH1-IgG1-P238K (-C-端 Lys)),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK
THTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 25;CH1-IgG1-P238K),

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPG (SEQ ID NO: 26; IgG1f-P238K (-C-端 Lys)),

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

[0033] YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 27; IgG1f-P238K),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 28;CH1-IgG1f-P238K (-C-端 Lys)),

或

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID No: 29; CH1-IgG1f-P238K) 。

[0034] 在某些实施例中,本申请所述的分离的抗体或其抗原结合部分包含人类IgG1 Fc域,其包含在(1)Kabat位置238会降低与Fc-γ受体(FcγR)的结合的突变,其中脯氨酸238(P238)经突变为选自由赖氨酸、丝氨酸、丙氨酸、精氨酸及色氨酸组成的组的残基中的一个,且其中抗体或其抗原结合部分具有降低的FcγR结合;或(2)取代在Kabat位置297的丙氨酸,包含重链可变区,该重链可变区包括包含SYWMH(SEQ ID NO:1)的CDR1,包含QINPTTGRSQYNEKFKT(SEQ ID NO:2)的CDR2,包含WGLQPFAY(SEQ ID NO:3)的CDR3;和轻链可变区,其包括包含KASQDVSTAVA(SEQ ID NO:7)的CDR1,包含SASYRYT(SEQ ID NO:8)的CDR2及包含QQHYSTPWT(SEQ ID NO:9)的CDR3。

[0035] 分离的抗体或其抗原结合部分可包含人类IgG1 Fc域,其包含SEQ ID NO:22或SEQ ID NO:23的氨基酸序列。

[0036] 在本申请所述的分离的抗体或其抗原结合部分的一些实施例中,该第一多肽部分包含选自由以下的氨基酸序列组成的组或由其组成:

QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGL
EWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**WG**
LQPFAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN*
*SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD
KTHTCPPCPAPELLGG**K**SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K-无末端赖氨酸),

QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGL
EWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**WG**
LQPFAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN*
*SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD
KTHTCPPCPAPELLGG**K**SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K (SEQ ID NO: 6; HC_Y12XX-hz28-CH1-IgG1-P238K-具有末端赖氨酸),

[0037] QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGL
EWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**WG**
LQPFAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN*
*SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD
KTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO: 30; HC_Y12XX-hz28-CH1-IgG1f-P238K-无末端赖氨酸), 及

QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGL
EWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**WG**
LQPFAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN*
*SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD
KTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K (SEQ ID NO: 31; HC_Y12XX-hz28-CH1-IgG1f-P238K-具有末端赖氨酸);
及

[0038] 该第二多肽部分包含以下的氨基酸序列或由其组成：

[0039] DIQMTQSPSFLSASVGDRVTITC**KASQDVSTAVA**WYQQKPGKAPKLLIY**SASYRYT**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQHYSTPWT**FGGGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11; LC_Y12XX-hz28-CL)。

[0040] 在本申请所述的分离的抗体或其抗原结合部分的一些实施例中，该第一多肽部分包含以下的氨基酸序列或由其组成：

[0041] QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGLEWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**WGLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCDKTHTCPPCPAPELLGG**K**SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K- 无末端赖氨酸)；

及

[0042] 该第二多肽部分包含以下的氨基酸序列或由其组成：

[0043] DIQMTQSPSFLSASVGDRVTITC**KASQDVSTAVA**WYQQKPGKAPKLLIY**SASYRYT**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQHYSTPWT**FGGGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11; LC_Y12XX-hz28-CL)。

[0044] 在某些实施例中，本申请所述的分离的抗体或其抗原结合部分包含人类IgG1 Fc域，其包含在Kabat位置297含有丙氨酸取代的人类IgG1 Fc域。

[0045] 如本申请所述的分离的抗体或其抗原结合部分可拮抗CD40的活性。本申请所述的分离的抗体或其抗原结合部分可为嵌合抗体。本申请所述的分离的抗体或其抗原结合部分可为人源化抗体。本申请所述的分离的抗体或其抗原结合部分可包含人类重链恒定区及人类轻链恒定区。

[0046] 本申请所述的抗体或其抗原结合部分为选自以下的抗原结合部分：Fv、Fab、F(ab')2、Fab'、dsFv、scFv、sc(Fv)2、双抗体及scFv-Fc。如本申请所述的分离的抗体或其抗原结合部分为scFv-Fc。

[0047] 本申请所述的抗体或其抗原结合部分可与治疗剂连接。

[0048] 本申请所述的抗体或其抗原结合部分可与具有不同于该抗体或其抗原结合部分的结合特异性的第二功能部分连接。

[0049] 本申请所述的抗体或其抗原结合部分可进一步包含另外的部分。

[0050] 本申请所述编码分离的抗体或其抗原结合部分的核酸分子。本申请批露了包含核酸分子的表达载体。本申请还批露了预期用表达载体转染的细胞。还披露了一种制备抗人

类CD40抗体或其抗原结合部分的方法，包括：

[0051] a)在用表达载体转染的细胞中表达抗体或其抗原结合部分，该表达载体包含编码本申请所述的分离的抗体或其抗原结合部分的核酸分子；及

[0052] b)自细胞分离抗体或其抗原结合部分。

[0053] 本申请还提供了药物组合物，其包含：a)本申请所述的抗体或其抗原结合部分；b)药学上可接受的载体。

[0054] 提供一种治疗或预防受试者的免疫反应的方法，该方法包括向受试者给予本申请所述的抗体或其抗原结合部分。进一步提供一种治疗或预防受试者的自体免疫或发炎性疾病的方法，其包括向受试者给予本申请所述的抗体或抗原结合部分。视需要地，抗体或其抗原结合部分与免疫抑制剂/免疫调节剂及/或消炎剂一起给予。给予可为同时或依序。示例性试剂为CTLA4突变体分子例如L104EA29Y-Ig(贝拉希普(belatacept))。在该种治疗或预防受试者的免疫反应的方法中，及在该种治疗或预防受试者的自体免疫或发炎性疾病的方法中，优选地受试者患有选自以下组成的组的疾病：艾迪生氏病(Addison'sdisease)、过敏、过敏性反应、僵直性脊椎炎、哮喘、动脉粥样硬化、异位性过敏、耳部自体免疫疾病、眼部自体免疫疾病、自体免疫性肝炎、自体免疫性腮腺炎、支气管哮喘、冠心病、克罗恩病(Crohn's disease)、糖尿病、附睾炎、肾小球肾炎、格雷夫斯病(Graves'disease)、格林兰-巴雷症候群(Guillain-Barre syndrome)、桥本病(Hashimoto's disease)、溶血性贫血、特发性血小板减少性紫癜、发炎性肠病、对重组药物的免疫反应(例如血友病中的因子VII)、狼疮性肾炎、狼疮性肾炎、全身性系统性红斑狼疮、多发性硬化症、重症肌无力、天疱疮、牛皮癣、风湿热、类风湿关节炎、结节病、硬皮病、休格连氏症候群(Sjogren's syndrome)、脊椎关节炎、甲状腺炎、移植排斥、血管炎及溃疡性结肠炎。

[0055] 还预期用作药物的本申请所述的抗体或其抗原结合部分。也预期本申请所述的抗体或其抗原结合部分或包含该抗体或其抗原结合部分的药物，用于治疗有此需要的受试者。另外预期治疗有效量的本申请所述的抗体或其抗原结合部分，其用于治疗或预防免疫反应，其中该抗体或其抗原结合部分用于给予至需要其的患者。

[0056] 附图简单说明

[0057] 包含图1A至1D的图1描述抗体与人类FcγR结合的SPR感应图数据。图1A描述对照抗体(对照IgG1)的数据。图1B描述Y12XX-hx28-IgG1-P238K(对照IgG1)的数据。图1C描述对照抗体(抗体B)的数据。图1D为汇总抗体/FcγR相互作用的KD值的表格。KD值为获自1:1朗谬尔(Langmuir)拟合(hCD64)或1:1稳态拟合(hCD32a-H131、hCD32a-R131、hCD32b、hCD16a-V158及hCD16a-F158)。

[0058] 包含图2A至2C的图2描述使用人源化Y12XX抗体或对照抗体在添加或不添加表达CD32a的CHO细胞下处理iDC的iDC活化数据。评定来自细胞培养基及细胞表面标志物表达的IL-6(白因子-6)的增加，如用抗CD86及抗CD54抗体的流式细胞术平均荧光染色所指示。图2A描述IL-6数据。图2B描述CD86数据。图2C描述CD54数据。在图2B及图2C中，均在Y轴上测量平均荧光强度(MFI)。每个符号代表来自单个供体的iDC数据。测试来自4个供体的细胞中的Y12XX-hz42-P238K，测试来自6个供体的细胞中的Y12XX-hz40-P238K，及测试10个供体中的Y12XX-hz28-P238K。指示以μg/ml计的抗体浓度(10、30或100μg/ml)。在分析中包括CHO-CD32细胞如所指示以介导FcγR介导的交联或集群。使用Ly6-IgG作为阴性对照。使用部分

CD40激动剂2141及BMS986090-100作为阳性对照。

[0059] 包含图3A及3B的图3描述来自对人源化Y12XX抗体、CD40抗体及对照抗体的补体依赖性细胞毒性(CDC)分析的示例性数据。CDC分析进行两次。在第二次分析中，使用新鲜解冻的人类补体血清。图3A描述来自分析的第一次重复的数据，及图3B描述来自分析的第二次重复的数据。

[0060] 包含图4A及4B的图4描述使用来自两个不同供体的CD14+单核细胞作为效应细胞，来自人源化Y12XX抗体或对照抗体的抗体依赖性细胞吞噬作用(ADCP)分析的示例性数据。图4A描述使用供体#8CD14+单核细胞作为效应细胞获得的数据。图4B描述使用供体#65CD14+单核细胞作为效应细胞获得的数据。

[0061] 包含图5A及5B的图5描述使用来自两个不同供体的NK细胞作为效应细胞，来自人源化Y12XX抗体或对照抗体的抗体依赖性细胞毒性(ADCC)分析的示例性数据。图5A描述使用供体#38NK细胞作为效应细胞获得的数据。图5B描述使用供体#55NK细胞作为效应细胞获得的数据。

[0062] 包含图6A、6B、6C及6D的图6描述来自旨在评定用不同抗CD40抗体刺激后Ramos Blues细胞上NF-kB/AP-1诱导的SEAP活性的分析的数据。来自CD40 mAb活性的三项独立研究的代表性结果显示于图6A及6b中。图6C及6D描述阳性对照CD40L-IZ的数据。AIMV:AIM V™培养基(1×)(Thermo Fisher Scientific,Waltham,MA)。

[0063] 发明详述

[0064] 本申请关于抗CD40抗体，且特别是拮抗性抗CD40抗体。对于例如CD40的治疗靶点，FcγR介导的抗CD40抗体交联具有导致非所欲的激动剂信号传导的潜力及潜在毒性。本申请还描述了具有“低亲合力”FcγR的降低接合:hCD32a/FcγRIIa、hCD32b/FcγRIIb及hCD16a/FcγRIIIa，及降低接合至“高亲合力”FcγR hCD64的拮抗性抗CD40抗体。预期低亲合力FcγR的降低接合减少非所欲的激动剂信号传导的可能性及非所欲的毒性潜力。

[0065] 定义及缩写

[0066] 下文提供进一步的缩写及定义。

[0067] APC 抗原呈递细胞

[0068] CD54 还称作ICAM-1

[0069] CDR 互补决定区

[0070] C_H或CH 恒定重链

[0071] C_L或CL 恒定轻链

[0072] CHO cell 中国仓鼠卵巢细胞

[0073] dAb 功能域抗体

[0074] DC 树突状细胞

[0075] FcgR 可与FcγR互换

[0076] FcγR Fc-γ-受体

[0077] FR 框架区

[0078] GM-CSF 粒细胞巨噬细胞群落刺激因子

[0079] HC 重链

[0080] ICAM-1 细胞内黏附分子1

[0081]	iDC	未成熟树突状细胞
[0082]	IFN	干扰素
[0083]	IgG	免疫球蛋白G
[0084]	IL-6	白因子-6
[0085]	LC	轻链
[0086]	mAb	单克隆抗体
[0087]	mg	毫克
[0088]	ml或mL	毫升
[0089]	ng	纳克
[0090]	nM	纳摩尔
[0091]	pI	等电点
[0092]	SPR	表面胞质基因共振
[0093]	TNF	肿瘤坏死因子
[0094]	μg	微克
[0095]	μM	微摩尔
[0096]	V_L或VL	可变轻链域
[0097]	Vk或VK	κ可变轻链域
[0098]	V_H或VH	可变重链域

[0099] 根据该详细描述,以下缩写及定义适用。必须注意地是,如本文所用,除非内容另外明确指出,否则单数形式“一(a)”、“一个(an)”及“该(the)”包括复数指示物。因此,例如,提及“一个抗体(an antibody)”包括复数个此类抗体,提及“该剂量(the dosage)”包括提及本领域技术人员已知的一个或多个剂量及其等效物,等等。

[0100] 如本文所用,术语“约”为一般技术人员所理解且将在使用其的内容中在某种程度上变化。一般而言,除非说明书中另外指出,否则“约”涵盖为参考值的正/负10%的值范围。

[0101] 应当理解,本申请所述范围之间的任何及所有整数或部分整数均包括在内。

[0102] CD40还已知且称为B细胞表面抗原CD40、Bp50、CD40L受体、CDw40、CDW40、MGC9013、p50、TNFRSF5及肿瘤坏死因子受体超家族成员5。“人类CD40”为指包含以下氨基酸序列的CD40:

[0103] MVRLPLQCVL WGCLLTAVHP EPPTACREKQ YLINSQCCSL CQPGQKLVSD CTEFTETECL PCGESEFLDT WNRETHCHQH KYCDPNLGLR VQQKGTSETD TICTCEEGWH CTSEACESCV LHRSCSPGFG VKQIATGVSD TICEPCPVGF FSNVSSAFEK CHPWTSCETK DLVVQQAGTN KTDVVCGPQD RLRALVVIPI IFGILFAILL VLVFIKKVAK KPTNKAPHPK QEPQEINFPD DLPGSNTAAP VQETLHGCQP VTQEDGKESR ISVQERQ (SEQ ID NO: 20)。

[0104] 如本文所用,术语“可变域”为指由Kabat等人,Sequences of Immunological Interest,第5版,美国卫生与人类服务部,华盛顿特区(U.S.Dept.Health&Human Services,Washington,D.C.),(1991)定义的免疫球蛋白可变域。可变域内的CDR氨基酸残基的编号及定位为根据熟知的Kabat编号惯例。VH、“可变重链”及“可变重链域”为指重链的

可变域。VL、“可变轻链”及“可变轻链域”为指轻链的可变域。

[0105] 当应用于抗体时，术语“人类”意指该抗体具有衍生自人类免疫球蛋白的序列，例如FR及/或CH域。当序列为：(a)自人类受试者或自人类个体的细胞或细胞系分离；(b)自选殖人类抗体基因序列或人类抗体可变域序列的文库分离；(c)通过突变及选自上述一种或多种多肽而多样化时，该序列为“源自”人类免疫球蛋白编码序列。

[0106] 如本文所用，“经分离”化合物意指将该化合物自与该化合物本质上自然地相关联的至少一种组分移除。

[0107] 本申请的抗CD40抗体包含可变重链及可变轻链，其各包含按以下顺序自氨基端至羧基端排列的三个互补决定区(CDR)及四个框架区(FR)：FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。CDR包含与抗原形成特异性相互作用且主要负责抗原识别的大多数残基。

[0108] 本申请的抗CD40抗体可包含人源化抗体Y12XX-hz28(Vh-hz14;Vk-hz2)，Y12XX-hz40(Vh-hz12;Vk-hz3)或Y12XX-hz42(Vh-hz14;Vk-hz3)的CDR。表1提供重链可变区及轻链可变区的氨基酸序列的概述。该表格包括每个氨基酸序列的简写名称及更详细的名称，以及序列标识符。

[0109] 表1

[0110]

抗体	HC可变区	LC可变区
Y12XX-hz28	Vh-hz14 (Y1268_IGHV1.6908-S54T-N55T-Vh) (SEQ ID NO: 4)	Vk-hz2 (Y1258_IGKV1.3902-Vk) (SEQ ID NO: 10)

[0111]

Y12XX-hz40	Vy-hz12 (Y1268_IGHV1.6908-N55Q-Vh) (SEQ ID NO: 13)	Vk-hz3 (Y1258_IGKV3.1501-Vk) (SEQ ID NO: 16)
Y12XX-hz42	Vh-hz14 (Y1268_IGHV1.6908-S54T-N55T-Vh) (SEQ ID NO: 4)	Vk-hz3 (Y1258_IGKV3.1501-Vk) (SEQ ID NO: 16)

[0112] 在一具体实施例中，本申请的抗CD40抗体包含人源化抗体Y12XX-hz28(Vh-hz14;Vk-hz2)的CDR。表2提供Y12XX-hz28的氨基酸序列的详细信息。

[0113] 表2

[0114] Y12XX-hz28序列(Vh-hz14;Vk-hz2)

[0115]

重链可变区	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPG QGLEWMG**QINPTTGRSQYNEKFKT**RVTITADKSTST AYMELSSLRSEDTAVYYCAR**WGLQPFAY**WGQGTLVTVSS SEQ ID NO: 4)	Vh-hz14 (SEQ ID NO: 4； CDR 加底线)
VH-CDR1	SYWMH SEQ ID NO: 1)	SEQ ID NO: 4的氨基酸31至35
VH-CDR2	QINPTTGRSQYNEKFKT (SEQ ID NO: 2)	SEQ ID NO: 4的氨基酸50至66
VH-CDR3	WGLQPFAY (SEQ ID NO:3)	SEQ ID NO: 4的氨基酸99至106
HC_Y12XX-hz28-CH1-IgG1-P238K (为	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPG QGLEWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSL RSEDTAVYYCAR**WGLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAP*	CDR 加底线； CH1=氨基酸118

[0116]

具有及不具有C端赖氨酸的IgG1)	*SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ* *SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD KTHTCPPCPAPELLGG**K**SVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 5)	至215（斜体）；IgG1-P238K=氨基酸216至446；P238K加底线；无C端赖氨酸
	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPG QGLEWMG**QINPTTGRSQYNEKFKT**RVTITADKSTSTAYMELSSL RSEDTAVYYCAR**WGLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAP* *SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ* *SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCD KTHTCPPCPAPELLGG**K**SVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 6)	CDR加底线；CH1=氨基酸118至215（斜体）；IgG1-P238K=氨基酸216至447；P238K加底线；存在C端赖氨酸
轻链可变区	DIQMTQSPSFLSASVGDRVTITC**KASQDVSTAVA**WYQQKPGKA PKLLIY**SASYRYT**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQ HYSTPWT**FGGGTKVEIK (SEQ ID NO: 10)	Vk-hz2 (SEQ ID NO: 10；CDR加底线)
VL-CDR1	KASQDVSTAVA (SEQ ID NO: 7)	SEQ ID NO: 10的氨基酸24至34
VL-CDR2	SASYRYT (SEQ ID NO: 8)	SEQ ID NO: 10的氨基酸50至56

[0117]

VL-CDR3	QQHYSTPWT (SEQ ID NO: 9)	SEQ ID NO: 10 的氨基酸89至97
LC_Y12XX-hz28	DIQMTQSPSFLSASVGDRVTITC**KASQDVSTAVA**WYQQKPGKAPKLLIY**SASYRYT**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQHYSTPWT**FGGGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11)	CDR 加底线；CL=氨基酸108至214 (斜体)

[0118] 在一具体实施例中，本申请的抗CD40抗体包含人源化抗体Y12XX-hz40(Vh-hz12；Vk-hz3)的CDR。表3提供Y12XX-hz40的氨基酸序列。

[0119] 表3

[0120] Y12XX-hz40序列(Vh-hz12;Vk-hz3)

[0121]

重链可变区	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW****MH**WVRQAPGQGLEWMG**QINPSQGRSQYNEK****FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W****GLQPFAY**WGQGTLVTVSS (SEQ ID NO: 13)	Vh-hz12 (SEQ ID NO: 13；CDR加底线)
VH-CDR1	SYWMH (SEQ ID NO:1)	SEQ ID NO: 13的氨基酸31至35
VH-CDR2	QINPSQGRSQYNEKFKT (SEQ ID NO: 12)	SEQ ID NO: 13的氨基酸50至66
VH-CDR3	WGLQPFAY (SEQ ID NO:3)	SEQ ID NO: 13的氨基酸99至106
HC_Y12XX-hz40-P238K–具有及不具有C端赖氨酸的IgG1a	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW****MH**WVRQAPGQGLEWMG**QINPSQGRSQYNEK****FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W****GLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCDKTHTCPPCPAPELLGG**K**S	CDR加底线；CH1=氨基酸118至215 (斜体)；IgG1-P238K=氨基酸216至446；P238K加底线；无C端赖氨酸

[0122]

	VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 14)	
	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW MH**WVRQAPGQGLEWMG**QINPSQGRSQYNEK FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W GLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRV*EPKSCDKTHTCPPCPAPELLGG**K**S VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 15)	CDR 加底线；CH1= 氨基酸 118 至 215 (斜体)；IgG1-P238K= 氨基酸 216 至 447；P238K 加底线；存在C端赖氨酸
轻链可变区	EIVMTQSPATLSVSPGERATLSC**KASQDVSTAVA** WYQQKPGQAPRLLIY**SASYRYT**GIPARFSGSGSGT EFTLTISSLQSEDFAVYYC**QQHYSTPWT**FGGGTKV EIK (SEQ ID NO: 16)	Vk-hz3 (SEQ ID NO: 16；CDR 加底线)
VL-CDR1	KASQDVSTAVA (SEQ ID NO: 7)	SEQ ID NO: 16的氨基酸24至34
VL-CDR2	SASYRYT	SEQ ID NO: 16的

[0123]

	(SEQ ID NO: 8)	氨基酸50至56
VL-CDR3	QQHYSTPWT (SEQ ID NO: 9)	SEQ ID NO: 16的氨基酸89至97
LC_Y12XX-hz40	EIVMTQSPATLSVSPGERATLSC**KASQDVSTAVA** WYQQKPGQAPRLLIY**SASYRYT**GIPARFSGSGSGT EFTLTISSLQSEDFAVYYC**QQHYSTPWT**FGGGTKV EIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY* *PREAKVQWKVDNALQSGNSQESVTEQDSKDSTY* *SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF* *NRGEC* (SEQ ID NO: 17)	CDR加底线；CL=氨基酸108至214(斜体)

[0124] 在一具体实施方案中，本申请的抗CD40抗体包含人源化抗体Y12XX-hz42(Vh-hz14;Vk-hz3)的CDR。表4提供Y12XX-hz42的氨基酸序列的详细信息。

[0125] 表4

[0126] Y12XX-hz42序列(Vh-hz14;Vk-hz3)

[0127]

重链可变区	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW** **MH**WVRQAPGQGLEWMG**QINPTTGRSQYNEK** **FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W** **GLQPFAY**WGQGTLVTVSS SEQ ID NO: 4)	Vh-hz14 (SEQ ID NO: 4; CDR加底线)
VH-CDR1	SYWMH SEQ ID NO: 1)	SEQ ID NO: 4的氨基酸31至35
VH-CDR2	QINPTTGRSQYNEKFKT (SEQ ID NO: 2)	SEQ ID NO: 4的氨基酸50至66
VH-CDR3	WGLQPFAY (SEQ ID NO:3)	SEQ ID NO: 4的氨基酸99至106
HC_Y12XX-hz42-P238K –具有及不具有C端赖氨酸的IgG1a	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW** **MH**WVRQAPGQGLEWMG**QINPTTGRSQYNEK** **FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W** **GLQPFAY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS* *TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH* *TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH* *KPSNTKVDKRV*EPKSCDKTHTCPPCPAPELLGG**K**S VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PG (SEQ ID NO: 5)	CDR 加底线； CH1=氨基酸118至215（斜体）； IgG1-P238K=氨基酸216至446； P238K加底线； 无C端赖氨酸
	QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYW** **MH**WVRQAPGQGLEWMG**QINPTTGRSQYNEK** **FKT**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**W**	CDR 加底线； CH1=氨基酸118至215（斜体）；

[0128]

	GLQPFAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRV*EPKSCDKTHTCPPCPAPELLGG**K**S VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 6)	IgG1-P238K=氨基酸216至447；P238K加底线；存在C端赖氨酸
轻链可变区	EIVMTQSPATLSVSPGERATLSC**KASQDVSTAVA** WYQQKPGQAPRLLIY**SASYRYT**GIPARFSGSGSGT EFTLTISSLQSEDFAVYYC**QQHYSTPWT**FGGGTKV EIK (SEQ ID NO: 16)	Vk-hz3 (SEQ ID NO: 16；CDR加底线)
VL-CDR1	KASQDVSTAVA (SEQ ID NO: 7)	SEQ ID NO: 16的氨基酸24至34
VL-CDR2	SASYRYT (SEQ ID NO: 8)	SEQ ID NO: 16的氨基酸50至56
VL-CDR3	QQHYSTPWT (SEQ ID NO: 9)	SEQ ID NO: 16的氨基酸89至97
LC_Y12XX-hz42	EIVMTQSPATLSVSPGERATLSC**KASQDVSTAVA** WYQQKPGQAPRLLIY**SASYRYT**GIPARFSGSGSGT EFTLTISSLQSEDFAVYYC**QQHYSTPWT**FGGGTKV EIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC* (SEQ ID NO: 17)	CDR加底线；CL=氨基酸108至214(斜体)

[0129] 在一个实施方案中，本申请的抗体可包含人源化Y12XX-hz28可变重链及轻链序列的CDR1、CDR2及CDR3区的氨基酸序列(参见例如SEQ ID NO:4及10分别作为实例)。单克隆抗

体包含所有6个CDR(VH为3个及VL为3个),例如SYWMH(SEQ ID NO:1)、QINPTTGRSQYNEKFKT(SEQ ID NO:2)及WGLQPFAY(SEQ ID NO:3)分别为可变重链CDR 1至3及KASQDVSTAVA(SEQ ID NO:7)、SASYRYT(SEQ ID NO:8)及QQHYSTPWT(SEQ ID NO:9)分别为可变轻链CDR 1至3。

[0130] 在一个实施例中,本申请的抗体可包含人源化Y12XX-hz40可变重链及轻链序列的CDR1、CDR2及CDR3区的氨基酸序列(分别参见例如:SEQ ID NO:13及16作为实例)。单克隆抗体包含所有6个CDR(V_H有3个及V_L有3个),例如分别为可变重链CDR 1至3的SYWMH(SEQ ID NO:1)、QINPSQGRSQYNEKFKT(SEQ ID NO:12)及WGLQPFAY(SEQ ID NO:3);及分别为可变轻链CDR 1至3的KASQDVSTAVA(SEQ ID NO:7)、SASYRYT(SEQ ID NO:8)及QQHYSTPWT(SEQ ID NO:9)。

[0131] 在一个实施例中,本申请的抗体可包含人源化Y12XX-hz42可变重链及轻链序列的CDR1、CDR2及CDR3区的氨基酸序列(分别参见例如SEQ ID NO:4及16作为实例)。单克隆抗体包含所有6个CDR(V_H有3个及V_L有3个),例如分别为可变重链CDR 1至3的SYWMH(SEQ ID NO:1)、QINPTTGRSQYNEKFKT(SEQ ID NO:2)及WGLQPFAY(SEQ ID NO:3);及分别为可变轻链CDR 1至3的KASQDVSTAVA (SEQ ID NO:7)、SASYRYT(SEQ ID NO:8)及QQHYSTPWT(SEQ ID NO:9)。

[0132] "抗体"(Ab)应包括(但不限于)与抗原特异性结合且包含通过二硫键互连的至少两条重(H)链及两条轻(L)链的免疫球蛋白或其抗原结合部分。每条H链包含重链可变区(本文缩写为V_H)及重链恒定区。重链恒定区包含三个恒定域:C_{H1}、C_{H2}及C_{H3}。每条轻链包含轻链可变区(在本文中缩写为V_L)及轻链恒定区。轻链恒定区包括一个恒定域C_L。V_H及V_L区可进一步细分为高变区,称为互补决定区(CDR),其间散布着更为保守的区,称为框架区(FR)。每个V_H及V_L包含按以下顺序自氨基端至羧基端排列的三个CDR及四个FR:FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。重链及轻链的可变区包含与抗原相互作用的结合域。

[0133] Ab的"抗原结合部分"(也称为"抗原结合片段")或其抗原结合部分为指Ab的一个或多个序列(全长或全长抗体的片段),其保留与全Ab所结合的抗原特异性结合的能力。抗原结合片段的实例包括Fab、F(ab')$_2$、scFv(单链可变片段)、Fab'、dsFv、sc(Fv)2及scFv-Fc。

[0134] "人源化"抗体为指其中非人类Ab的CDR域之外的一些、大部分或全部氨基酸被衍生自人免疫球蛋白的相应氨基酸置换的Ab。在Ab的人源化形式的一个实施例中,CDR域外的一些、大多数或全部氨基酸已经来自人免疫球蛋白的氨基酸置换,而一个或多个CDR区内的一些、大多数或全部氨基酸未改变。氨基酸的少量新增、缺失、插入、取代或修饰系允许,只要它们不消除Ab结合特定抗原的能力即可。"人源化"Ab保留与原始Ab抗原特异性相似的抗原特异性。

[0135] "嵌合抗体"为指其中可变区衍生自一个物种且恒定区衍生自另一物种的Ab,例如其中可变区衍生自小鼠Ab及恒定区衍生自人类Ab。

[0136] 如本文所用,"特异性结合"为指通过例如表面胞质基因共振(SPR)测得的具有约1μM或更低的解离常数(K_d)的抗体与抗原的结合。合适的分析系统包括BIAcore™(GE Healthcare Life Sciences,Marlborough,MA)表面胞质基因共振系统及BIAcore™动力学评估软件(例如2.1版)。

[0137] 本申请抗体与CD40的结合会拮抗至少一种CD40活性。"CD40活性"包括但不限于T细胞活化(例如,诱导T细胞增殖或细胞因子分泌)、巨噬细胞活化(例如,诱导巨噬细胞中的

活性氧及一氧化氮)及B细胞活化(例如,B细胞增殖、抗体同型物转换或分化为浆细胞)。CD40活性可通过与其他分子的相互作用来介导。“CD40活性”包括CD40与以下分子之间的功能相互作用,该等分子通过括号内的其Uniprot登录号识别:

CALR (P27797);
ERP44 (Q9BS26);
FBL (P22087);
POLR2H (P52434);

[0138] RFC5 (P40937);
SGK1 (O00141);
SLC30A7 (Q8NEW0);
SLC39A7 (Q92504);
TRAF2 (Q5T1L5);
TRAF3 (Q13114);
TRAF6 (Q9Y4K3);

[0139] TXN (Q5T937);
UGGT1 (Q9NYU2); 及
USP15 (Q9Y4E8)。

[0140] 例如,CD40“活性”包括与TRAF2的相互作用。CD40/TRAF2相互作用活化NF-κB及JNK。参见Davies等人,Mol.Cell Biol.25:9806-19(2005)。因此,此CD40活性可通过相对于参考的CD40依赖性细胞NF-κB及JNK活化来确定。

[0141] 如本文所用,术语“活化”及“经活化”为指给定的可量测CD40活性相对于参考增加至少10%,例如至少10%、25%、50%、75%或甚至100%或更高。若CD40活性相对于不存在拮抗剂降低至少10%,及在一个示例性实施例中降低至少约20%、30%、40%、50%、60%、70%、80%、90、95%、97%或甚至100%(即,没有可侦测的活性),则CD40活性为“被拮抗”。例如,抗体可拮抗一些或全部CD40活性,而不活化CD40。例如,抗体可不活化B细胞增殖。抗体可能不活化T细胞的细胞因子分泌,其中细胞因子为至少一种选自由IL-2、IL-6、IL-10、IL-13、TNF-α及IFNγ组成的组的细胞因子。

[0142] 可变域可包含一或多个与人类生殖系抗体基因片段编码的相应框架区具有相同氨基酸序列的框架区(FR)。用于本文描述的抗体的优选框架序列为那些与本文描述的抗体使用的框架序列在结构上类似者。V_H CDR1、2及3序列以及V_L CDR1、2及3序列可移植至具有与框架序列所源自的生殖系免疫球蛋白基因中发现的序列相同的序列的框架区上,或与生殖系序列相比CDR序列可移植至含有多达20个(优选保守)的氨基酸取代的框架区上。例如,已经发现在某些情况下,使框架区内的残基突变以维持或增强抗体的抗原结合能力系有益(参见例如,Queen等人的美国专利案第5,530,101号;第5,585,089号;第5,693,762号及第6,180,370号)。

[0143] 示例性框架区包括但不限于下表5及6中的框架区。

[0144] 表5

[0145]

重链框架区	序列
FR1	实施例中的表8 (SEQ ID NO: 53至75)或表10 (SEQ ID NO: 4、13、及99至113)中的任何VH序列的氨基酸残基1至30
FR2	实施例中的表8 (SEQ ID NO: 53-75)或表10 (SEQ ID NO: 4、13、及99至113)中的任何VH序列的氨基酸残基36至49
FR3	实施例中的表8 (SEQ ID NO: 53-75)或表10 (SEQ ID NO: 4、13、及99至113)中的任何VH序列的氨基酸残基67至98
FR4	实施例中的表8 (SEQ ID NO: 53-75)或表10 (SEQ ID NO: 4、13、及99至113)中的任何VH序列中的氨基酸残基107至117

[0147] 表6

[0148]

轻链框架区	序列
FR1	实施例中的表8 (SEQ ID NO: 76至98)或表10 (SEQ ID NO: 10、16、及114至116)中的任何VL序列的氨基酸残基1至23
FR2	实施例中的表8 (SEQ ID NO: 76至98)或表10 (SEQ ID NO: 10、16、及114至116)中的任何VL序列的氨基酸残基35至49
FR3	实施例中的表8 (SEQ ID NO: 76至98)或表10 (SEQ ID NO: 10、16、及114至116)中的任何VL序列的氨基酸残基57至88
FR4	实施例中的表8 (SEQ ID NO: 76至98)或表10 (SEQ ID NO: 10、16、及114至116)中的任何VL序列的氨基酸残基98至107

[0149] 变体可变域可与人源化Y12XX-hz28、Y12XX-hz40或Y12XX-hz42序列的可变域相差多达10个氨基酸或其间的任何整数值，其中变体可变域特异性结合CD40。或者，相对于各自人源化Y12XX-hz28、Y12XX-hz40或Y12XX-hz40的序列，变体可变域可具有至少90％序列一致性(例如，至少92％、95％、98％或99％序列一致性)。两个序列之间不同的非一致氨基酸残基或氨基酸可代表氨基酸取代、新增或缺失。当两个序列通过适当的氨基酸序列比对算法例如BLAST®(美国国家医学图书馆的注册商标)比对时，两个序列之间不同的残基表现为非一致位置。

[0150] 本申请的示例性CD40抗体可包括与人类CD40特异性结合的分离的抗体或其抗原

结合部分,其中该抗体包括包含重链可变区的第一多肽部分及包含轻链可变区的第二多肽部分,其中:

[0151] 该重链可变区包含以下之一:(i)包含SYWMH(SEQ ID NO:1)的CDR1,包含QINPTTGRSQYNEKFKT(SEQ ID NO:2)的CDR2,包含WGLQPFAY(SEQ ID NO:3)的CDR3及(ii)包含SYWMH(SEQ ID NO:1)的CDR1,包含QINPSQGRSQYNEKFKT(SEQ ID NO:12)的CDR2,包含WGLQPFAY(SEQ ID NO:3)的CDR3;及

[0152] 该轻链可变区包括包含KASQDVSTAVA(SEQ ID NO:7)的CDR1,包含SASYRYT(SEQ ID NO:8)的CDR2及包含QQHYSTPWT(SEQ ID NO:9)的CDR3。

[0153] 分离的抗体或其抗原结合部分可拮抗CD40的一或多种活性。分离的抗体或其抗原结合部分可为嵌合抗体。嵌合抗体的示例性可变重链及可变轻链在实施例的表8中。分离的抗体或其抗原结合部分可为人源化抗体。示例性人源化可变重链及可变轻链在实施例的表10中。分离的抗体或其抗原结合部分可包含人类重链恒定区及人类轻链恒定区。

[0154] Fc域及恒定区

[0155] 重链的羧基端“一半”定义恒定区(Fc)且其主要负责效应功能。如本文所用,术语“Fc域”指包含CH2及CH3恒定域的恒定区抗体序列,如根据Kabat等,Sequences of Immunological Interest,第5版,美国卫生与人类服务部,华盛顿特区(1991)界定。Fc区可源自人类IgG。例如,Fc区可源自人类IgG1或人类IgG4 Fc区。重链可变域可与Fc域融合。可变域的羧基端可与Fc CH2域的氨基端连接或融合。任选地,可变域的羧基端可与接头氨基酸序列的氨基端连接或融合,接头氨基酸序列本身与Fc域的氨基端融合。任选地,可变域的羧基端可与CH1域的氨基端连接或融合,CH1域本身与Fc CH2域融合。视需要地,蛋白质可全部或部分地在CH1域之后包含铰链区。视需要地,可变域及Fc域之间存在氨基酸接头序列。轻链可变域的羧基端可与CL域的氨基端连接或融合。

[0156] 重链CH1的示例性序列为SEQ ID NO:5的氨基酸118至215(ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV;SEQ ID NO:18)。轻链CL的示例性序列为SEQ ID NO:11的氨基酸108至214(RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC;SEQ ID NO:19)。

[0157] 抗体可为融合抗体,其包含特异性结合人类CD40的第一可变域及包含Fc域的第二域。

[0158] 融合蛋白中使用的示例性Fc域可包括人类IgG域。示例性的人类IgG Fc域包括IgG4 Fc域及IgG1 Fc域。尽管人类IgG重链基因编码C端赖氨酸,但由于在血液循环中的裂解,内源性抗体通常不存在赖氨酸。当在哺乳动物细胞培养物中表达时,具有包括C端赖氨酸的IgG重链的抗体还可存在可变程度的C端赖氨酸(Cai等人,2011,Biotechnol Bioeng.108(2):404-12)。因此,可省略本申请所述的任何IgG重链Fc域的C端赖氨酸。

[0159] 本申请所述的分离的抗体或其抗原结合部分可包含Fc域,其包含以下氨基酸序列:

[0160] EPKSCDKTHTCPPCPAPELLGG(P/K)SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY(N/A)STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR(D/E)E(L/M)TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ

GNVFSCSVMHEALHNHYTQKSLSLSPG(K/不存在)(Fc共有序列;SEQ ID NO:21)。括号表示该位置可能的氨基酸身份。例如,Kabat位置238可为脯氨酸(P)或赖氨酸(K),其记为(P/K)。另外示例性非限制性共有序列为SEQ ID NO:118至120。

[0161] 本申请所述的分离的抗体或其抗原结合部分可包含人类IgG1 Fc域,其在Kabat位置238包含会降低与Fc-γ-受体(FcγR)的结合的突变,其中脯氨酸238(P238)突变为选自由赖氨酸(K)、丝氨酸(S)、丙氨酸(A)、精氨酸(R)及色氨酸(W)组成的组的残基中的一个,且其中抗体或其抗原结合部分具有降低的FcγR结合。本申请所述的分离的抗体或其抗原结合部分可在人类IgG1 Fc域中具有突变为赖氨酸的P238。

[0162] 分离的抗体或其抗原结合部分包含Fc域,该Fc域包含选自SEQ ID NO:22至29的氨基酸序列。

[0163] 包含上述IgG1 Fc域的示例性序列包括:SEQ ID NO:5、SEQ ID NO:6、SEQ ID NO:30及SEQ ID NO:31。

[0164] 本申请所述的分离的抗体或其抗原结合部分可包含人类IgG1 Fc域,其包含取代在Kabat位置297的丙氨酸。例如,分离的抗体或其抗原结合部分包括包含选自SEQ ID NO:32至39的氨基酸序列的Fc域。

[0165] 本申请所述的分离的抗体或抗原结合部分可包含(1)选自实施例中的表8或表10的可变重链(V_H)或其CDR,及/或(2)选自实施例中的表8或表10的可变轻链(V_L)或其CDR。

[0166] 本申请所述的分离的抗体或其抗原结合部分可包含选自Vh-hz12(SEQ ID NO:13)及Vh-hz14(SEQ ID NO:4)的重链氨基酸序列。

[0167] 本申请所述的分离的抗体或其抗原结合部分可包含选自Vk-hz2(SEQ ID NO:10)及Vk-hz3(SEQ ID NO:16)的轻链氨基酸序列。

[0168] 本申请所述的分离的抗体或其抗原结合部分可为选自以下组成的组的抗体:

[0169] a)Y12XX-hz28-P238K,其具有SEQ ID NO:5或6的重链及SEQ ID NO:11的轻链;

[0170] b)Y12XX-hz40-P238K,其具有SEQ ID NO:14或15的重链及SEQ ID NO:17的轻链;及

[0171] c)Y12XX-hz42-P238K,其具有SEQ ID NO:5或6的重链及SEQ ID NO:17的轻链。

[0172] 本申请所述的抗体或其抗原结合部分,其中抗原结合部分为选自由Fv、Fab、F(ab')2、Fab'、dsFv、scFv、sc$(Fv)_2$、双抗体及scFv-Fc组成的组。

[0173] 本申请所述的抗体或其抗原结合部分可为免疫偶联物,其中该抗体或其抗原结合部分与治疗剂连接。

[0174] 本申请所述的抗体或其抗原结合部分可为双特异性抗体,其中该抗体或其抗原结合部分为与具有不同于该抗体或其抗原结合部分的结合特异性的第二功能部分连接。

[0175] 本申请所述的抗体或其抗原结合部分可进一步包含另外部分。

[0176] 本申请抗体的可变区可视需要地通过“氨基酸接头”或“接头”与Fc域连接。例如,可变重链域的C端可与氨基酸接头的N端融合,及Fc域可与接头的C端融合。尽管氨基酸接头可为任何长度且可由氨基酸的任何组合组成,但接头长度可相对较短(例如,五个或更少氨基酸),以减少所连接的域之间的相互作用。还可调节接头的氨基酸组成以减少具有大侧链的氨基酸或可能引入二级结构的氨基酸的数量。合适的氨基酸接头包括但不限于长度多达3、4、5、6、7、10、15、20或25个氨基酸的氨基酸接头。代表性氨基酸接头序列包括GGGGS(SEQ

ID NO:40)，及包含2、3、4或5个GGGGS拷贝的接头(分别为SEQ ID NO:41至44)。表7列出用于本揭示的合适的接头序列。

[0177] 表7

[0178] 代表性接头序列

[0179]

GGGGS	SEQ ID NO: 40
$(GGGGS)_2$	SEQ ID NO: 41
$(GGGGS)_3$	SEQ ID NO: 42
(GGGGS)4	SEQ ID NO: 43
$(GGGGS)_5$	SEQ ID NO: 44

[0180]

AST	SEQ ID NO: 45
TVAAPS	SEQ ID NO: 46
TVA	SEQ ID NO: 47
ASTSGPS	SEQ ID NO: 48

[0181] 抗体制备

[0182] 抗体可使用一般技术在合适哺乳动物宿主细胞系例如CHO、293、COS、NSO及类似物中产生及纯化，然后使用一种方法或方法组合(包括蛋白A亲合力层析、离子交换、反相技术或类似方法)纯化。

[0183] 如本领域中所熟知，多个密码子可编码相同氨基酸。因此，编码蛋白质序列的核酸包括具有密码子简并性的核酸。本申请所述的多肽序列可由多种核酸编码。遗传密码为通用且熟知。编码本申请所述的任何多肽序列的核酸可基于本领域的公知常识容易地构思出，且可经优化以进行生产。尽管编码给定多肽的核酸序列的可能数目很大，给定遗传密码的标准表下，且在计算器的辅助下，本领域技术人员可容易地产生编码给定多肽的核酸序列的每种可能的组合。

[0184] 编码包括恒定区CH1及Fc域IgG1-P238K的Y12XX-hz28的Y12XX重链可变域的代表性核酸序列为：

[0185] ATGAGGGCTTGGATCTTCTTTCTGCTCTGCCTGGCCGGGAGAGCGCTCGCACAGGTGCAGCTGGTGCAGTCTGGTGCCGAGGTCAAAAAGCCAGGCTCCAGCGTGAAGGTGAGCTGCAAGGCCTCTGGCTACGCTTTCACCTCTTATTGGATGCACTGGGTGAGACAGGCTCCTGGACAGGGCCTGGAGTGGATGGGCCAGATCAACCCAACCACCGGCAGAAGCCAGTACAATGAGAAGTTTAAGACCCGCGTGACCATCACAGCCGACAAGTCCACCAGCACAGCTTATATGGAGCTGTCTTCCCTGAGGTCCGAGGATACAGCCGTGTACTATTGCGCTCGGTGGGGCCTGCAGCCTTTCGCTTACTGGGGCCAGGGCACCCTGGTGACAGTGAGCTCTGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACT

CCTGGGGGGAAAGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTC
ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC
ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCA
CCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACC
ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA
GCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA
CGCAGAAGAGCCTCTCCCTGTCTCCGGGTTGA(SEQ ID NO:49)。在该序列中,核苷酸1至51编码信号肽(可选),核苷酸52至402编码重链可变区,其中核苷酸141至155编码重链的Y12XX可变域的CDR1,核苷酸198至249编码其CDR2,核苷酸346至369编码其CDR3。核苷酸403至696编码CH1结构域,及核苷酸697至1399编码IgG1-P238K。核苷酸1400至1402为终止密码子。

[0186] 编码包括恒定区CL的Y12XX-hz28的Y12XX轻链可变域的代表性核酸序列为:

[0187] ATGAGGGCTTGGATCTTCTTTCTGCTCTGCCTGGCCGGGCGCGCCTTGGCCGACATCCAGATGACCCA
GTCCCCCTCCTTCCTGTCTGCCTCCGTGGGCGACAGAGTGACCATCACCTGTAAGGCTTCCCAGGATGTGAGCACA
GCCGTGGCTTGGTACCAGCAGAAGCCAGGCAAGGCCCCCAAGCTGCTGATCTATTCCGCCTCTTACAGGTATACCG
GCGTGCCCTCTCGGTTCTCCGGCAGCGGCTCTGGCACAGACTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGA
TTTCGCCACCTACTATTGCCAGCAGCACTACTCCACCCCATGGACATTTGGCGGCGGCACCAAGGTGGAGATCAAG
CGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTG
TGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
CTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAA
GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCT
TCAACAGGGGAGAGTGTTAG(SEQ ID NO:50)。在该序列中,核苷酸1至51编码信号肽(可选),核苷酸52至372编码轻链可变区,其中核苷酸121至153编码CDR1,核苷酸199至219编码CDR2,及核苷酸316至342编码CDR3。核苷酸373至693编码CL。核苷酸694至696为终止密码子。

[0188] 重链及/或轻链的编码序列可视需要地在编码序列的5'端编码信号肽,例如MRAWIFFLLCLAGRALA(SEQ ID NO:51)。如上所述,该信号肽的示例性核酸编码序列为:

[0189] ATGAGGGCTTGGATCTTCTTTCTGCTCTGCCTGGCCGGGAGAGCGCTCGCA(SEQ ID NO:52)。

[0190] 因此,还预期编码本申请所述的抗体的核酸。该核酸可插入载体例如合适的表达载体,例如pHEN-1(Hoogenboom等人(1991)Nucleic Acids Res.19:4133-4137)中。还提供包含载体及/或核酸的经分离宿主细胞。

[0191] 本申请的抗体可仅使用一般技术于任何合适的哺乳动物宿主细胞系例如CHO(中国仓鼠卵巢细胞)、293(人类胚肾293细胞)、COS细胞、NSO细胞及类似物中产生及纯化,然后使用一种方法或方法组合(包括蛋白A亲合力层析、离子交换、反相技术或类似方法)纯化。

[0192] 药物组合物及治疗方法

[0193] 药物组合物包含治疗有效量的一或多种抗体及视需要的药学上可接受的载体。药学上可接受的载体包括例如水、盐水、磷酸盐缓冲盐水、右旋糖、甘油、乙醇及类似物,以及其组合。药学上可接受的载体可进一步包含少量辅助物质,例如增加融合蛋白的储架期或有效性的润湿剂或乳化剂、防腐剂或缓冲剂。该等组合物可经调配以在给予后提供活性成

分的快速、持续或延迟释放。合适的药物组合物及其制备方法为本领域已知。参见，例如，Remington,THE SCIENCE AND PRACTICE OF PHARMACY,A.Gennaro等人编辑，第21版,Mack Publishing Co.(2005)。

[0194] 该药物组合物可单独或与免疫抑制/免疫调节及/或消炎剂以组合疗法(即，同时或依序)给予。药剂的示例性类型为细胞毒性T淋巴细胞相关蛋白4(CTLA4)突变体分子。示例性CTLA4突变体分子为L104EA29Y-Ig(贝拉希普)，其为经修饰CTLA4-Ig。不同免疫疾病可需要使用可用于治疗免疫疾病的特定辅助化合物，此可取决于患者与患者之间的具体情况决定。例如，药物组合物可与一或多种合适的佐剂例如细胞因子(例如IL-10及IL-13)或其他免疫刺激剂例如趋化因子、肿瘤相关抗原及肽组合给予。合适的佐剂为本领域中已知。

[0195] 治疗需要该治疗的患者中的免疫疾病的方法可包括向该患者给予治疗有效量的抗体或其抗原结合部分，如本申请所述。进一步提供一种治疗或预防需要该治疗的患者中的自体免疫或发炎性疾病的方法，该方法可包括向该患者给予治疗有效量的抗体或其抗原结合部分，如本申请所述。还提供本申请的抗体或其抗原结合部分或其医药上可接受的盐用于治疗需要该治疗的患者中的免疫疾病及/或于治疗或预防需要该治疗的患者中的自体免疫或发炎性疾病中的用途，其可包括向患者给予治疗有效量的抗体或其抗原结合部分。拮抗CD40介导的T细胞活化可抑制例如在自体免疫、移植排斥或过敏反应期间发生的非所欲T细胞反应。抑制CD40介导的T细胞活化可减轻这些疾病的进展及/或严重程度。

[0196] 还提供本申请的抗体或其抗原结合部分或其医药上可接受的盐在制备用于治疗需要该治疗的患者中的免疫疾病及/或用于治疗或预防自体免疫或发炎性疾病的药物中的用途。该药物可例如与免疫抑制剂/免疫调节剂及/或消炎剂组合给予。

[0197] 如本文所用，“患者”意指动物，例如哺乳动物，包括人类。患者可经诊断患有免疫疾病。“治疗”为指涉及减轻症状、病状、病症或疾病的进展或严重程度的过程。“免疫疾病”指与个体的免疫反应(包括细胞及/或体液免疫反应)的发展有关的任何疾病。免疫疾病的实例包括但不限于发炎、过敏、自体免疫疾病或移植物相关疾病。因此，患者可经诊断患有自体免疫疾病或发炎性疾病。“自体免疫疾病”为指与个体中自体免疫反应(包括细胞及/或体液免疫反应)的发展有关的任何疾病。自体免疫疾病的一个实例为发炎性肠病(IBD)，包括但不限于溃疡性结肠炎及克罗恩病。其他自体免疫疾病包括系统性红斑狼疮、多发性硬化症、类风湿关节炎、糖尿病、牛皮癣、硬皮病及动脉粥样硬化。移植相关疾病包括移植物抗宿主病(GVHD)、急性移植排斥及慢性移植排斥。

[0198] 可通过给予本申请的抗体治疗的疾病可选自以下组成的组：艾迪生氏病、过敏、过敏性反应、僵直性脊椎炎、哮喘、动脉粥样硬化、异位性过敏、耳部自体免疫疾病、眼部自体免疫疾病、自体免疫性肝炎、自体免疫性腮腺炎、支气管哮喘、冠心病、克罗恩病(Crohn's disease)、糖尿病、附睾炎、肾小球肾炎、格雷夫斯病(Graves' disease)、格林兰-巴雷症候群(Guillain-Barre syndrome)、桥本病(Hashimoto's disease)、溶血性贫血、特发性血小板减少性紫癜、发炎性肠病、对重组药物的免疫反应(例如血友病中的因子VII)、狼疮性肾炎、系统性红斑狼疮、多发性硬化症、重症肌无力、天疱疮、牛皮癣、风湿热、类风湿关节炎、结节病、硬皮病、休格连氏症候群(Sjogren's syndrome)、脊椎关节炎、甲状腺炎、移植排斥、血管炎及溃疡性结肠炎。

[0199] 该药物组合物可单独或与免疫抑制剂/免疫调节剂及/或消炎剂一起作为组合疗

法(即同时或依序)给予。不同免疫疾病可需要使用适用于治疗免疫疾病的特定辅助化合物,此可取决于患者的具体情况决定。例如,药物组合物可与一或多种合适的佐剂例如细胞因子(例如IL-10及IL-13)或其他免疫刺激剂例如趋化因子、肿瘤相关抗原及肽组合给予。合适的佐剂为本领域中已知。

[0200] 可使用任何合适的方法或途径来给予抗体或其抗原结合部分或药物组合物。给予途径包括例如静脉内、腹膜内、皮下或肌内给予。所给予抗体的治疗有效剂量取决于许多因素,包括例如所治疗的免疫疾病的类型及严重程度、组合疗法的使用、抗体的给予途径,或其抗原结合部分或药物组合物,及患者的体重。功能域抗体的治疗有效量的非限制性范围为相对于患者的体重,为0.1至20毫克/千克(mg/kg),及在一方面中,为1至10mg/kg。

[0201] 试剂盒

[0202] 提供一种用于治疗人类患者的免疫疾病的试剂盒。还提供一种用于治疗或预防人类患者的自体免疫疾病或发炎性疾病的试剂盒。该试剂盒可包含(a)本申请的抗体或其抗原结合部分的剂量及(b)在治疗免疫疾病的方法中使用该抗体或其抗原结合部分的指导材料,或在治疗或预防患者的自体免疫或发炎性疾病的方法中使用该抗体或其抗原结合部分的指导材料。

[0203] “指导材料”(如该术语在本文所用)包括出版物、记录、图表或任何其他表述媒体,其可用于传达试剂盒中本申请的组合物及/或化合物的有用性。试剂盒的指导材料可例如固定在含有本申请的化合物及/或组合物的容器上,或与含有该化合物及/或组合物的容器一起运输。或者,指导材料可与容器分开运输,以使接收者配合地使用指导材料及化合物。指导材料的递送可例如通过出版物或传达试剂盒的有用性的其他表述媒体的物理递送,或可替代地通过电子传输例如通过计算机,例如通过电子邮件,或自网站下载而达成。

实施例

[0204] 实施例1:小鼠抗人类CD40抗体与人类CD40的结合

[0205] 产生小鼠抗人类CD40抗体并通过表面胞质基因共振(SPR)测试与人类CD40的结合。表8显示每种抗体的Vh及Vk序列。

[0206] 表8

[0207] 小鼠抗人类CD40可变重链及轻链序列

[0208]

ID	VH序列	VL序列
	ADX_Y1060.ZZ0-1-Vh	ADX_Y1060.ZZ0-1-Vk
ADX_Y1060.ZZ0-1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSS (SEQ ID NO: 53)	DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIK (SEQ ID NO: 76)
	ADX_Y1072.ZZ0-1-Vh	ADX_Y1072.ZZ0-1-Vk
ADX_Y1072.ZZ0-1	QVQFQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLEWIGTIYPGDGDSRYNQKFKGKALLTADKSSSIAYMQLNSLASEDSAVYFCARFSLYDGYPYYFDYWGQGTTLTVSS (SEQ ID NO: 54)	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHRNGNTYLHWYLQKPGQSPKLLIYRVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGIYFCSQSTHFPYTFGGGTKLEIK (SEQ ID NO: 77)
	ADX_Y1234.ZZ0-1-Vh	ADX_Y1234.ZZ0-1-Vk

[0209]

ID	VH序列	VL序列
ADX_Y1234.ZZ0-1	EVQLVESGGGLVKPGGSLKLSCAASGFAFSSYDMSWVRQTPEKRLEWVAYINSGVGNTYYPDTVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYCARHGNYAWFAYWGQGTLVTVSA (SEQ ID NO: 55)	DILLTQSPAILSVSPGERVSFSCRASQSIGTSIHWYQQRTIGSPRLLIKYASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQINSWPLTFGAGTKLELK (SEQ ID NO: 78)
	ADX_Y1236.ZZ0-1-Vh	ADX_Y1236.ZZ0-1-Vk
ADX_Y1236.ZZ0-1	DVQLVESGGGLVQPGGSRKLSCAASGFTFSSFGMHWVRQAPEKGLEWVAYISSGSSTIYYADTVKGRFTISRDNPKNTLFLQMTSLRSEDTAMYYCARYGNYAMDYWGQGTSVTVSS (SEQ ID NO: 56)	DIVMTQSQKFMSTSVGDRISITCKASQNVRTAVAWYQQKPGQSPKALIYLASNRHTGVPARFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPLTFGAGTKLELK (SEQ ID NO: 79)
	ADX_Y1238.ZZ0-1-Vh	ADX_Y1238.ZZ0-1-Vk
ADX_Y1238.ZZ0-1	QVQLQQSGAELVRPGTSVKVSCKASGYAFTNYLIEWVKQRPGQGLEWIGVINPGSGGTNYNEKFKGKATLTADKSSSTAYMQLSSLTSDDSAVYFCARSQLGRRFDYWGQGTTLTVSS SEQ ID NO: 57)	DIVMTQSHKFMSTSVGDRVSITCKASQDVRTGVAWYQQKPGQSPKLLIYSASYRNTGVPDRFTGSRSGTDFTFTISSVQAEDLAVYYCQQHYSPPYTFGGGTKLEIK (SEQ ID NO: 80)
	ADX_Y1241.ZZ0-1-Vh	ADX_Y1241.ZZ0-1-Vk
ADX_Y1241.ZZ0-1	EFQLQQSGPELVKPGASVKMSCKASGYTFTNYIIQWVKKQPGQGLEWIGYINPYSSETNYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAIYFCARDLIGNY	DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPLTFGAGTKLE

[0210]

ID	VH序列	VL序列
	WGQGTTLTVSS (SEQ ID NO: 58)	LK (SEQ ID NO: 81)
	ADX_Y1242.ZZ0-1-Vh	ADX_Y1242.ZZ0-1-Vk
ADX_Y1242.ZZ0-1	EFQLQQSGPELVKPGASVKMSCKASGYSFTSYVMHWVKQKPGQALEWIGYINPSNDGSEYNERFKGKATLTSDKSSTTAYMELSSLTSEDSAVYYCARWAPYPFAYWGQGTLVTVSA (SEQ ID NO: 59)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPYTFGGGTKLEIK (SEQ ID NO: 82)
	ADX_Y1249.ZZ0-1-Vh	ADX_Y1249.ZZ0-1-Vk
ADX_Y1249.ZZ0-1	QVQLQQSGAELARPGASVKMSCKASGYTFTSYTMHWVKQRPGQGLEWIGYIDPSSHYTNYNQKFKGTATLTADKSSNTAYMQLSSLTSEDSAVYYCARDYRYAYWYFDVWGAGTTLTVSS (SEQ ID NO: 60)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 83)
	ADX_Y1256.ZZ0-1-Vh	ADX_Y1256.ZZ0-1-Vk
ADX_Y1256.ZZ0-1	QVQLQQSGAELAKPGSSVKMSCKASGYAFTSYWMHWVKQRPGQGLEWIGYINPTTGYSAYNQKFKDKATLTADKSSSTAYLQLTSLTSEDSAVYFCSRWGLPPFAYWGQGTLVTVSA (SEQ ID NO: 61)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 84)
	ADX_Y1257.ZZ0-1-Vh	ADX_Y1257.ZZ0-1-Vk
ADX_Y	QVQLQQSGAELAKPGSSVK	DIVMTQSHKFMSTSVGDRVSI

[0211]

ID	VH序列	VL序列
1257.ZZ0-1	MSCKASGYAFTSYWMHWVKQRPGQGLEWIGYINPTTGYSAYNQKFKAKTTLTADKSSSTAYMQLTSLTFEDSAVYFCSRWGLPPFAYWGQGTLVTVSA (SEQ ID NO: 62)	TCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 85)
	ADX_Y1258.ZZ0-1-Vh	ADX_Y1258.ZZ0-1-Vk
ADX_Y1258.ZZ0-1	QVQLQQSGAELAKPGSSVKMSCKASGYAFTSYWMHWIKQRPGQGLEWIGFINPTTGYSEYNQKFKDKATLTADKSSSTAYMQLNSLTSEDSAVYFCARWGLPPFAYWGQGTLVTVSA (SEQ ID NO: 63)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 86)
	ADX_Y1259.ZZ0-1-Vh	ADX_Y1259.ZZ0-1-Vk
ADX_Y1259.ZZ0-1	QVQLQQSGAELAKPGASVKMSCKTSGYSFTSYWMHWIKQRPGQGLEWIGFINPTTGYTEYNQKFKDKATLTADKSSSTAYMQLSSLSSEDSAVYYCSRWGLPPFAYWGQGTLVTVSA (SEQ ID NO: 64)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 87)
	ADX_Y1260.ZZ0-1-Vh	ADX_Y1260.ZZ0-1-Vk
ADX_Y1260.ZZ0-1	QVQLQQSGAELTKPGASVKMSCKASGYSFTSYWMHWVKQRPGQGLEWIGSINPSTGYTEDNQKFKDKATLTADKSSTTAYMQLSSLTSEDSAVYYCARWGLPPFAYWGQGTLVTVSA	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK

[0212]

ID	VH序列	VL序列
	(SEQ ID NO: 65)	(SEQ ID NO: 88)
	ADX_Y1261.ZZ0-1-Vh	ADX_Y1261.ZZ0-1-Vk
ADX_Y1261.ZZ0-1	QVQLQQSGAERAKPGASVKMSCKASGYSFTSYWMHWIKQRPGQGLEWIGFINPNTGHTDYNQKFKDKATLTADKSSSTAYMQLSSLTSEDSAVYFCSRWGLPPFAYWGQGTLVTVSA (SEQ ID NO: 66)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 89)
	ADX_Y1262.ZZ0-1-Vh	ADX_Y1262.ZZ0-1-Vk
ADX_Y1262.ZZ0-1	QVQLQQSGAELAKPGSSVKMSCKASGYAFTSYWMHWVKQRPGQGLEWIGYINPTTGYSAYNQKFKDKATLTADKSSSTAYMQLNSLTSEDSAVYYCARWDPRPFAYWGQGTLVTVSA (SEQ ID NO: 67)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGYGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 90)
	ADX_Y1263.ZZ0-1-Vh	ADX_Y1263.ZZ0-1-Vk
ADX_Y1263.ZZ0-1	QVQLQQSGAELAKPGTSVKMSCKASGYSFTSYWVHWVKERPGQGLEWIGHTNPNTGYTEYNQKFKDKATLTVDRSSSTAYMQLNSLTSEDSAVYYCARWDPRPFAYWGQGTLVTVSA (SEQ ID NO: 68)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 91)
	ADX_Y1264.ZZ0-1-Vh	ADX_Y1264.ZZ0-1-Vk
ADX_Y1264.ZZ0-1	EVQLQQSGTVLARPGASVKMSCRASGYSFSSYWMHWVKQRPGQGLEWIGSINPGNSDAF	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFT

[0213]

ID	VH序列	VL序列
	YNQQFKGKAKLTAVTSASTA YMELSSLTNEDSAVYYCTRW GLPPFAYWGQGTLVTVSA (SEQ ID NO: 69)	GSGSGTDFTFTISSVQAEDLAV YYCHQHYSTPWTFGGGTKLEI K (SEQ ID NO: 92)
	ADX_Y1265.ZZ0-1-Vh	ADX_Y1265.ZZ0-1-Vk
ADX_Y1265.ZZ0-1	EVQLQQSGTVLAGPGASVK MSCKASGYSFTSYWMHWVK QRPGQDLEWIGTINPGKGDS NYNQKFKGKAKLTAVTSAST AYMELSSLTNEDSAVYYCTR WGLPPFAYWGQGTLVTVSA (SEQ ID NO: 70)	DIVMTQSHKFMSTSVGDRVSI TCKASQDVSTAVAWYQQKPG QSPKLLIYSASYRYTGVPDRFT GSGSGTDFTFTISSVQAEDLAV YYCQQHYSTPWTFGGGTKLEI K (SEQ ID NO: 93)
	ADX_Y1266.ZZ0-1-Vh	ADX_Y1266.ZZ0-1-Vk
ADX_Y1266.ZZ0-1	QVQLQQPGAELVKPGASVRL SCKASGYSFTSYWMHWVKQ RPGQGLEWIGQINPSNGRTQ YNEKFKSMATLTVDKSSSTA YIQLSSLTSEDSAVYYCARWG LQPFAYWGQGTLVTVSA (SEQ ID NO: 71)	DIVMTQSHKFMSTSVGDRVSI TCKASQDVSTAVAWYQQKPG QSPKLLIYSASYRYTGVPDRFT GSGSGTDFTFTISSVQAEDLAV YYCQQHYSTPWTFGGGTKLEI K (SEQ ID NO: 94)
	ADX_Y1267.ZZ0-1-Vh	ADX_Y1267.ZZ0-1-Vk
ADX_Y1267.ZZ0-1	QVQLQQPGAELVKPGASVRL SCEASGYSFTSYWMHWVKQ RPGQGLEWIGQINPSNGRTQ YNEKFKSMATLTVDKSSSTA YIQLNSLTSEDSAVYYCARW GLQPFAYWGQGTLVTVSA (SEQ ID NO: 72)	DIVMTQSHKFMSTSVGDRVSI TCKASQDVSTAVAWYQQKPG QSPKLLIYSASYRYTGVPDRFT GSGSGTDFTFTISSVQAEDLAV YYCLQHYTTPWTFGGGTKLEI K (SEQ ID NO: 95)
	ADX_Y1268.ZZ0-1-Vh	ADX_Y1268.ZZ0-1-Vk

[0214]

ID	VH序列	VL序列
ADX_Y1268.ZZ0-1	QVQLQQPGAELVKPGASVRLSCKASGYAFTSYWMHWVKQRPGQGLEWIGQINPSNGRSQYNEKFKTMATLTVDKSSSTAYIQLSSLTSEDSAVYYCARWGLQPFAYWGQGTLVTVSA (SEQ ID NO: 73)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK (SEQ ID NO: 96)
	ADX_Y1269.ZZ0-1-Vh	ADX_Y1269.ZZ0-1-Vk
ADX_Y1269.ZZ0-1	QVQLQQSGAELPRPGASVKMSCKASGYTFTDYTVHWVKQRPGQGLEWIGYINPSSSYTSYDQKFKDKATVTADKSSSTAYMQLSSLTSEDSAVYYCARRTMYWYFDIWGAGTTVTVSS (SEQ ID NO: 74)	DIVMTQSHKFMSTSVGDRVSITCKASQDVSPNVAWYQQKPGQSPKLLIYSTSYRYTGVPDRFTGSRSGTDFTFTISSVQAEDLAIYYCQQHYSTPLTFGAGTKLELK (SEQ ID NO: 97)
	ADX_Y1297.ZZ0-1-Vh	ADX_Y1297.ZZ0-1-Vk
ADX_Y1297.ZZ0-1	QVQLQQSGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEIDPSDSYTNYNQNFKGKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARETYYYGSRFPYWGQGTLVTVSA (SEQ ID NO: 75)	DIVMTQSHKFMSTSVGDRVSVTCKASQNVRINVAWYQQKPGQSPKALIYSASYRYSGVPDRFTGSGSGTDFTLTITNVQSEDLAEYFCQQYNTYPLTFGAGTKLELK (SEQ ID NO: 98)

[0215] 通过SPR评估人类CD40单体与捕获在蛋白A传感器芯片表面上的小鼠抗人类CD40抗体结合的CD40动力学及亲合力数据。数据显示于表9中。显示的数据为针对单一浓度CD40分析物(1μM)且因此报告为表观(app)值。

[0216] 表9

[0217] SPR动力学/亲合力数据

[0218]

抗体	$ka_{,app}$ (1/Ms)	$kd_{,app}$ (1/s)	KD_{app} (M)
ADX_Y1072.ZZ0-1	7.7E+04	9.2E-03	1.2E-07
ADX_Y1238.ZZ0-1	5.5E+04	1.2E-04	2.2E-09
ADX_Y1258.ZZ0-1	1.7E+04	1.3E-04	7.9E-09
ADX_Y1260.ZZ0-1	5.2E+04	2.1E-04	4.0E-09
ADX_Y1262.ZZ0-1	3.7E+05	2.5E-03	6.6E-09
ADX_Y1264.ZZ0-1	1.4E+04	2.3E-04	1.7E-08
ADX_Y1267.ZZ0-1	3.7E+05	4.1E-04	1.1E-09
ADX_Y1268.ZZ0-1	3.2E+05	4.6E-04	1.4E-09

[0219] 基于SPR数据及序列数据,选择三种抗体ADX_Y1258.ZZ0-1、ADX_Y1262.ZZ0-1及ADX_Y1268.ZZ0-1用于人源化。

[0220] 实施例2:Y12XX的人源化及人源化变体的选择

[0221] 人源化背景/程序为如WO2017004006中的章节“II.经工程改造及修饰的抗体(Engineered and Modified Antibodies)”中所讨论,其以全文引用的方式并入本文。基于此分析,选择九(9)个人源化Vh序列(Vh-hz1、Vh-hz2、Vh-hz3、Vh-hz4、Vh-hz5、Vh-hz6、Vh-hz9、Vh-hz10及Vh-hz11)及三(3)个人源化Vκ序列(Vk-hz1、Vk-hz2及Vk-hz3)进行测试。此外,设计五(5)个人源化Vh序列(Vh-hz7、Vh-hz8、Vh-hz12、Vh-hz13及Vh-hz14)以包含旨在降低所设计的化学责任风险的突变。突变包括D100Q(Y1262_IGHV1.6908-D100Q)及P101A(Y1262_IGHV1.6908-P101A)突变,以减轻Y1262_IGHV1.6908中潜在的水解风险。突变还包括N55Q(Y1268_IGHV1.6908-N55Q)、G56A(Y1268_IGHV1.6908-G56A)及S54T-N55T双突变(Y1268_IGHV1.6908-S54T-N55T),以减轻Y1268_IGHV1.6908中潜在的脱酰胺风险。S54T-N55T双突变为基于ADX_Y1262.ZZ0-1-Vh中这些位置发现的相应氨基酸残基设计。参见表10。

[0222] 这些变体的序列显示于表10中。

[0223] 表10

[0224]

ID	可变 Hz#	SEQ ID NO:	序列
Y1258-Vh	Vh-C1	99	QVQLQQSGAELAKPGSSVKMSCKASGY AFTSYWMHWIKQRPGQGLEWIGFINPTT GYSEYNQKFKDKATLTADKSSSTAYMQL NSLTSEDSAVYFCARWGLPPFAYWGQGT LVTVSA
Y1258_IGHV1 .6908-Vh	Vh-hz1	100	QVQL**V**QSGAE**VK**KPGSSVK**V**SCKASGY AFTSYWMHW**VR**QA**P**GQGLEW**M**GFINP TTGYSEYNQKFKD**RV**T**I**TADKS**T**STAYM **E**L**S**SL**R**SED**T**AV**Y**YCARWGLPPFAYWGQ GTLVTVS**S**
Y1258_IGHV1 .6908_A40R-V h	Vh-hz2	101	QVQL**V**QSGAE**VK**KPGSSVK**V**SCKASGY AFTSYWMH**WVR**QRPGQGLEW**M**GFINP TTGYSEYNQKFKD**RV**T**I**TADKS**T**STAYM **E**L**S**SL**R**SED**T**AV**Y**YCARWGLPPFAYWGQ GTLVTVS**S**
Y1258_IGHV1 .6908_ A40R-M48I-S 84N-Vh	Vh-hz3	102	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQRPGQGLEWIGFINPTTG YSEYNQKFKDRVTITADKSTSTAYMELNS LRSEDTAVYYCARWGLPPFAYWGQGTLV TVSS
Y1262-Vh	Vh-C2	103	QVQLQQSGAELAKPGSSVKMSCKASGY

[0225]

ID	可变 Hz#	SEQ ID NO:	序列
			AFTSYWMHWVKQRPGQGLEWIGYINPT TGYSAYNQKFKDKATLTADKSSSTAYMQ LNSLTSEDSAVYYCARWDPRPFAYWGQG TLVTVSA
Y1262_IGHV1 .6908-Vh	Vh-hz4	104	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQAPGQGLEWMGYINPTT GYSAYNQKFKDKATLTADKSTSTAYMEL SSLRSEDTAVYYCARWDPRPFAYWGQGT LVTVSS
Y1262_IGHV1 .6908_A40R-V h	Vh-hz5	105	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQRPGQGLEWMGYINPTT GYSAYNQKFKDKATLTADKSTSTAYMEL SSLRSEDTAVYYCARWDPRPFAYWGQGT LVTVSS
Y1262_IGHV1 .6908_A40R-M48I-S84N-V h	Vh-hz6	106	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQRPGQGLEWIGYINPTT GYSAYNQKFKDKATLTADKSTSTAYMEL NSLRSEDTAVYYCARWDPRPFAYWGQGT LVTVSS
Y1262_IGHV1 .6908-D100Q-Vh	Vh-hz7	107	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQAPGQGLEWMGYINPTT GYSAYNQKFKDKATLTADKSTSTAYMEL SSLRSEDTAVYYCARWQPRPFAYWGQGT LVTVSS
Y1262_IGHV1 .6908-P101A-Vh	Vh-hz8	108	QVQLVQSGAEVKKPGSSVKVSCKASGYA FTSYWMHWVRQAPGQGLEWMGYINPTT GYSAYNQKFKDKATLTADKSTSTAYMEL SSLRSEDTAVYYCARWDARPFAYWGQGT

[0226]

ID	可变 Hz#	SEQ ID NO:	序列
			LVTVSS
Y1268-Vh	Vh-C3	109	QVQLQQPGAELVKPGASVRLSCKASGYAFTSYWMHWVKQRPGQGLEWIGQINPSNGRSQYNEKFKTMATLTVDKSSSTAYIQLSSLTSEDSAVYYCARWGLQPFAYWGQGTLVTVSA
Y1268_IGHV1.6908-Vh	Vh-hz9	110	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSNGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1268_IGHV1.6908_A40R-Vh	Vh-hz10	111	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQRPGQGLEWMGQINPSNGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1268_IGHV1.6908_A40R-M48I-Vh	Vh-hz11	112	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQRPGQGLEWIGQINPSNGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1268_IGHV1.6908-N55Q-Vh	Vh-hz12	13	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1268_IGHV1	Vh-hz1	113	QVQLVQSGAEVKKPGSSVKVSCKASGYA

[0227]

ID	可变 Hz#	SEQ ID NO:	序列
.6908-G56A-Vh	3		FTSYWMHWVRQAPGQGLEWMGQINPSNARSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1268_IGHV1.6908-S54T-N55T-Vh	Vh-hz14	4	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS
Y1258-Vk	Vk-C1	114	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK
Y1262-Vk	Vk-C2	115	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTGSGYGTDFTFTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLEIK
Y1258_IGKV1.3301-Vk	Vk-hz1	116	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQHYSTPWTFGGGTKVEIK
Y1258_IGKV1.3902-Vk	Vk-hz2	10	DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIK
Y1258_IGKV3.1501-Vk	Vk-hz3	16	EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGI

[0228]

ID	可变 Hz#	SEQ ID NO:	序列
			PARFSGSGSGTEFTLTISSLQSEDFAVYYC QQHYSTPWTFGGGTKVEIK

[0229] 表10提供用于构建人源化抗体以及嵌合抗体对照的重链及轻链可变域序列,以用于使用BIAcore™表面胞质基因共振(SPR)的CD40结合分析以及Octet BLI效价分析(下文讨论)。

[0230] Vh序列用IgG1-P238K同型物(CH1-IgG1-P238K;SEQ ID NO:25)格式化。Vκ序列被格式化为具有共同CL序列的全轻链(SEQ ID NO:11的氨基酸108至214)。在表11中,“Y1258”及“Y1262”为指含有小鼠可变区及人类恒定区的嵌合分子。人源化HC构建体及LC构建体以及嵌合Y1258及Y1262分子的各种不同组合表示为3毫升(ml)上清液,用于效价分析及CD40结合分析。分子家族统一地以“Y12XX”为前缀,后接“hz#”后缀,以唯一标识不同重链/轻链对加以识别。

[0231] 效价分析为在Octet RED仪器(Fortebio)上使用生物层干涉术(BLI),通过使用蛋白A传感器顶端自上清液捕获抗体,并测量相对于使用对照抗体样品获得的标准曲线的捕获反应进行。SPR数据为通过使用BIAcore™ T200仪器(GE Healthcare)在蛋白A表面捕获抗体并测试人类CD40分析物的500nM及50nM注射液的结合来获得。将两种浓度的hCD40单体的动力学数据拟合至1:1朗谬尔模型,以得出这些相互作用的动力学及亲合力值的估计值,并比较不同分子。

[0232] Octet效价及BIAcore™ SPR CD40结合数据提供于表11中。除了测试上清液(“sup”)样品,通过SPR测试作为对照的含有人类野生型IgG1f同型物(ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK;SEQ ID NO:117)的纯化的嵌合Y1258、Y1262及Y1268抗体;这些在表11中命名为“Y1258-hIgG1f”、“Y1632-hIgG1f”及“Y1268-hIgG1f”,且Vh及Vk链记为“Chim-P”。)

[0233] 表11

[0234] Octet效价及BIAcore™ SPR CD40结合数据

[0235]

抗体ID	Vh	Vk	样品	效价 (μg/ml)	ka (1/Ms)	kd (1/s)	KD (M)
Y1258-hIgG1f	Chim-P	Chim-P	纯化	n/a	5.8E+04	*5.9E-07*	*1.0E-11*
Y1258	Vh-C1	Vk-C1	sup	54.2	5.6E+04	*3.8E-06*	*6.7E-11*
Y12XX-hz1	Vh-hz1	Vk-hz1	sup	3.8	1.5E+04	1.6E-05	1.1E-09
Y12XX-hz15	Vh-hz1	Vk-hz2	sup	34.6	1.6E+04	1.3E-04	8.0E-09
Y12XX-hz29	Vh-hz1	Vk-hz3	sup	56.7	3.7E+04	*2.6E-06*	*6.9E-11*
Y12XX-hz2	Vh-hz2	Vk-hz1	sup	4.5	1.7E+04	7.1E-05	4.1E-09
Y12XX-hz16	Vh-hz2	Vk-hz2	sup	58.6	2.0E+05	6.4E-04	3.2E-09
Y12XX-hz30	Vh-hz2	Vk-hz3	sup	82.6	4.1E+04	*7.3E-07*	*1.8E-11*
Y12XX-hz3	Vh-hz3	Vk-hz1	sup	6.4	1.5E+04	6.7E-05	4.5E-09
Y12XX-hz17	Vh-hz3	Vk-hz2	sup	50.7	3.7E+05	7.7E-02	2.1E-07
Y12XX-hz31	Vh-hz3	Vk-hz3	sup	93.9	4.1E+04	*2.9E-07*	*7.0E-12*
Y1262-hIgG1f	Chim-P	Chim-P	纯化	n/a	4.8E+05	5.5E-03	1.2E-08
Y1262	Chim	Chim	sup	92.2	3.5E+05	2.8E-03	8.0E-09
Y12XX-hz4	Vh-hz4	Vk-hz1	sup	4.7	4.6E+05	2.2E-03	4.7E-09
Y12XX-hz18	Vh-hz4	Vk-hz2	sup	73.6	3.5E+05	2.4E-03	7.1E-09
Y12XX-hz32	Vh-hz4	Vk-hz3	sup	104.3	2.9E+05	3.0E-03	1.0E-08
Y12XX-hz5	Vh-hz5	Vk-hz1	sup	4.5	3.5E+05	2.5E-03	7.2E-09
Y12XX-hz19	Vh-hz5	Vk-hz2	sup	56.7	3.8E+05	2.3E-03	6.2E-09
Y12XX-hz33	Vh-hz5	Vk-hz3	sup	85.5	2.9E+05	3.3E-03	1.1E-08
Y12XX-hz6	Vh-hz6	Vk-hz1	sup	6.7	3.8E+05	2.4E-03	6.4E-09
Y12XX-hz20	Vh-hz6	Vk-hz2	sup	50.3	3.1E+05	2.5E-03	8.2E-09
Y12XX-hz34	Vh-hz6	Vk-hz3	sup	93.7	3.7E+05	2.8E-03	7.6E-09
Y12XX-hz8	Vh-hz8	Vk-hz1	sup	11.2	7.2E+05	1.5E-01	2.1E-07

[0236]

抗体ID	Vh	Vk	样品	效价(μg/ml)	ka (1/Ms)	kd (1/s)	KD (M)
Y12XX-hz22	Vh-hz8	Vk-hz2	sup	49.1	3.7E+05	7.9E-02	2.1E-07
Y12XX-hz36	Vh-hz8	Vk-hz3	sup	136.7	3.9E+05	1.0E-01	2.5E-07
Y1268-hIgG1f	Chim-P	Chim-P	纯化	n/a	4.0E+05	1.3E-03	3.2E-09
Y12XX-hz9	Vh-hz9	Vk-hz1	sup	5.1	2.0E+05	8.9E-04	4.6E-09
Y12XX-hz23	Vh-hz9	Vk-hz2	sup	59.4	2.0E+05	6.4E-04	3.2E-09
Y12XX-hz37	Vh-hz9	Vk-hz3	sup	138.4	2.6E+05	8.4E-04	3.3E-09
Y12XX-hz10	Vh-hz10	Vk-hz1	sup	8.6	2.0E+05	7.3E-04	3.6E-09
Y12XX-hz24	Vh-hz10	Vk-hz2	sup	48.1	1.9E+05	8.2E-04	4.4E-09
Y12XX-hz38	Vh-hz10	Vk-hz3	sup	185.5	2.5E+05	8.8E-04	3.6E-09
Y12XX-hz11	Vh-hz11	Vk-hz1	sup	7.5	1.8E+05	8.8E-04	5.0E-09
Y12XX-hz25	Vh-hz11	Vk-hz2	sup	55.4	1.9E+05	6.4E-04	3.4E-09
Y12XX-hz39	Vh-hz11	Vk-hz3	sup	134.2	2.4E+05	8.4E-04	3.5E-09
Y12XX-hz12	Vh-hz12	Vk-hz1	sup	2.7	1.7E+05	1.4E-03	8.3E-09
Y12XX-hz26	Vh-hz12	Vk-hz2	sup	36.8	1.6E+05	1.2E-03	7.5E-09
Y12XX-hz40	Vh-hz12	Vk-hz3	sup	99.8	2.4E+05	1.1E-03	4.7E-09
Y12XX-hz13	Vh-hz13	Vk-hz1	sup	3.0	2.1E+05	8.3E-04	3.9E-09
Y12XX-hz27	Vh-hz13	Vk-hz2	sup	49.5	1.9E+05	8.8E-04	4.7E-09
Y12XX-hz41	Vh-hz13	Vk-hz3	sup	52.7	2.5E+05	9.4E-04	3.8E-09
Y12XX-hz14	Vh-hz14	Vk-hz1	sup	5.0	1.7E+05	8.3E-04	5.0E-09
Y12XX-hz28	Vh-hz14	Vk-hz2	sup	70.1	1.8E+05	6.2E-04	3.5E-09
Y12XX-hz42	Vh-hz14	Vk-hz3	sup	100.0	2.4E+05	8.3E-04	3.5E-09

[0237] 对于给定重链构建体,当与含有Vk-hz3(SEQ ID NO:18)的轻链配对时,效价一般最高,对于与Vk-hz2(SEQ ID NO:10)配对的重链,效价较低,及对于与含有Vk-hz1(SEQ ID NO:116)的轻链配对的重链,效价最低。

[0238] SPR分析数据显示抗体以可变亲合力结合CD40,其中KD值的范围从大于1E-07至小于1E-09。对于某些抗体,亲合力太强以致于无法在此分析法中以置信度准确地确定,因为解离速率太慢以致于无法测量。在表中以斜体显示的这些值超出此分析法中准确定量的限值。

[0239] 基于序列、效价及SPR结合数据,选择抗体用于大规模表达、纯化及进一步表征。使用纯化抗体的SPR分析为通过在25℃或37℃的PBS-T pH 7.1缓冲液中捕获蛋白A表面上结合500-3.9nM(2:1)稀释系列的人类CD40单体的抗体来进行;滴定数据拟合至1:1朗谬尔模型。数据提供于表12中。

[0240] 表12

[0241] SPR动力学/亲合力数据

[0242]

		25℃			37℃		
配位体	样品	ka (1/Ms)	kd (1/s)	KD (nM)	ka (1/Ms)	kd (1/s)	KD (nM)
Y12XX-hz28	hCD40	2.2E+05	6.9E-04	3.1	4.4E+05	3.7E-03	8.5
Y12XX-hz40	hCD40	2.9E+05	1.3E-03	4.4	5.2E+05	5.7E-03	10.9
Y12XX-hz42	hCD40	3.1E+05	7.3E-04	2.3	6.3E+05	3.4E-03	5.5
抗体B		6.1E+04	2.3E-03	37			

[0243] 这些数据显示,所选择的Y12XX抗体在25℃下以高亲合力及KD＝1E-9M的范围内的KD值结合。将该结合与另一种抗CD40抗体(抗体BI-mAb-B(美国专利案第9,090,696号,重链序列SEQ ID NO:32及轻链序列SEQ ID NO:31;在本文中称为“抗体B”及“BI-LALA”))的结合进行比较。如表12中的数据所示,抗体B以比人源化Y12XX分子低得多的亲合力结合CD40。

[0244] 所有三种人源化形式的Y12XX抗体为用CD40L-IZ三聚体激动剂刺激的B细胞增殖的强效拮抗剂。参见表13。

[0245] 表13

[0246] 可溶性CD40L三聚体诱导的B细胞增殖的抑制。

[0247]

	平均值(IC_{50} ng/ml)	标准偏差 (STDEV)	n个供体
抗体B	9.4	3.9	6
Y12XX-hz28-P238K	6.7	3.6	8
Y12XX-hz40-P238K	6.0	4.7	2
Y12XX-hz42-P238K	12.1	2.3	2

[0248] Y12XX-hz28-P238K还为用来自表达CD40L的CHO细胞的细胞CD40L刺激的B细胞增殖的强效拮抗剂。参见表14。

[0249] 表14

[0250] 抑制B细胞增殖的表达CD40L的CHO细胞刺激的效力

[0251]

	效力(抑制%的IC50 ng/ml)	标准偏差	n个供体
抗体B	62%*	25%	6
Y12XX-hz28-P238K	38.1	9.8	8

[0252] *在所测试的最高剂量(1至3μg/ml)下的抑制%

[0253] 将人源化Y12XX抗体的数据与抗体B的数据进行比较,抗体B显示可溶性CD40L信号驱动的B细胞增殖的强效抑制,但对细胞CD40L(过度表达CD40L的CHO细胞)驱动的B细胞增殖的抑制的效果则差得多。相反,人源化Y12XX抗体在抑制细胞表面CD40L刺激的效力上仅显示<10倍的变化,从而提供对CD40L的B细胞反应的更稳健阻断。

[0254] 用IgG1-P238K同型物(CH1-IgG1-P238K;SEQ ID NO:25)格式化人源化Y12XX抗体,以降低对FcγR的结合亲合力并减少FcγR介导的信号传导。将具有此IgG1-P238K同型物的代表性人源化Y12XX抗体(Y12XX-hz28-IgG1-P238K)的FcγR结合与以野生型IgG1同型物格式化的对照抗体(对照-IgG1)以及具有含有突变L234A-L235A的IgG1同型物的抗体B的结合进行比较。这些L234A-L235A突变还经引入以减少FcγR结合。

[0255] FcγR结合的SPR研究为通过在蛋白A传感器芯片表面捕获抗体并结合经纯化的His标记的人类FcγR作为分析物来进行。hCD64结合由10μM-1.5nM hCD64的滴定(2:1稀释系列)组成,而低亲合力FcγR hCD32a-H131、hCD32a-R131、hCD32b、hCD16a-V158及hCD16a-F158的数据由10uM-13.7nM FcγR蛋白的滴定组成

[0256] 对照-IgG1抗体证实与所有测试的FcγR结合。参见图1A。与野生型相比,Y12XX-hz28-IgG1-P238K抗体证实与hCD64的结合弱125倍,且证实未侦测到与测试的任何低亲合力FcγR hCD32a-H131、hCD32a-R131、hCD32b、hCD16a-V158及hCD16a-F158的结合。参见图1B。抗体B还证实比野生型IgG1弱的hCD64结合,但也证实与hCD16a-V158的明显结合(KD=7μM)及与hCD32a-H131及hCD32a-R131的一些弱结合。参见图1C。KD值提供于图1D中。

[0257] 进一步测试在Fc区中具有P238K突变的抗体Y12XX的人源化形式的任何激动剂活性。单核细胞衍生的未成熟树突状细胞(iDC)对CD40活化非常敏感,CD40刺激后增加细胞因子产生(IL-6)并上调活化的表面标志物(CD86及CD54)。因此,测试最有希望的人源化Y12XX抗体,以评定其刺激iDC的能力。CD40抗体促效CD40的能力可通过将该分子的Fc部分与细胞表面FcγR的集群或交联结合来增强。添加高过度表达CD32a的CHO细胞,使用低亲合力FcγR来评估FcγR介导的集群/交联的潜力。在这些实验中,CHO细胞与iDC的比率为1:6,表示集群/交联的潜在夸大程度。使用BMS-986090及2141作为阳性对照。BMS-986090为与IgG4 Fc融合的抗CD40拮抗剂功能域抗体(参见WO 2012/145673中的SEQ ID NO:1287)。2141(mAb 134-2141)为部分CD40激动剂(参见Robert Vonderheide等人,2007,J.Clin.Oncol.25(7):876-883)。L6-IgG4为无CD40结合能力的融合蛋白,且可用作阴性对照。

[0258] 如图2中的数据所示,部分激动剂2141或BMS-986090的添加仅导致供体的子集中iDC的弱活化。然而,将表达CD32a的CHO细胞添加至2141或BMS-986090中导致几乎每个所测

试的供体中的IL-6产生(图2B)及CD86及CD54上调(分别为图2B及图2C)的稳健增加,与这些分子经由其Fc部分的FcγR介导的集群从而导致CD40活化相一致。相反,单独Y12XX-hz28-P238K及Y12XX-hz40-P238K或与CD32依赖性集群并不显示iDC活化高于使用6至10个供体的iDC细胞的阴性对照观测到的iDC活化的任何迹象。Y12XX-hz42-P238K在来自4个供体的细胞中进行测试,且仅在四个供体中的一个显示弱活化(包括IL-6产生及CD86及CD54上调)的迹象,与利用2141或BMS-986090所见的活性不同,此不依赖于表达CD32a的CHO细胞的添加。

[0259] 用于实施例1及2的材料及方法

[0260] FcγR结合SPR:FcγR结合可使用经纯化的FcγR,使用方法例如BIAcore™表面胞质基因共振(SPR)于体外加以测量。一种方法测试经纯化的His标记的FcγR蛋白(FcγR-his)与包含蛋白A的传感器表面上捕获的抗体的结合,蛋白A已使用标准乙基(二甲基胺基丙基)碳二亚胺(EDC)/N-羟基琥珀酰亚胺(NHS)化学过程以乙醇胺阻断固定。这些实验为在25℃的BIAcore™ T200仪器(GE Healthcare,Marlborough,MA)上进行。例如,首先以10μl/min流速使用15秒接触时间将3μg/ml浓度的经纯化抗体样品捕获在经固定的蛋白A表面上。接着使用120秒缔合及解离时间,以30μ/min流速使各种浓度例如10μM-1.5nM(2:1稀释系列)或10μM-13.7nM(2:1稀释系列)的经纯化的FcγR-His蛋白结合。所有步骤均在由10mM $NaPO_4$、130mM NaCl、0.05%p20(PBS-T)pH 7.1组成的运行缓冲液中进行。这些研究中测试的FcγR蛋白包括“高亲合力”FcγRCD64(hFcγRI),以及“低亲合力”FcγR CD32a-H131(FcγRIIa-H131)、CD32a-R131(FcγRIIa-R131)、CD32b(FcγRIIb)、CD16a-V158(FcγRIIIa-V158)及CD16a-F158(FcγRIIIa-F158),其在内部经表达并纯化。使用BIAcore™ T200评估软件将SPR数据拟合至1:1朗谬尔模型或1:1稳态模型,以获得缔合速率常数(ka)、解离速率常数(kd)及解离常数(K_D)的值。

[0261] 为比较不同FcγR的结合反应,SPR数据可使用以下等式,通过计算最大结合反应占理论最大结合反应的百分比(%Rmax)来分析:

[0262] 等式1:%Rmax=(结合反应分析物)/[((Mw分析物)/(Mw配位体))x(反应配位体)x(分析物:配位体化学计量)]

[0263] 其中“分析物”为FcγR及“配位体”为捕获的抗体。此分析未考虑抗体或FcγR的糖基化质量,并假设捕获的配位体具有100%分率的活性。由于FcγR为经糖基化,因此在饱和条件下,%Rmax值通常大于100%。

[0264] CD40结合动力学及亲合力:抗体分子的单价CD40结合亲合力为通过在BIAcore™ T200仪器(GE Healthcare Life Sciences)上在25℃或37℃下的表面胞质基因共振(SPR),通过在经固定的蛋白A传感器芯片表面上捕获抗体,及然后于PBS-T(pH 7.1)中使用例如180秒缔合时间及180秒或360秒解离时间以30μl/min的速度结合人类-CD40-单体蛋白(在内部产生)来量测。使用BIAcore™ T200评估软件将SPR数据拟合至1:1朗谬尔模型,以获得缔合速率常数(ka)、解离速率常数(kd)及解离常数(KD)的值。

[0265] 效价分析:效价分析为在25℃下在Octet®RED仪器(ForteBio,Freemont,CA)上使用生物层干涉术(BLI)进行。使用蛋白A传感器顶端,使用120秒缔合时间自上清液中捕获抗体,并测量结合反应,并将结合反应与使用对照抗体样品获得的标准曲线进行比较,以确定上清液中的抗体浓度。

[0266] 原代细胞的分离及培养:通过Ficoll密度梯度分离自肝素化人类血液分离的外周

血单核细胞(PBMC)。按照Manual EasySep™方案(STEMCELL,Vancouver,Canada)自PBMC分离单核细胞。将一百万个经分离单核细胞接种在6孔板的每个孔中的含有IL-4(100ng/ml)及GM-CSF(100ng/ml)的6mL完全培养基(RPMI-1640,10%热灭活的胎牛血清,100单位/ml青霉素-链霉素)中,并在37℃/5%CO_2下培养6天,隔天更换培养基,并用含有相同浓度细胞因子的新鲜培养基替换。在第6天收获iDC(未成熟树突状细胞),彻底洗涤,及重悬于完全培养基中。

[0267] 在存在或不存在FcγR集群/交联的情况下,用抗CD40抗体处理iDC:在完全培养基中滴定各种生物试剂,并添加至双份96孔板中。在交联的情况下,在以1:6的比率添加表达CD32a的CHO之前,将抗体添加至细胞持续30分钟。将细胞在37℃/5%CO_2下培养约18至20小时,自每个孔移除150μL上清液,以1:5稀释,并使用市售ELISA试剂盒(R&D Systems,Minneapolis,MN)根据制造商的说明评估IL-6、TNFα及IL-12的蛋白质浓度。每次重复处理后,将自收获的上清液中保留在板中的细胞合并为1个样品,并转移至新96孔圆底(RB)板中,并置于4℃下。细胞用不含Ca++及Mg++的D-PBS洗涤,并针对细胞存活率,使用LIVE /DEAD®可固定的近红外死细胞染色试剂盒(Invitrogen,Carlsbad,CA)在冰上染色30分钟。将细胞洗涤并重悬于D-PBS(不含Ca++及Mg++)、2%FBS、0.1%NaN_3(染色缓冲液)中,并用5μl/孔的含在染色缓冲液中的Human TruStain FcX™(Fc受体阻断溶液,Biolegend,San Diego,CA)阻断。

[0268] 用以下物质免疫染色DC:PerCpCy5.5-结合的αCD3、αCD19、αCD14(Lin^-)、BUV395-结合的αCD11c(BD Biosciences,San Diego,CA),APC-结合的αCD86(Biolegend,San Diego,CA)、PE-结合的αCD83(eBioscience,San Diego,CA)、FITC-结合的αCD54(Biolegend,San Diego,CA),并在4℃下培养45分钟。将细胞在染色缓冲液中洗两次,并通过添加100μl BD Cytofix固定缓冲液(BD Bioscience,San Diego,CA)进行固定(在室温下15次,避光)。使用LSRII-Fortessa流式细胞仪(BD Biosciences,San Diego,CA)及FlowJo分析软件(Treestar,Ashland,OR)评估DC的CD86、ICAM-1及CD83表达。

[0269] CD40L诱导的人类B细胞增殖的抑制:在常规扁桃体切除术期间从儿科患者获得人类扁桃体B细胞,并通过切碎及轻轻捣碎组织,使细胞通过筛网并使用人类Lympholyte®-H分离培养基(Cedarlane Labs,Burlington,ON)以密度梯度分离法分离单核细胞来分离。从界面收集单核细胞,洗涤,并在4℃下用绵羊红血球(SRBC,Colorado Serum Company;Denver,CO)进行玫瑰染色(rosetted)1小时,接着进行密度梯度分离以移除T细胞。再次洗细胞,并重悬于含有10%FBS的RPMI(完全培养基)中。在完全培养基中滴定抗体,并一式三份添加至96孔圆底(RB)板中。添加1X 10^5个扁桃体人类B细胞并用可溶性IZ-hCD40L(2μg/mL)或用经10,000rad辐射的人类CD40L(CHO-hCD40L)稳定转染的中国仓鼠卵巢细胞刺激,并以2X 10^3个细胞/孔接种,每个孔中的最终体积为200μL。将板在37℃/5%CO_2下培养72小时,最后6小时每孔用0.5μCi的^3[H]-胸苷标记,收获,并通过液体闪烁计数。B细胞增殖为基于胸苷并入定量。

[0270] 实施例3:活体外Fc受体分析

[0271] 抗体可通过使Fc区与免疫细胞表面的Fcγ受体(FcγR)或补体因子结合发挥效应功能,例如补体依赖性细胞毒性(CDC)及抗体依赖性细胞毒性(ADCC)。抗体依赖性细胞吞噬作用为另一种潜在Fc效应功能。为进一步表征人源化Y12XX抗体的性质,分析抗体的补体依赖

性细胞毒性(CDC)、抗体依赖性细胞吞噬作用(ADCP)及抗体依赖性细胞毒性(ADCC)。表15列出在该实施例中分析的抗体。

[0272] 表15

[0273]

	名称	参考
1	BMS-986291 (Y1238-hz1-P238K)	参见WO 2018/217976
2	15B5-hz61-P238K	抗-CD40抗体(自行产生)
3	5F11-45-P238K	参见WO 2018/217976
4	Y12XX-hz28-P238K	
5	Y12XX-hz40-P238K	
6	Y12XX-hz42-P238K	
7	抗体C	抗-CD40抗体(参见Ristov等人(2018) Am J Transplant. 18(12):2895-2904. Epub 2018年5月24日.)
8	BI-LALA	参见美国专利案第9,090,696号，重链序列SEQ ID NO: 32及轻链序列SEQ ID NO: 31；含有突变L234A-L235A的IgG1同型物
9	BMS-986090	CD40功能域抗体(BMS3h-56-269-IgG_4 Fc融合多肽)；参见例如WO 2012/145673)
10	TT hIgG1	人类抗-破伤风毒素抗体，IgG1同型物(在内部产生) (同型物对照)
11	CD20 hIgG1	人类抗-CD20，IgG2同型物(在内部产生) (阳性对照)

[0274] CDC分析为如下进行。“CDC分析培养基”为指罗斯维尔帕克纪念研究所(Roswell Park Memorial Institute)培养基(RPMI)1640(HyClone)，其含有L-谷氨酰胺，不含酚红(HyClone)，补充有0.1％BSA(Sigma)及1％青霉素-链霉素(Life Technologies)。将五十(50)微升的靶细胞(在CDC分析培养基中为$5x10^5$个细胞/mL)添加至96孔分析板的孔中。靶

细胞为Raji细胞，其内源表达CD40(自ATCC获得)。为所测试的每种抗体制备系列稀释液(133至0.002nM)，并将25微升每种抗体浓度添加至每个孔中。将25微升人类补体(自Quidel获得;用CDC分析培养基以1:3稀释)添加至每个孔中。将分析板在增湿培养箱中在37℃下培养放置4小时。培养后，将100微升CellTiter-Glo®(Promega，Madison,WI)添加至每个孔中。然后使用PerkinElmer EnVision®板读取器(PerkinElmer，Waltham,MA)获取发光数据。计算相对于同型物对照(100％存活率)的存活率百分比。将所得值相对于抗体浓度作图。使用GraphPad Inc.的Prism v5.01软件绘制每种抗体的细胞存活率百分比。

[0275] CDC分析进行两次。在第二次分析中，使用新鲜解冻的人类补体血清。结果描述在图3中。图3A描述该分析的第一次重复，及图3B描述该分析的第二次重复。CD20 hIgG1为阳性对照，并显示细胞毒性。对于分析的抗CD40抗体，没有可侦测的CDC活性，及具体而言，分析的人源化Y12XX抗体均未诱导补体依赖性细胞毒性。

[0276] ADCP分析如下进行。“ADCP分析培养基”为指(RPMI)1640培养基，其含有L-谷氨酰胺，不含酚红(HyClone)，补充有10％超低IgG FBS(Gibco)。效应细胞为2个不同健康人类供体的新鲜PBMC纯化的原代人类CD14+单核细胞。靶细胞仍为Raji细胞。Raji细胞用2.0μM PKH26(红色荧光染料;Sigma)标记，及在ADCP分析培养基中的浓度调整为4×10^6个细胞/mL。用抗体预涂覆经标记的靶细胞，方法为通过将标记的靶细胞(50μL/孔)添加至含有50μL/孔的测试抗体或对照抗体的V型底96孔板中，并在冰上培养30分钟。洗涤细胞，然后添加效应细胞($CD14^+$单核细胞)(100μL/孔)，以使最终效应细胞与靶细胞的比率(E:T)为1:4及最终抗体浓度为30nM至0.1nM。然后将板放置在加湿的37℃培养箱中1小时。细胞在冰上用APC-抗CD89(BioLegend)染色30分钟，并通过流式细胞仪(BD Canto™，BD Biosciences，San Jose,CA)进行分析。针对细胞中的CD89+细胞门控及随后针对染色的经吞噬效应子(CD89+、PKH26+)门控。吞噬作用的百分比计算为总CD89+细胞中CD89+、PKH26+细胞的种群。自同型物对照中减去背景值以达成吞噬作用的最终百分比。使用GraphPad Inc.的FlowJo软件及Prism v5.01软件分析数据。

[0277] 使用来自两个不同供体的$CD14^+$单核细胞的示例性数据描述于图4中。CD20 hIgG1为阳性对照，且如所预期般诱导Raji细胞的吞噬作用。BMS-986090还诱导吞噬作用。相反，测试的其他抗体(包括本申请的人源化Y12XX抗CD40抗体)在该分析中均未诱导可侦测的吞噬作用。

[0278] ADCC分析如下进行。“ADCC分析培养基”为指(RPMI)1640培养基，其含有L-谷胺酰胺，不含酚红(HyClone)，补充有10％超低IgG FBS(Gibco)及1mM丙酮酸钠(Life Technologies)。原代人类NK(自然杀伤)细胞为纯化自来自2个不同内部供体的新鲜PBMC，并用作效应细胞。PBMC为纯化自通过密度梯度离心分离的肝素化全血样品，并用补充有2％FBS的PBS(HyClone)洗涤。NK细胞为使用基于磁珠的分离试剂盒(Miltenyi Biotec)，通过阴性选择自PBMC分离。为活化NK细胞，将纯化的NK细胞以1×10^6个细胞/mL重悬于补充有1μM氢化可体松(StemCell Technologies)及500IU/mL重组人类IL-2(Peprotech)的MyeloCult H5100培养基(StemCell Technologies)中，并在37℃下培养过夜。第二天，将活化的NK效应细胞在ADCC分析培养基中洗两次，并在ADCC分析培养基中将浓度调整至5×10^5个细胞/mL。如下所述，用钙黄绿素标记Raji细胞(靶细胞)。钙黄绿素AM(Life Technologies)试剂为通过将20μL超纯DMSO添加至含有50μg冻干试剂的试剂管中制备。针

对每1mL体积，向悬浮的Raji细胞中添加2μL体积重组的钙黄绿素AM。将细胞涡旋并放置于增湿37℃培养箱中30分钟。培养期后，将标记的靶细胞用ADCC分析培养基洗涤3次，并在ADCC分析培养基中将浓度调整至10^5个细胞/mL。将标记的靶细胞(50μL/孔)添加至含有50μL/孔的测试抗体或对照抗体的V型底96孔板中。然后添加活化的NK效应细胞(100μL/孔)，以使最终效应细胞与靶细胞的比率(E:T)为10:1，及最终抗体浓度为0.0002至1μg/mL。然后将板置于加增湿37℃培养箱中2小时。将上清液(50μL/孔)转移至96孔光学黑色板上，并使用设置为485激发及535nm发射滤光片的EnVision®板读取器(PerkinElmer，Waltham，MA)通过读取荧光强度来测量钙黄绿素释放。

[0279] 在不存在抗体的情况下与效应细胞一起培养的靶细胞提供对照用于抗体非依赖性溶解(自发溶解)的背景，而用20μL/孔的10％Tween-20溶解缓冲液溶解的靶细胞在分析中表示最大释放。

[0280] 抗体依赖性细胞溶解的百分比为基于平均荧光强度(MFI)，使用以下式计算：

[0281] 方程式2：$$\left(\frac{\text{测试MFI-平均背景}}{\text{平均最大值-平均背景}}\right) X\ 100$$

[0282] 使用GraphPad Inc.的Prism v5.01软件绘制每种抗体的靶细胞溶解百分比。

[0283] 图5中描述使用来自两个不同供体的NK细胞的示例性数据。靶细胞被阳性对照抗CD20抗体杀死。相反，ADCC对于所有抗CD40抗体均为低至负，指示这些抗体不会诱导Raji细胞的抗体依赖性细胞毒性，并证明这些抗体的CD40拮抗作用。

[0284] 总之，在此实施例中，使用表达内源性CD40的Raji细胞作为靶点测试本申请的人源化Y12XX抗CD40抗体及特别是Y12XX-hz28-P238K、Y12XX-hz40-P238K及Y12XX-hz42-P238K介导ADCC(抗体依赖性细胞毒性)、ADCP(抗体依赖性细胞吞噬作用)或CDC(补体依赖性细胞毒性)的潜力。使用抗-CD20抗体作为阳性对照。对于ADCC，使用NK细胞作为效应细胞，并对来自不同供体的效应细胞运行两次实验。在每种情况下，Y12XX-hz28-P238K、Y12XX-hz40-P238K及Y12XX-hz42-P238K均不诱导Raji细胞溶解。Y12XX-hz28-P238K、Y12XX-hz40-P238K及Y12XX-hz42-P238K均不诱导Raji细胞的CDC超出人类IgG1同型物对照的效应。对于ADCP，使用CD14+单核细胞作为效应细胞，及在此系统中，Y12XX-hz28-P238K、Y12XX-hz40-P238K及Y12XX-hz42-P238K均未促进细胞吞噬作用。相反，BMS-986090显示细胞吞噬作用。

[0285] 实施例4:NF-κB/AP-1讯号的分析

[0286] 该实施例的目标为欲评定由抗CD40抗体刺激引起的对Ramos-Blue™细胞(InvivoGen)的NF-κB/AP-1可诱导的SEAP(分泌性胚胎碱性磷酸盐)活性。

[0287] Ramos-Blue™细胞为表达NF-κB/AP-1可诱导的分泌性胚胎碱性磷酸盐(SEAP)报告分子基因的人类B淋巴细胞报告分子细胞系。Ramos-Blue™细胞系已用于NF-κB/AP1信号传导以及Toll-样受体(TLRs)信号通路，Ramos-Blue™细胞内源性表达CD40，并对CD40及TLR有反应。当刺激Ramos-Blue™细胞系时，其会在细胞培养上清液中产生SEAP。SEAP可通过使用QUANTI-Blue™侦测培养基(InvivoGen，San Diego，CA)侦测。SEAP的浓度可目测或通过使用分光亮度计在620nm下观测到。Ramos-Blue™细胞不表达CD32(FcγRII)。

[0288] 表16列出在此实施例中分析的测试材料(抗体及其他多肽)。所有测试材料均由

BMS在内部制备。

[0289] 表16

[0290]

测试材料	描述
BMS-986325	Y12XX-hz28-P238K (全人类抗-CD40同型物hIgG (P238K) mAb
BMS-986090	全人类抗-CD40功能域抗体IgG4 Fc融合蛋白
mAb 134-2142 (CD40-2142 (hIgG2-Fc))	全人类抗-CD40单克隆抗体(激动剂)
抗-DT1D12-B16F7-hIgG1.3f mAb	阴性对照
CD40L-IZ	人类CD40L-三聚体 (h-IZ-hCD40L-三聚体)

[0291] Ramos-Blue™细胞购自InvivoGen。对于此分析，通过用人类CD32(FcγRII)转导Ramos-Blue™细胞来制备本文中称为Ramos Blue Cells#4的转导细胞系。两种类型的Ramos-Blue™细胞均在Ramos细胞培养基(伊斯科夫氏改良杜贝卡氏培养基(IMDM)，补充有10％胎牛血清(FBS)、2mM L-谷氨酰胺、青霉素及链霉素(100U/mL，-100ug/mL)、100ug/mL的Normomicin及Zeocin作为药物选择(100ug/mL))中培养。将细胞在37℃的5％CO_2中培养。两种类型的细胞每3天传代一次，并维持在0.5x10^6个细胞/ml的细胞密度。使用细胞直至细胞传代#21(P21)。在P21之后，将细胞丢弃。

[0292] 该分析如下进行。“AIM V™培养基”指补充有L-谷氨酰胺、50μg/mL硫酸链霉素、10μg/mL硫酸庆大霉素的无血清培养基(Thermo Fisher Scientific)。为评定CD40拮抗剂抗体对Ramos Blue Cells#4中NF-κB/AP-1活性的CD40激动剂活性，将细胞用不含抗生素Normocin/Zeocin的AIM V™培养基洗两次(2x)。然后将细胞在室温下以2,000rpm离心10分钟。小心吸出培养基以不破坏细胞集结粒。将一(1)mL AIM V™添加至细胞集结粒以重悬细胞集结粒，及重悬后再添加9ml AIM V™。通过添加20微升(μl)ViaStain™ AOPI(吖啶橙/碘化丙啶)染色溶液(Nexcelom Bioscience,LLC,Lawrence,MA)及20μl Ramos-Blue™细胞悬浮液，使用细胞计数器计数细胞。

[0293] 在AIM V™无血清培养基中将Ramos-Blue™细胞调整至4×10^6个细胞/mL。在平底组织培养板中，每孔添加一百(100)μl 400K Ramos-Blue™细胞。然后，将100μl BMS-986325、BMS-986090、mAb134-2141(CD40-2142)或对照添加至每个相应的孔中。使用CD40L-IZ作为阳性对照。包含AIM V™中的Ramos-Blue™细胞(0.4x10^6个细胞/孔)作为分析的阴性对照。最终体积为200μl/孔。

[0294] 将板在37℃/5％CO_2培养箱中培养20小时。细胞培养20小时后，将板以2000rpm离心10分钟。

[0295] 将来自经刺激的Ramos细胞的四十(40)μl细胞培养上清液添加至平底板的孔中。然后，每孔添加160μl QUANTI-Blue™溶液。最终体积为200μl/孔。

[0296] 将板在37℃/5％CO_2培养箱中培养1至6小时。使用EnVision®光学读取器(OD：

620nm)在620nm下每60分钟测量SEAP浓度。

[0297] 示例性数据描述于图6中。在此实施例中,通过评定在抗CD40抗体刺激后,对Ramos-Blue™细胞的NFκ-B/AP-1可诱导的SEAP活性,来测试抗CD40单克隆抗体抗缺乏CD32的Ramos-Blue™细胞或经CD32转导的Ramos-Blue™细胞(Ramos Blue#4)。

[0298] 在此分析中,CD40-2142的添加会诱导明显的信号传导反应(图6A及6b)。这些结果指示CD40-2142在此分析系统中为完全激动剂。BMS-986090的添加显示使用Ramos-Blue™细胞(-CD32)无反应(图6A),但在使用Ramos Blue Cells#4(经CD32转导的Ramos-Blue™细胞)的分析中显示部分促效作用(图6B)。此结果指示FcγR依赖性介导通过添加BMS-986090诱导的促效反应。如图6C及6D所反映,对照多肽三聚体CD40L-IZ在两种分析中均诱导反应。

[0299] 相反,使用Ramos-Blue™细胞($CD32^-$)(图6A)或Ramos#4($CD32^+$)(图6B),BMS-986325的添加不会诱导明显的NFκB/AP-1反应。这些数据指示,BMS-986325不促效CD40且不接合CD32(FcγRII)。这些数据支持降低的低亲合力FcγR(例如CD32(FcγRII))的接合会降低非所欲的激动剂信号传导及非所欲的毒性潜力的可能性。

[0300] 实施例5:BMS-986325的非临床药物动力学评估概述

[0301] 在小鼠及食蟹猴中评估BMS-986325(Y12XX-hz28-P238K)的药物动力学(PK)。由于BMS-986325不会与鼠CD40受体交叉反应,因此在小鼠中评估的PK为固有或非特异性PK。BMS-986325与猴子CD40受体交叉反应,因此评估猴子中的总PK(特异性及非特异性PK)。向小鼠静脉内(IV)给予BMS-986325(单剂量1-及10-mg/kg剂量)后,BMS-986325显示0.5至1.02mL/d/kg的低总血清清除率“CLT”,在稳态“Vss”下0.12至0.19L/kg的有限体积分布及118至183小时(～5至8天)的长表观消除半衰期“T-HALF”。

[0302] 在猴子中,给予单一皮下(SC)剂量的BMS-986325。给予的剂量为比清除率(靶点介导的药物处置“TMDD”)不饱及的剂量。单一SC剂量后,BMS-986325被良好吸收,绝对生物利用度为70.4%(相对于相同IV剂量下的暴露)。向猴子IV给予BMS-986325(单一剂量10mg/kg)后,BMS-986325显示0.41mL/d/kg的CLT,0.05L/kg的有限Vss,及100小时(～4天)的T-HALF。在给猴子单一SC剂量的BMS-986325(给予1、10及100mg/kg的剂量)后,达到最大血浆浓度的时间“Tmax”为24至54小时。暴露量的增加超过剂量比例的增加(最大浓度“Cmax”及从时间零至无穷大外推的浓度与时间曲线下面积“AUC[INF]”),T-HALF随着剂量的增加(在1、10及100mg/kg下分别为～31、～119及～197小时)。这些数据表明非线性PK及可饱和清除机制;此可能由靶点(CD40)介导的清除率所致,这反映TMDD。在此单一剂量PK研究中,在～50%的猴子中侦测到抗药物抗体(ADA)形成,但对总体PK参数没有明显影响。

[0303] 使用药物动力学/药效动力学建模(具有准稳态假设的TMDD模型[TMDD-Qss])描述在猴子中观测到的非线性PK,建立血清药物暴露与CD40受体占有率(RO)及随后的人类剂量投射之间的关系。

[0304] 尽管已经参考上文实施例详细描述本申请实施例,但应当了解,可在不脱离这些实施例的精神的情况下进行各种修改,且为本领域技术人员容易知道。

[0305] 自本文包含的教示知晓本申请所述的这些及其他方面,包括本文列出的示例性具体治疗方法、药物及用途。

[0001] 【序列表】
[0002] <110> 百时美施贵宝公司
[0003] <120> 拮抗性CD40单克隆抗体及其用途
[0004] <130> 200896-0015-00-CN-000006
[0005] <140>
[0006] <141>
[0007] <150> 62/769,514
[0008] <151> 2018-11-19
[0009] <160> 120
[0010] <170> PatentIn version 3.5
[0011] <210> 1
[0012] <211> 5
[0013] <212> PRT
[0014] <213> 人工序列
[0015] <220>
[0016] <223> 合成多肽:VH-CDR1
[0017] <400> 1
[0018] Ser Tyr Trp Met His
[0019] 1 5
[0020] <210> 2
[0021] <211> 17
[0022] <212> PRT
[0023] <213> 人工序列
[0024] <220>
[0025] <223> 合成多肽:VH-CDR2
[0026] <400> 2
[0027] Gln Ile Asn Pro Thr Thr Gly Arg Ser Gln Tyr Asn Glu Lys Phe Lys
[0028] 1 5 10 15
[0029] Thr
[0030] <210> 3
[0031] <211> 8
[0032] <212> PRT
[0033] <213> 人工序列
[0034] <220>
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[0036] <400> 3
[0037] Trp Gly Leu Gln Pro Phe Ala Tyr
[0038] 1 5
[0039] <210> 4
[0040] <211> 117
[0041] <212> PRT

[0042] <213> 人工序列

[0043] <220>

[0044] <223> 合成多肽:Vh-hz14

[0045] <400> 4

[0046] Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

[0047] 1 5 10 15

[0048] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr

[0049] 20 25 30

[0050] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

[0051] 35 40 45

[0052] Gly Gln Ile Asn Pro Thr Thr Gly Arg Ser Gln Tyr Asn Glu Lys Phe

[0053] 50 55 60

[0054] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

[0055] 65 70 75 80

[0056] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

[0057] 85 90 95

[0058] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu

[0059] 100 105 110

[0060] Val Thr Val Ser Ser

[0061] 115

[0062] <210> 5

[0063] <211> 446

[0064] <212> PRT

[0065] <213> 人工序列

[0066] <220>

[0067] <223> 合成多肽:HC_Y12XX-hz28-CH1-IgG1-P238K (为无C端

[0068] 赖氨酸的IgG1)

[0069] <400> 5

[0070] Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

[0071] 1 5 10 15

[0072] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr

[0073] 20 25 30

[0074] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

[0075] 35 40 45

[0076] Gly Gln Ile Asn Pro Thr Thr Gly Arg Ser Gln Tyr Asn Glu Lys Phe

[0077] 50 55 60

[0078] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

[0079] 65 70 75 80

[0080] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

[0081] 85 90 95

[0082] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu

[0083] 100 105 110

[0084] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[0085] 115 120 125
[0086] Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
[0087] 130 135 140
[0088] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[0089] 145 150 155 160
[0090] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[0091] 165 170 175
[0092] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
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[0094] Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
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[0096] Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
[0097] 210 215 220
[0098] Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Lys Ser Val
[0099] 225 230 235 240
[0100] Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
[0101] 245 250 255
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[0103] 260 265 270
[0104] Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
[0105] 275 280 285
[0106] Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
[0107] 290 295 300
[0108] Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
[0109] 305 310 315 320
[0110] Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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[0112] Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
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[0116] Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
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[0119] 385 390 395 400
[0120] Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
[0121] 405 410 415
[0122] Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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[0124] His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[0125] 435 440 445

[0126] <210> 6

[0127] <211> 447

[0128] <212> PRT

[0129] <213> 人工序列

[0130] <220>

[0131] <223> 合成多肽:HC_Y12XX-hz28-CH1-IgG1-P238K (为具有C

[0132] 端赖氨酸的IgG1)

[0133] <400> 6

[0134] Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

[0135] 1 5 10 15

[0136] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr

[0137] 20 25 30

[0138] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

[0139] 35 40 45

[0140] Gly Gln Ile Asn Pro Thr Thr Gly Arg Ser Gln Tyr Asn Glu Lys Phe

[0141] 50 55 60

[0142] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr

[0143] 65 70 75 80

[0144] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

[0145] 85 90 95

[0146] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu

[0147] 100 105 110

[0148] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu

[0149] 115 120 125

[0150] Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys

[0151] 130 135 140

[0152] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

[0153] 145 150 155 160

[0154] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser

[0155] 165 170 175

[0156] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser

[0157] 180 185 190

[0158] Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn

[0159] 195 200 205

[0160] Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His

[0161] 210 215 220

[0162] Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Lys Ser Val

[0163] 225 230 235 240

[0164] Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

[0165] 245 250 255

[0166] Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

[0167] 260 265 270

[0168] Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
[0169] 275 280 285
[0170] Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
[0171] 290 295 300
[0172] Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
[0173] 305 310 315 320
[0174] Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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[0229] 35 40 45
[0230] Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
[0231] 50 55 60
[0232] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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[0234] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
[0235] 85 90 95
[0236] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[0237] 100 105
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[0248] 20 25 30
[0249] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[0250] 35 40 45
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[0252] 50 55 60

[0253] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

[0254] 65 70 75 80

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[0257] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

[0258] 100 105 110

[0259] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

[0260] 115 120 125

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[0262] 130 135 140

[0263] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

[0264] 145 150 155 160

[0265] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

[0266] 165 170 175

[0267] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

[0268] 180 185 190

[0269] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

[0270] 195 200 205

[0271] Phe Asn Arg Gly Glu Cys

[0272] 210

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[0277] <220>

[0278] <223> 合成多肽:VH-CDR2 (Vh-hz12)

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[0287] <220>

[0288] <223> 合成多肽:Vh-hz12

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[0293] 20 25 30

[0294] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0295] 35 40 45
[0296] Gly Gln Ile Asn Pro Ser Gln Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[0297] 50 55 60
[0298] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[0299] 65 70 75 80
[0300] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0301] 85 90 95
[0302] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[0303] 100 105 110
[0304] Val Thr Val Ser Ser
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[0315] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr
[0316] 20 25 30
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[0318] 35 40 45
[0319] Gly Gln Ile Asn Pro Ser Gln Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[0320] 50 55 60
[0321] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[0322] 65 70 75 80
[0323] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0324] 85 90 95
[0325] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[0326] 100 105 110
[0327] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
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[0329] Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
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[0331] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[0332] 145 150 155 160
[0333] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[0334] 165 170 175
[0335] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser

[0336] 180 185 190

[0337] Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn

[0338] 195 200 205

[0339] Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His

[0340] 210 215 220

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[0343] Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

[0344] 245 250 255

[0345] Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu

[0346] 260 265 270

[0347] Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys

[0348] 275 280 285

[0349] Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser

[0350] 290 295 300

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[0353] Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile

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[0355] Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro

[0356] 340 345 350

[0357] Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

[0358] 355 360 365

[0359] Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn

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[0363] Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg

[0364] 405 410 415

[0365] Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

[0366] 420 425 430

[0367] His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

[0368] 435 440 445

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[0371] <212> PRT

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[0381] 35 40 45
[0382] Gly Gln Ile Asn Pro Ser Gln Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[0383] 50 55 60
[0384] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[0385] 65 70 75 80
[0386] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0387] 85 90 95
[0388] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[0389] 100 105 110
[0390] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[0391] 115 120 125
[0392] Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
[0393] 130 135 140
[0394] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[0395] 145 150 155 160
[0396] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
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[0399] 180 185 190
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[0405] 225 230 235 240
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[0408] Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
[0409] 260 265 270
[0410] Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
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[0415] 305 310 315 320
[0416] Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
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[0428] Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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[0430] His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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[0444] 35 40 45
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[0446] 50 55 60
[0447] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
[0448] 65 70 75 80
[0449] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
[0450] 85 90 95
[0451] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[0452] 100 105
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[0465] 35 40 45
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[0467] 50 55 60
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[0470] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
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[0476] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
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[0483] 180 185 190
[0484] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
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[0487] 210
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[0504] 65 70 75 80
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[0506] 85 90 95
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[0522] 50 55 60
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[0524] 65 70 75 80
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[0526] 85 90 95
[0527] Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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[0539] 35 40 45
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[0541] 50 55 60
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[0545] 85 90 95

[0546] Ser Glu Thr Asp Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr
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[0567] 260 265 270
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[0609] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
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[0613] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Xaa Glu Xaa Thr
[0614] 130 135 140
[0615] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[0616] 145 150 155 160
[0617] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[0618] 165 170 175
[0619] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[0620] 180 185 190
[0621] Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
[0622] 195 200 205
[0623] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[0624] 210 215 220
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[0638] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

[0639] 35 40 45

[0640] Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val

[0641] 50 55 60

[0642] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln

[0643] 65 70 75 80

[0644] Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln

[0645] 85 90 95

[0646] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala

[0647] 100 105 110

[0648] Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro

[0649] 115 120 125

[0650] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr

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[0652] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

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[0654] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

[0655] 165 170 175

[0656] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr

[0657] 180 185 190

[0658] Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

[0659] 195 200 205

[0660] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys

[0661] 210 215 220

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[0663] 225 230

[0664] <210> 23

[0665] <211> 232

[0666] <212> PRT

[0667] <213> 人工序列

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[0676] 35 40 45
[0677] Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
[0678] 50 55 60
[0679] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
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[0681] Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
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[0683] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
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[0970] 325 330
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[1260] 260 265 270
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[1296] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
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[1298] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
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[1318] 35 40 45
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[1320] 50 55 60
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[1330] 130 135 140
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[1333] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[1334] 165 170 175
[1335] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
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[1367] 130 135 140
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[1412] 100 105 110
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[1426] 210 215 220
[1427] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

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[1488] Gly Gly Gly Ser Gly Gly Gly Gly Ser
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[1591] <223> 合成多肽:信号肽的编码序列
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[1612] 85 90 95
[1613] Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
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[1615] Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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[1629] 35 40 45
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[1675] 35 40 45
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[1725] 65 70 75 80
[1726] Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Ile Tyr Phe Cys
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[1729] 100 105 110
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[1744] 35 40 45
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[1767] 35 40 45
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[1770] Lys Gly Thr Ala Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
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[1773] 85 90 95
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[1775] 100 105 110
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[1790] 35 40 45
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[1792] 50 55 60
[1793] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
[1794] 65 70 75 80
[1795] Leu Gln Leu Thr Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
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[1797] Ser Arg Trp Gly Leu Pro Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[1799] Val Thr Val Ser Ala
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[1813] 35 40 45
[1814] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
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[1816] Lys Ala Lys Thr Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
[1817] 65 70 75 80
[1818] Met Gln Leu Thr Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe Cys
[1819] 85 90 95
[1820] Ser Arg Trp Gly Leu Pro Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[1821] 100 105 110
[1822] Val Thr Val Ser Ala
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[1836] 35 40 45
[1837] Gly Phe Ile Asn Pro Thr Thr Gly Tyr Ser Glu Tyr Asn Gln Lys Phe
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[1840] 65 70 75 80
[1841] Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
[1842] 85 90 95
[1843] Ala Arg Trp Gly Leu Pro Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[1846] 115

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[1865] 85 90 95
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[1882] 35 40 45
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[1886] 65 70 75 80
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[1888] 85 90 95

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[1890] 100 105 110
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[1928] 35 40 45
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[1936] 100 105 110
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[1953] 50 55 60
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[2110] 20 25 30
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[2115] Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
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[2120] 100 105 110
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[2135] 35 40 45
[2136] Tyr Thr Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
[2137] 50 55 60
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[2156] 35 40 45
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[2159] Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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[2163] Thr His Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[2164] 100 105 110
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[2309] 85 90 95
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[2329] Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
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[2689] 50 55 60
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[2693] 85 90 95
[2694] Ala Arg Trp Gly Leu Pro Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2696] Val Thr Val Ser Ser
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[2710] 35 40 45
[2711] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
[2712] 50 55 60
[2713] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
[2714] 65 70 75 80
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[2716] 85 90 95
[2717] Ala Arg Trp Asp Pro Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2732] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[2733] 35 40 45
[2734] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
[2735] 50 55 60
[2736] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2737] 65 70 75 80
[2738] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2739] 85 90 95
[2740] Ala Arg Trp Asp Pro Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2753] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Ser Tyr
[2754] 20 25 30
[2755] Trp Met His Trp Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Met
[2756] 35 40 45
[2757] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
[2758] 50 55 60
[2759] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2760] 65 70 75 80
[2761] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2762] 85 90 95
[2763] Ala Arg Trp Asp Pro Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[2764] 100 105 110
[2765] Val Thr Val Ser Ser
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[2779] 35 40 45
[2780] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
[2781] 50 55 60
[2782] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2783] 65 70 75 80
[2784] Met Glu Leu Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2785] 85 90 95
[2786] Ala Arg Trp Asp Pro Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2788] Val Thr Val Ser Ser
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[2802] 35 40 45
[2803] Gly Tyr Ile Asn Pro Thr Thr Gly Tyr Ser Ala Tyr Asn Gln Lys Phe
[2804] 50 55 60
[2805] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2806] 65 70 75 80
[2807] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2808] 85 90 95
[2809] Ala Arg Trp Gln Pro Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2811] Val Thr Val Ser Ser
[2812] 115

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[2824] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[2825] 35 40 45
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[2827] 50 55 60
[2828] Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2829] 65 70 75 80
[2830] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2831] 85 90 95
[2832] Ala Arg Trp Asp Ala Arg Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[2833] 100 105 110
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[2837] <211> 117
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[2846] 20 25 30
[2847] Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
[2848] 35 40 45
[2849] Gly Gln Ile Asn Pro Ser Asn Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[2850] 50 55 60
[2851] Lys Thr Met Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
[2852] 65 70 75 80
[2853] Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
[2854] 85 90 95

[2855] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[2856] 100 105 110
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[2871] 35 40 45
[2872] Gly Gln Ile Asn Pro Ser Asn Gly Arg Ser Gln Tyr Asn Glu Lys Phe
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[2874] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2875] 65 70 75 80
[2876] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2877] 85 90 95
[2878] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
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[2894] 35 40 45
[2895] Gly Gln Ile Asn Pro Ser Asn Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[2896] 50 55 60

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[2898] 65 70 75 80
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[2903] Val Thr Val Ser Ser
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[2917] 35 40 45
[2918] Gly Gln Ile Asn Pro Ser Asn Gly Arg Ser Gln Tyr Asn Glu Lys Phe
[2919] 50 55 60
[2920] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2921] 65 70 75 80
[2922] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2923] 85 90 95
[2924] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[2925] 100 105 110
[2926] Val Thr Val Ser Ser
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[2936] 1 5 10 15
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[2939] Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[2940] 35 40 45
[2941] Gly Gln Ile Asn Pro Ser Asn Ala Arg Ser Gln Tyr Asn Glu Lys Phe
[2942] 50 55 60
[2943] Lys Thr Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
[2944] 65 70 75 80
[2945] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[2946] 85 90 95
[2947] Ala Arg Trp Gly Leu Gln Pro Phe Ala Tyr Trp Gly Gln Gly Thr Leu
[2948] 100 105 110
[2949] Val Thr Val Ser Ser
[2950] 115
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[2960] Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
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[2962] Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
[2963] 35 40 45
[2964] Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
[2965] 50 55 60
[2966] Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
[2967] 65 70 75 80
[2968] Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
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[2970] Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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[2984] 35 40 45
[2985] Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
[2986] 50 55 60
[2987] Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
[2988] 65 70 75 80
[2989] Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
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[2991] Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[2992] 100 105
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[2994] <211> 107
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[3004] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[3005] 35 40 45
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[3007] 50 55 60
[3008] Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
[3009] 65 70 75 80
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[3011] 85 90 95
[3012] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[3013] 100 105
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[3022] 20 25 30

[3023] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[3024] 35 40 45
[3025] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[3026] 50 55 60
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[3031] Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
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[3049] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
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[3089] 35 40 45
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[3096] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
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[3106] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr

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[3111] 210 215 220
[3112] Ser Leu Ser Leu Ser Pro Gly Xaa
[3113] 225 230
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[3137] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[3138] 35 40 45
[3139] Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
[3140] 50 55 60
[3141] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[3142] 65 70 75 80
[3143] Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[3144] 85 90 95
[3145] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
[3146] 100 105 110
[3147] Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
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[3150] 130 135 140
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[3153] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[3154] 165 170 175
[3155] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[3156] 180 185 190
[3157] Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
[3158] 195 200 205
[3159] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[3160] 210 215 220
[3161] Ser Leu Ser Leu Ser Pro Gly Xaa
[3162] 225 230
[3163] <210> 120
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[3195] 35 40 45

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[3197] 50 55 60

[3198] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln

[3199] 65 70 75 80

[3200] Tyr Xaa Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln

[3201] 85 90 95

[3202] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala

[3203] 100 105 110

[3204] Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro

[3205] 115 120 125

[3206] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Xaa Glu Xaa Thr

[3207] 130 135 140

[3208] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

[3209] 145 150 155 160

[3210] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

[3211] 165 170 175

[3212] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr

[3213] 180 185 190

[3214] Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

[3215] 195 200 205

[3216] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys

[3217] 210 215 220

[3218] Ser Leu Ser Leu Ser Pro Gly Xaa

[3219] 225 230

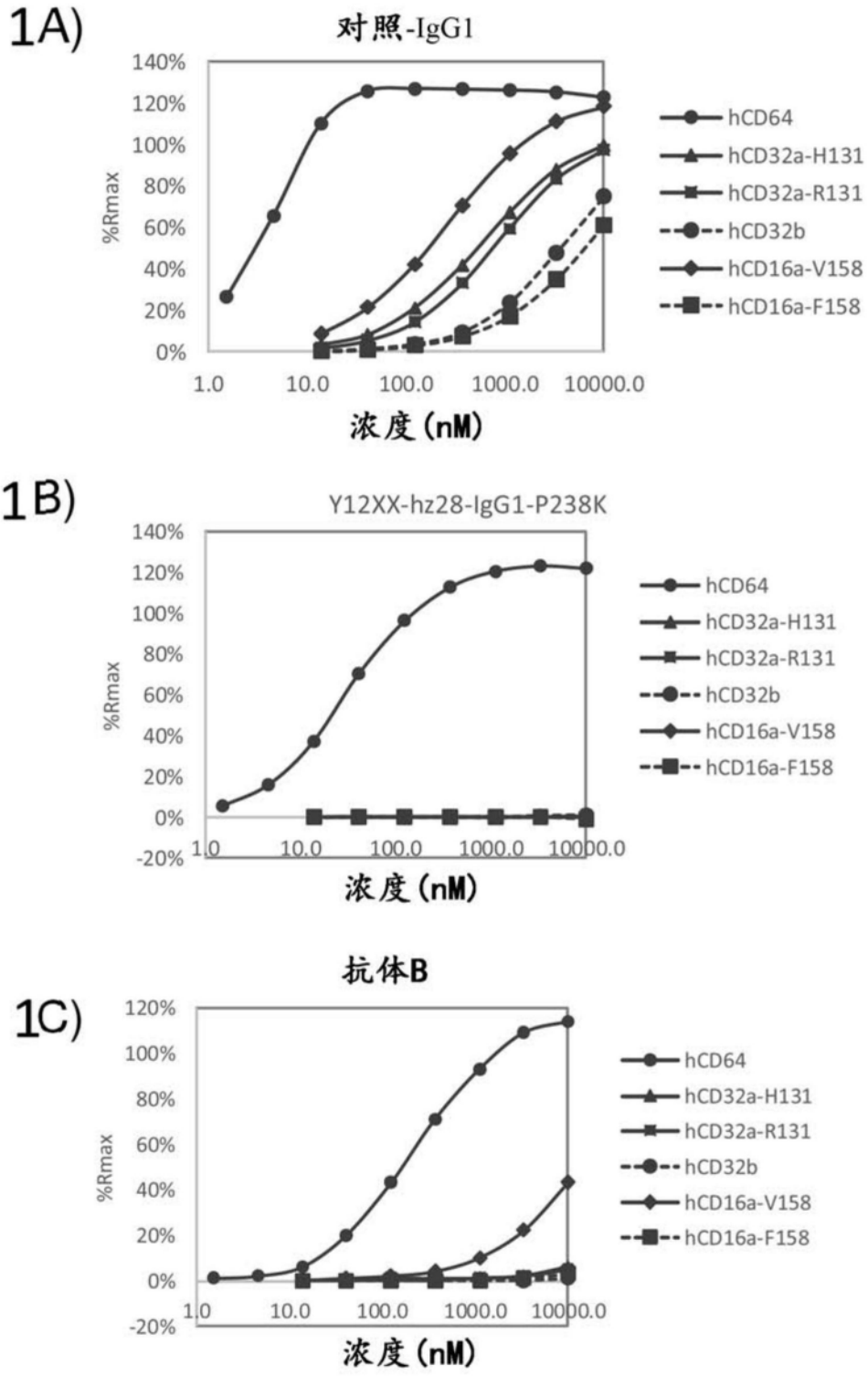

1A)
对照-IgG1
140%
120%
100%
80%
60%
40%
20%
0%
%Rmax
1.0
10.0
100.0
1000.0
10000.0
浓度(nM)
hCD64
hCD32a-H131
hCD32a-R131
hCD32b
hCD16a-V158
hCD16a-F158
1B)
Y12XX-hz28-IgG1-P238K
140%
120%
100%
80%
60%
40%
20%
0%
-20%
%Rmax
1.0
10.0
100.0
1000.0
10000.0
浓度(nM)
hCD64
hCD32a-H131
hCD32a-R131
hCD32b
hCD16a-V158
hCD16a-F158
抗体B
1C)
120%
100%
80%
60%
40%
20%
0%
-20%
%Rmax
1.0
10.0
100.0
1000.0
10000.0
浓度(nM)
hCD64
hCD32a-H131
hCD32a-R131
hCD32b
hCD16a-V158
hCD16a-F158

图1

1D) 抗体/Fc γ R相互作用的KD值

样品	对照-IgG1	Y12XX-hz28-IgG1-P238K	抗体B
hCD64	0.2 nM	25 nM	150 nM
hCD32a-H131	600 nM	>50 uM	>50 uM
hCD32a-R131	840 nM	>50 uM	>50 uM
hCD32b	3.9 uM	>50 uM	>50 uM
hCD16a-V158	270 nM	>50 uM	7 uM
hCD16a-F158	11 uM	>50 uM	>50 uM

图1继续

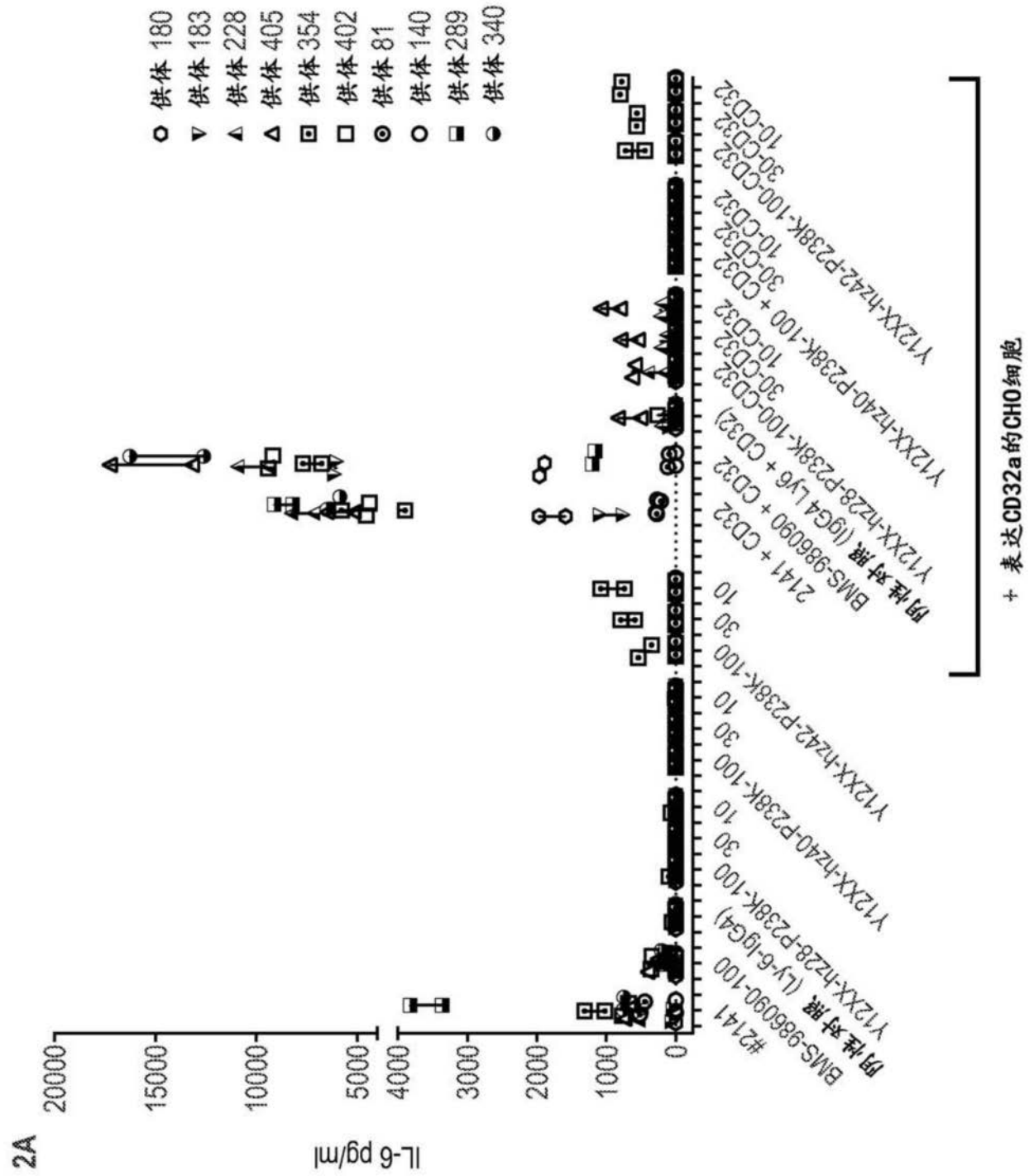

2A
IL-6 pg/ml
20000
15000
10000
5000
4000
3000
2000
1000
0
供体 180
供体 183
供体 228
供体 405
供体 354
供体 402
供体 81
供体 140
供体 289
供体 340
BMS-986090-100
#2141
Y12XX-hz28-P238K-100
Y12XX-hz40-P238K-100
Y12XX-hz42-P238K-100
2141 + CD32
BMS-986090 (IgG4 Lys-6 + CD32)
Y12XX-hz28-P238K-100-CD32
Y12XX-hz40-P238K-100 + CD32
Y12XX-hz42-P238K-100-CD32
10
30
10-CD32
30-CD32
+ 表达CD32a的CHO细胞
阴性对照
阴性对照

图2

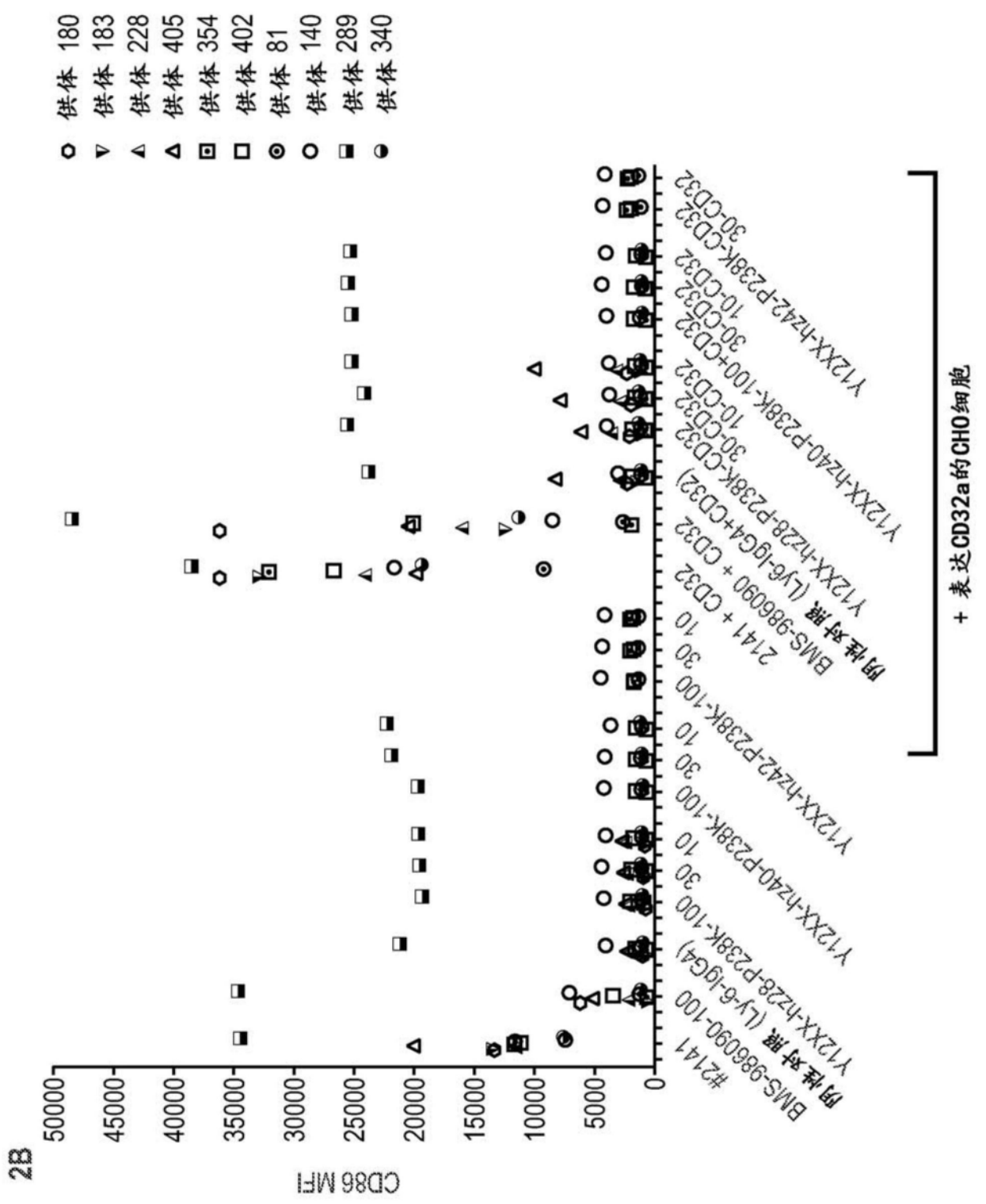

2B
CD86 MFI
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
供体 180
供体 183
供体 228
供体 405
供体 354
供体 402
供体 81
供体 140
供体 289
供体 340
#2141
BMS-986090-100
阴性对照 (Ly-6-IgG4)
Y12XX-h228-P238K-100
Y12XX-h240-P238K-100
Y12XX-h242-P238K-100
2141 + CD32
BMS-986090 + CD32
阴性对照 (Ly6-IgG4+CD32)
Y12XX-h228-P238K-30-CD32
Y12XX-h240-P238K-100+CD32
Y12XX-h240-P238K-30-CD32
Y12XX-h240-P238K-10-CD32
Y12XX-h242-P238K-30-CD32
+ 表达CD32a的CHO细胞

图2继续

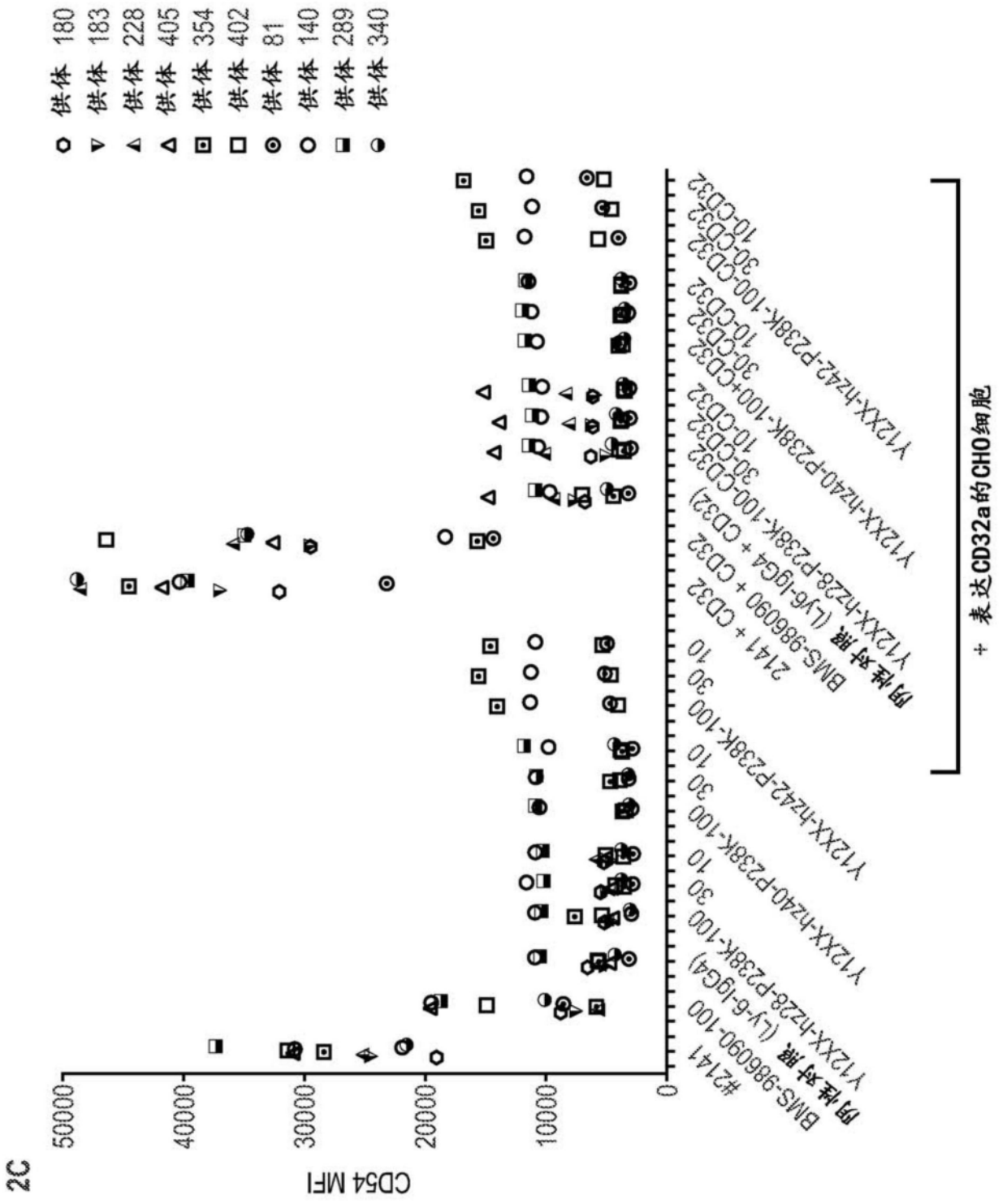
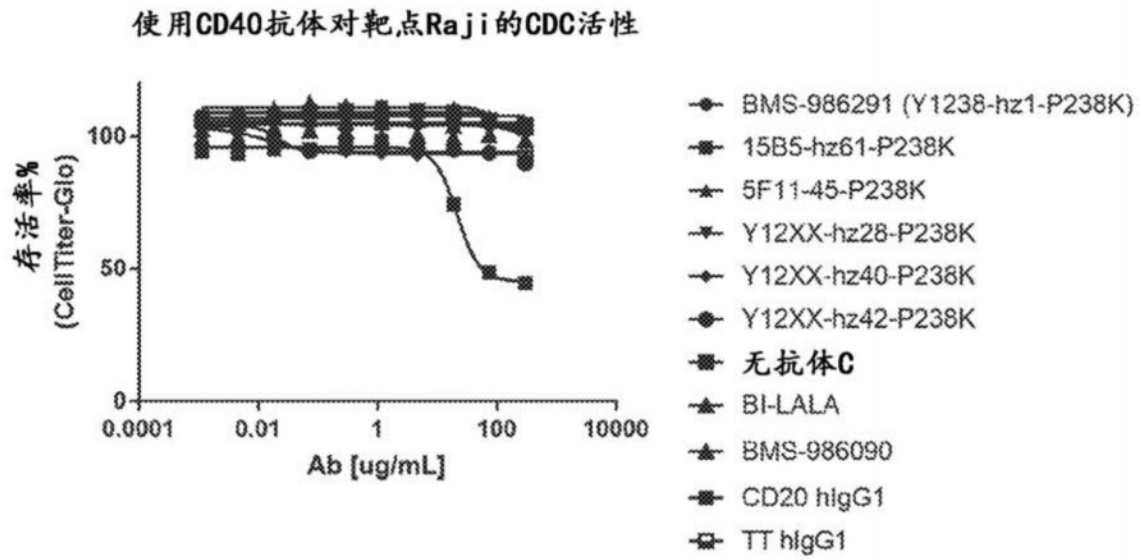

2C
CD54 MFI
50000
40000
30000
20000
10000
0
供体 180
供体 183
供体 228
供体 405
供体 354
供体 402
供体 81
供体 140
供体 289
供体 340
#2141
BMS-986090-100
内性对照 (Ly-6-IgG4)
Y12XX-h228-P238K-100
Y12XX-h240-P238K-100
Y12XX-h242-P238K-100
10
30
100
2141 + CD32
BMS-986090 (Ly6-IgG4 + CD32)
内性对照
Y12XX-h228-P238K-100+CD32
Y12XX-h240-P238K-100+CD32
Y12XX-h242-P238K-100+CD32
+ 表达CD32a的CHO细胞

图2继续

3A


使用CD40抗体对靶点Raji的CDC活性
存活率%
(CellTiter-Glo)
100
50
0
0.0001
0.01
1
100
10000
Ab [ug/mL]
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
无抗体C
BI-LALA
BMS-986090
CD20 hIgG1
TT hIgG1

3B

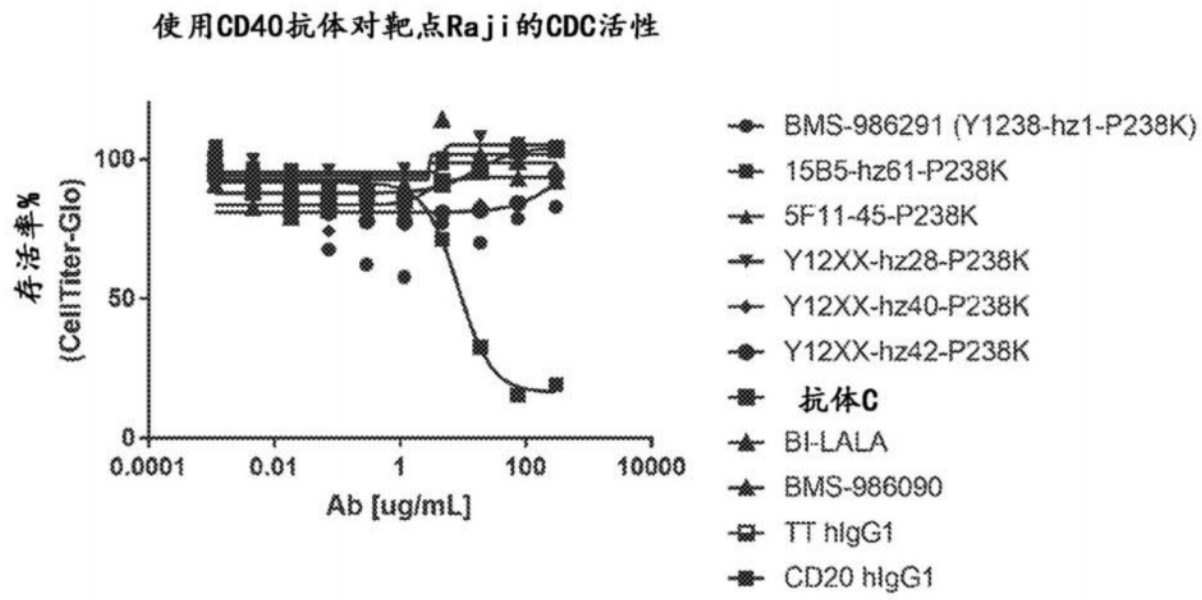
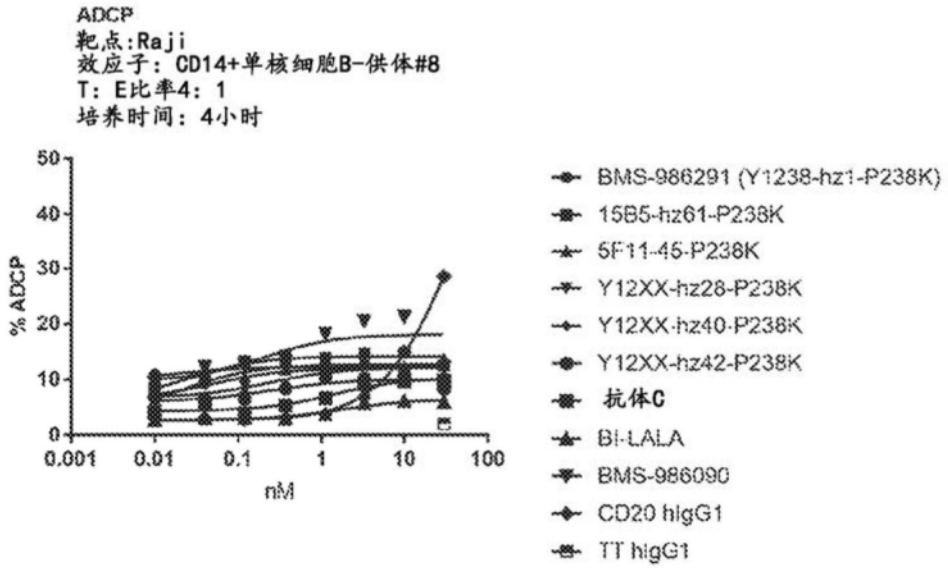

使用CD40抗体对靶点Raji的CDC活性
存活率%
(CellTiter-Glo)
100
50
0
0.0001
0.01
1
100
10000
Ab [ug/mL]
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
抗体C
BI-LALA
BMS-986090
TT hIgG1
CD20 hIgG1

图3

4A


ADCP
靶点:Raji
效应子: CD14+单核细胞B-供体#8
T: E比率4: 1
培养时间: 4小时
% ADCP
nM
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
抗体C
BI-LALA
BMS-986090
CD20 hIgG1
TT hIgG1

4B

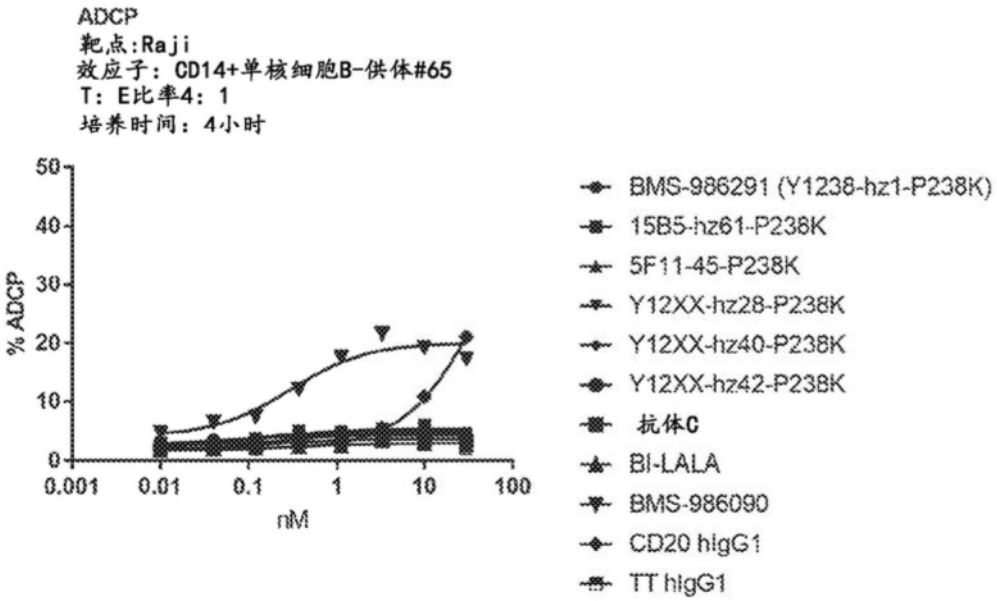
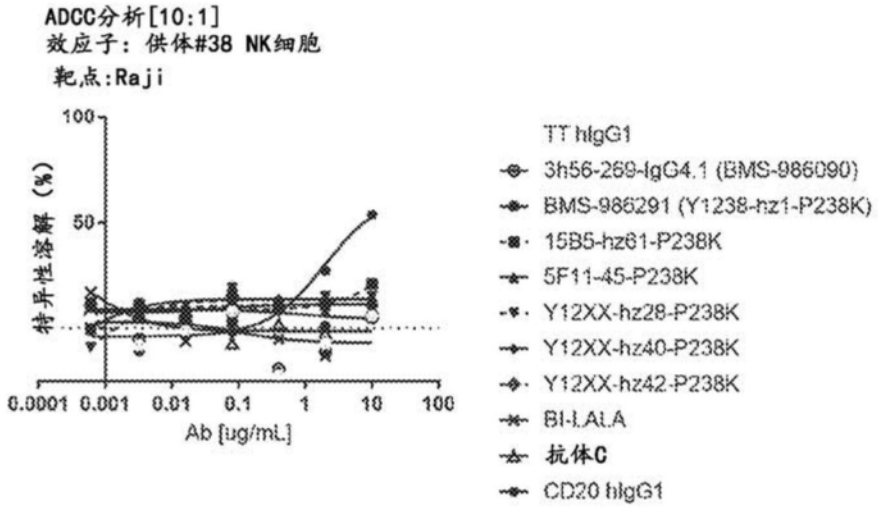

ADCP
靶点:Raji
效应子: CD14+单核细胞B-供体#65
T: E比率4: 1
培养时间: 4小时
% ADCP
nM
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
抗体C
BI-LALA
BMS-986090
CD20 hIgG1
TT hIgG1

图4

5A


ADCC分析[10:1]
效应子：供体#38 NK细胞
靶点:Raji
特异性溶解（%）
100
50
0
0.0001 0.001 0.01 0.1 1 10 100
Ab [ug/mL]
TT hIgG1
3h56-269-IgG4.1 (BMS-986090)
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
BI-LALA
抗体C
CD20 hIgG1

5B

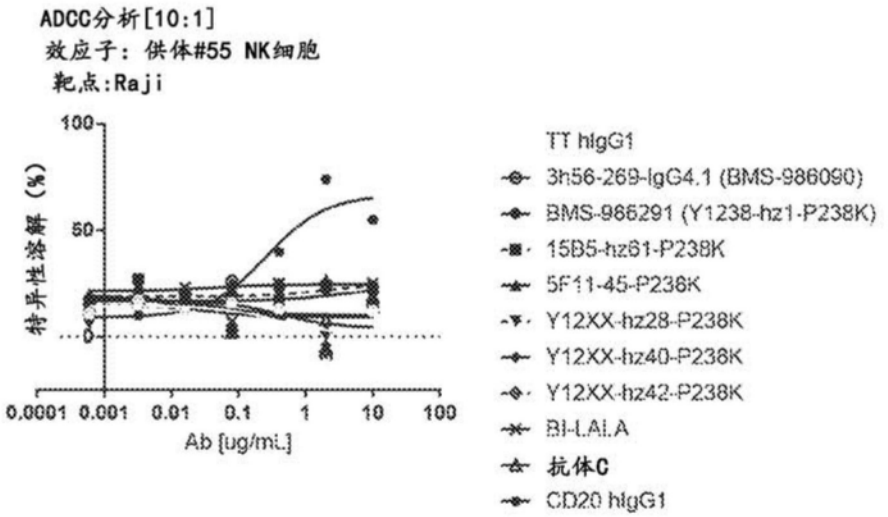
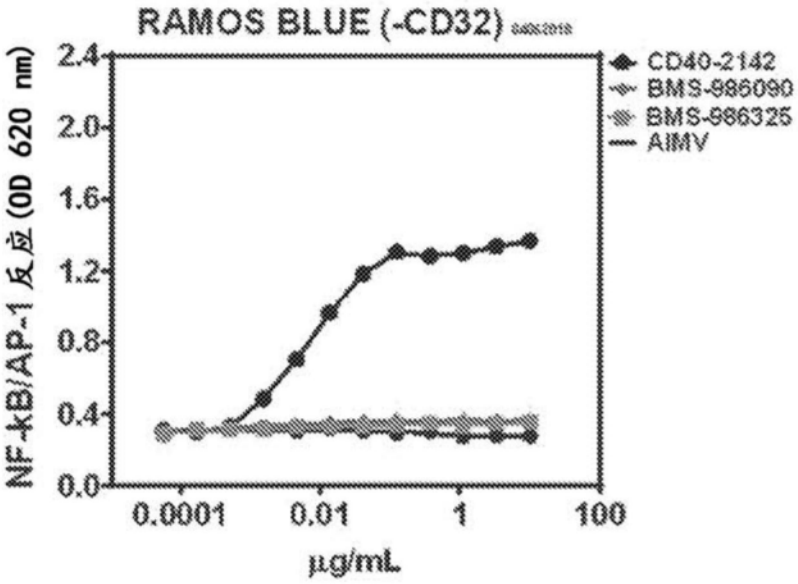

ADCC分析[10:1]
效应子：供体#55 NK细胞
靶点:Raji
特异性溶解（%）
100
50
0
0.0001 0.001 0.01 0.1 1 10 100
Ab [ug/mL]
TT hIgG1
3h56-269-IgG4.1 (BMS-986090)
BMS-986291 (Y1238-hz1-P238K)
15B5-hz61-P238K
5F11-45-P238K
Y12XX-hz28-P238K
Y12XX-hz40-P238K
Y12XX-hz42-P238K
BI-LALA
抗体C
CD20 hIgG1

图5

6A


RAMOS BLUE (-CD32)
NF-kB/AP-1 反应 (OD 620 nm)
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0.0001
0.01
1
100
µg/mL
CD40-2142
BMS-986090
BMS-986325
AIMV

6B

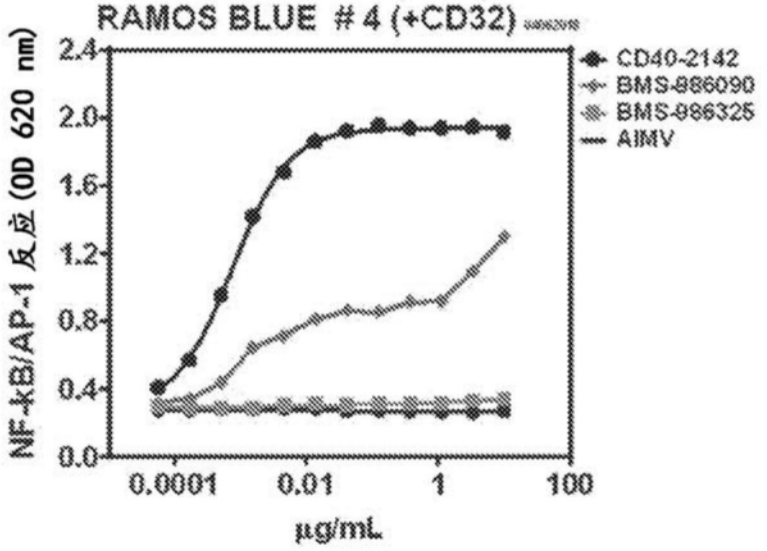
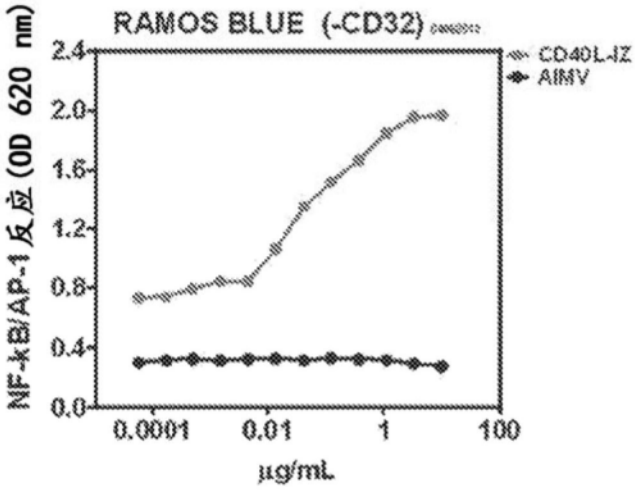

RAMOS BLUE # 4 (+CD32)
NF-kB/AP-1 反应 (OD 620 nm)
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0.0001
0.01
1
100
µg/mL
CD40-2142
BMS-986090
BMS-986325
AIMV

图6

6C


RAMOS BLUE (-CD32)
CD40L-IZ
AIMV
NF-kB/AP-1反应 (OD 620 nm)
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0.0001
0.01
1
100
µg/mL

6D

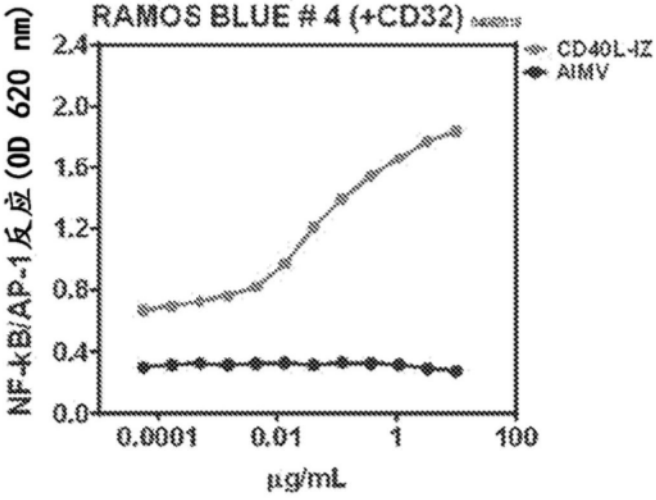

RAMOS BLUE # 4 (+CD32)
CD40L-IZ
AIMV
NF-kB/AP-1反应 (OD 620 nm)
2.4
2.0
1.6
1.2
0.8
0.4
0.0
0.0001
0.01
1
100
µg/mL

图6继续