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DESCRIPTION

FIELD

[0001] The present invention relates, in part, to binding agents which bind Clec9A and their use as therapeutic and diagnostic agents.

BACKGROUND

[0002] Dendritic cells (DCs) are antigen-presenting cells (APCs) equipped with the ability to induce primary immune responses and play an important role in various aspects of immunity. Activated dendritic cells are capable of recruiting additional immune cells such as macrophages, eosinophils, natural killer cells, and T cells such as natural killer T cells. Dendritic cells also capture antigens and present the antigens on their surfaces to activate T cells (*e.g.* cytotoxic T cells (CTLs)).

[0003] Despite major advances in cancer treatment, cancer remains one of the leading causes of death globally. Hurdles in designing effective therapies include cancer immune evasion, in which cancer cells escape destructive immunity, as well as the toxicity of many conventional cancer treatments such as radiation therapy and chemotherapy, which significantly impacts a patient's ability to tolerate the therapy and/or impacts the efficacy of the treatment.

[0004] One mechanism by which cancers evade immune detection and destruction is by crippling dendritic cell functionality through prevention of dendritic cell (DC) recruitment and activation. Accordingly, there remains a need for cancer therapies that can effectively derail tumor evasion and enhance anti-tumor immunity as mediated, for example, by dendritic cells.

[0005] Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with both autoimmune and neurodegenerative features. The most frequent form of MS is relapsing-remitting multiple sclerosis (RRMS), which is clinically characterized by recurring episodes of neurological symptoms. More than 2.3 million people worldwide suffer from MS, with 400,000 people in the U.S. alone having the disease.

[0006] Current pharmacological treatments for MS, including disease modifying therapies (DMTs), either modify or suppress the body's immune system. Many of the current pharmacological agents for MS are limited by incomplete efficacy, side effects and medical risks. These treatments have been shown to modestly reduce neurological relapses of the disease and, in some instances, incompletely slow the progression of neurological disability. Accordingly, there also remains a pressing need for improved MS treatments.

[0007] Lahoud et al. (J. Immunol. 2011, 187(2):842-850) and Picco et al. (Eur. J. Immunol. 2014, 44(7):1947-1955) disclose the targeting of antigens to DCs by means of anti-Clec9A antibodies.

[0008] US 2015/313965 A1 and US 2013/230517 A1 disclose modified interferon α signaling agents.

SUMMARY

[0009] In various aspects, the present invention relates to Clec9A binding agents having at least one targeting moiety that specifically binds to Clec9A. In various embodiments, these Clec9A binding agents bind to, but do not functionally modulate (*e.g.* partially or fully neutralize) Clec9A. Therefore, in various embodiments, the present Clec9A binding agents have use in, for instance, directly or indirectly recruiting a Clec9A-expressing cell to a site of interest while still allowing the Clec9A-expressing cell to signal via Clec9A (*i.e.* the binding of the Clec9A binding agent does not reduce or eliminate Clec9A signaling at the site of interest). The targeting moiety is a single domain antibody (VHH). The Clec9A binding agent further comprises a signaling agent, which is a human interferon alpha 2 comprising an amino acid sequence having at least 98% identity with a sequence selected from SEQ ID NO:86 and 87 and having one or more mutations at positions R149, L153, and M148 with respect to SEQ ID NO:86 or 87. In some embodiments, the present Clec9A binding agent may directly or indirectly recruit an immune cell (*e.g.* a dendritic cell) to a site of action (such as, by way of non-limiting example, the tumor microenvironment). In some embodiments, the present Clec9A binding agent facilitates the presentation of antigens (*e.g.*, tumor antigens) by dendritic cells.

[0010] The present Clec9A binding agents may find use in the treatment of various diseases or disorders such as cancer, infections, immune disorders, and other diseases and disorders.

BRIEF DESCRIPTION OF DRAWINGS

[0011]

Figure 1 panels A-F provide histograms showing the binding of six VHHs specific for mouse Clec9A to CHO cells transfected with Clec9A.

Figure 2 panel A shows that the administration of a fusion of a VHH specific for mouse Clec9A with a modified human interferon (Q124R mutant, "Clec9A-targeted AcTaferon") led to reductions in tumor size (lines from top to bottom at last time point: PBS, "untargeted AcTaferon" (*i.e.* modified human interferon (Q124R mutant) fused to a targeting moiety for an irrelevant target - hCD20, "Clec9A-targeted AcTaferon" - fusion of a VHH specific for mouse Clec9A with a modified human interferon (Q124R mutant), and "WT mIFN" (*i.e.* unmodified murine interferon). Panels B and C show that the administration of the fusion of a VHH specific for mouse Clec9A with a modified human interferon (Q124R mutant) did not result in weight loss or hematological toxicity, respectively (in panel B, lines from top to bottom at last time point: untargeted AcTaferon, PBS, Clec9A-targeted AcTaferon, and WT mIFN, in panel C all graphs, the histograms left to right are: naive mice, PBS, mIFN WT, untargeted AcTaferon, and Clec9A-targeted AcTaferon).

Figure 3 depicts the nucleotide sequence of 27 different VHHs specific for human Clec9A. Gaps were introduced in order to align sequences. The sequences of **Figure 3** are assigned sequence identifiers as shown in Example 2 below.

Figure 4 shows the amino acid sequences of 27 different VHHs specific for human Clec9A. Complementarity determining regions (CDR1, CDR2 and CDR3) as indicated are defined according to Kabat. Gaps were introduced in order to align sequences. The above 27 different VHHs belong to 11 different groups (see Figure 5).

VHHs belonging to the same group are very similar and their amino acid sequences suggest that they are from clonally-related B-cells resulting from somatic

hypermutation or from the same B-cell but diversified due to RT and/or PCR error during library construction. VHHs belonging to the same group recognize the same epitope but

their other characteristics (e.g. affinity, potency, stability, expression yield, etc.) can be different. The sequences of **Figure 4** are assigned sequence identifiers as shown in Example 2 below.

Figure 5 provides a table depicting that the 27 different VHHs belonged to 11 different groups. Members of groups 5 and 7 bind to both mouse and human Clec9A.

Figure 6 shows the anti-tumor potential of a chimeric protein comprising a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 (Q124R mutant, "Acta-Clec9A") in combination with tumor necrosis factor (TNF). Panel A demonstrates that combination treatment using the chimeric protein and TNF exhibited potent anti-tumor activity with no tumor recurrence by day 38 (or 23 days post-dosing). Panel B shows that the combination treatment was well tolerated with no significant hematological toxicity such as thrombocytopenia compared to treatment with wild type IFN or wild type IFN combined with TNF.

Figure 7 shows the combined effect of chimera of a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 (Q124R mutant) and an anti-PD-L1 antibody ("Clec9A-AcTaferon + anti-PD-L1") in comparison to PBS (negative control), chimera of a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 alone (Q124R mutant, "Clec9A-AcTaferon"), and anti-PD-L1 antibody alone ("anti-PD-L1").

Figure 8 shows the combined effect of a chimera of a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 (Q124R) and also fused to an anti-PD-L1 VHH and doxorubicin ("Clec9A-Q124R-PD-L1 + doxo"), compared to a chimera of a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 ("Q124R") and fused to an anti-PD-L1 VHH ("Clec9A-Q124R-PD-L1"), doxorubicin ("doxo"), and PBS (negative control).

Figure 9 shows a substantial induction of T cell proliferation in mice in response to administration of a VHH specific for mouse Clec9A fused to a modified human interferon alpha 2 (Q124R mutant, "Actakine").

Figure 10, panel A shows mean clinical scores as described in Example 7 for various treatments (including various fusions) also described in Example 7. **Figure 10**, panel B shows mean body weight as described in Example 7 for various treatments (including various fusions) also described in Example 7.

Figure 11 shows the cumulative clinical score for various treatments; the histograms are (left to right: PBS (negative control), fusion of anti-CD20 and human IFN with a Q124R mutation ("Q-CD20"), fusion of anti-CD8 and human IFN with a Q124R mutation ("Q-CD8"), fusion of anti-Clec9A and human IFN with a Q124R mutation ("Q-Clec9A"), fusion of anti-Bcl10 and human IFN with a Q124R mutation ("Q-Bcl10," i.e. the untargeted control), and wild type IFN at two doses as indicated. Q124R is a human IFN mutation that is suitable for use in the mouse (i.e. it is a human mutant IFN that functions in mouse). See Nat. Comm. 2014;5:3016. doi: 10.1038/ncomms4016.

Figure 12 shows various side effects in the treatments outlined in **Figure 11** above (same histogram order left to right for panels B-F).

Figure 13 shows a human dendritic cell pSTAT1 signaling assay. Chimeras studied were anti-human Clec9A VHH/human IFN R149A and anti-human Clec9A VHH/human IFN R33A/E120R. Two doses of the agents were studied: 100 ng/ml and 500 ng/ml. PBS was the control and the data are expressed as a fold change of the percentage of pSTAT1⁺ dendritic cells (data is an average of a triplicate data set).

Figure 14 shows anti-human Clec9a VHH/anti-human PD-L1 VHH/human IFN -R149A bi-specific chimera antitumor effects on a human tumor (RL) grown in humanized mice. With reference to day 18 on the X axis, the constructs studied were, from top to bottom: PBS (control); anti-human Clec9a VHH/anti-human PD-L1 VHH/human IFN-R149A bi-specific chimera; and anti-human Clec9a VHH/anti-human PD-L1 VHH/human IFN-R149A bi-specific chimera plus FMS-like tyrosine kinase 3 ligand (FLT3L).

DETAILED DESCRIPTION

[0012] The present invention is based, in part, on the discovery of agents (such as VHHs) that recognize and bind to Clec9A. The present Clec9A binding agents are part of a chimeric or fusion protein with one or more targeting moieties and/or one or more signaling agents. In some embodiments, these Clec9A binding agents bind to, but do not functionally modulate Clec9A.

[0013] In some embodiments, these Clec9A binding agents may bind and directly or indirectly recruit immune cells to sites in need of therapeutic action (e.g. a tumor or tumor microenvironment). In some embodiments, the Clec9A binding agents enhance tumor antigen presentation for elicitation of effective antitumor immune response.

[0014] In some embodiments, the Clec9A binding agents modulate antigen presentation. In some embodiments, the Clec9A binding agents temper the immune response to avoid or reduce autoimmunity. In some embodiments, the Clec9A binding agents provide immunosuppression. In some embodiments, the Clec9A binding agents cause an increase a ratio of Tregs to CD8⁺ T cells and/or CD4⁺ T cells in a patient. Methods disclosed herein relate to reduction of auto-reactive T cells in a patient.

[0015] The present invention provides pharmaceutical compositions comprising the Clec9A binding agents. Disclosed is their use in the treatment of various diseases, including cancer, autoimmune, and/or neurodegenerative diseases.

Clec9A Binding Agents

[0016] In various embodiments, the present Clec9A binding agent is a protein-based agent capable of specific binding to Clec9A. In various embodiments, the present Clec9A binding agent is a protein-based agent capable of specific binding to Clec9A without functional modulation (e.g., partial or full neutralization) of Clec9A. Clec9A is a group V C-type lectin-like receptor (CTLR) expressed on the surface of a subset of dendritic cells (i.e., BDCA3⁺dendritic cells) specialized for the uptake and processing of materials from dead cells. Clec9A recognizes a conserved component within nucleated and nonnucleated cells, exposed when cell membranes are damaged. Clec9A is expressed at the cell surface as a glycosylated dimer and can mediate endocytosis, but not phagocytosis. Clec9A possesses a cytoplasmic immunoreceptor tyrosine-based activation-like motif that can recruit Syk kinase and induce proinflammatory cytokine production (see Huysamen et al. (2008), JBC, 283:16693-701).

[0017] In various embodiments, the Clec9A binding agent of the invention comprises a targeting moiety having an antigen recognition domain that recognizes an

epitope present on Clec9A. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on Clec9A. As used herein, a linear epitope refers to any continuous sequence of amino acids present on Clec9A. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on Clec9A. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

[0018] In various embodiments, the Clec9A binding agent of the present invention may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of human Clec9A. In various embodiments, the Clec9A binding agent of the invention may bind to any forms of the human Clec9A, including monomeric, dimeric, heterodimeric, multimeric and associated forms. In an embodiment, the Clec9A binding agent binds to the monomeric form of Clec9A. In another embodiment, the Clec9A binding agent binds to a dimeric form of Clec9A. In a further embodiment, the Clec9A binding agent binds to glycosylated form of Clec9A, which may be either monomeric or dimeric.

[0019] In an embodiment, the present Clec9A binding agent comprises a targeting moiety with an antigen recognition domain that recognizes one or more epitopes present on human Clec9A. In an embodiment, the human Clec9A comprises the amino acid sequence of:

MHEEEIYTSLOWDSPAPDTYQKCLSSNKDSGACCLVMVISCVFOMGLLTA
SIFLGVKLLQVSTIAMQQQEKLIQGERALLNFTEWKRSCALQMKYQQAQFMQ
NSLSSAHNSSPCPNWQNRRESCYYVSEIWSIWHTSQENCLKEGSTLLQIE
SKEEMDFITGSLRKIKGSYDYWVGLSQDGHSGRWLWQDGSSPSPGLLPA
ERSQSANQVCGYVKSNLLSSNCSTWKYFICEKYALRSSV

(SEQ ID NO:1).

[0020] The Clec9A binding agent comprises a targeting moiety which is a single-domain antibody, such as a VHH. The VHH may be derived from, for example, an organism that produces VHH antibody such as a camelid, a shark, or the VHH may be a designed VHH. VHHs are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies. VHH technology is based on fully functional antibodies from camelids that lack light chains. These heavy-chain antibodies contain a single variable domain (VHH) and two constant domains (CH2 and CH3). VHHs are commercially available under the trademark of NANOBODIES.

[0021] In some embodiments, the Clec9A binding agent comprises a targeting moiety which is a VHH comprising a single amino acid chain having four "framework regions" or FRs and three "complementary determining regions" or CDRs. As used herein, "framework region" or "FR" refers to a region in the variable domain which is located between the CDRs. As used herein, "complementary determining region" or "CDR" refers to variable regions in VHHs that contains the amino acid sequences capable of specifically binding to antigenic targets.

[0022] In various embodiments, the Clec9A binding agent comprises a VHH having a variable domain comprising at least one CDR1, CDR2, and/or CDR3 sequences. In various embodiments, the Clec9A binding agent comprises a VHH having a variable region comprising at least one FR1, FR2, FR3, and FR4 sequences.

[0023] In exemplary embodiments, the CDR1 sequence is selected from:

GSISSINVMG (SEQ ID NO:2);

GSFSSINVMG (SEQ ID NO:3);

GSISSINIMG (SEQ ID NO:4);

GSISSINIMG (SEQ ID NO:5);

VSIFSINAMG (SEQ ID NO:6);

GSIFSLNAMG (SEQ ID NO:7);

GRTISNYDMA (SEQ ID NO:8);

GRTFTTSLMQ (SEQ ID NO:9);

ERNLRIYDMA (SEQ ID NO:10);

ERNLRSYDMA (SEQ ID NO:11);

GLTFSNYHMG (SEQ ID NO:12);

GLTFSSYHMG (SEQ ID NO:13);

GLTFSTRYHMG (SEQ ID NO:14);

GLTLSSYYIA (SEQ ID NO:15);

GLTFSSYYTG (SEQ ID NO:16);

GLTLSSYHMG (SEQ ID NO:17);

GRTSSPYVTG (SEQ ID NO:18);

GFTFSGYVMS (SEQ ID NO:19);

GFTFSGYVMT (SEQ ID NO:20); or

GFTFSGYLMS (SEQ ID NO:21).

[0024] In exemplary embodiments, the CDR2 sequence is selected from:

RITNLGLPNYADWLKD (SEQ ID NO:22);
RITNLGLPNYADSVTG (SEQ ID NO:23);
RITNIGLPNYADSVKG (SEQ ID NO:24);
RITNLGLPNYADSVEG (SEQ ID NO:25);
AITSGGRWYSDSVKG (SEQ ID NO:26);
AITSGGRTAYADSVKG (SEQ ID NO:27);
HITSDGRIVYADPVKG (SEQ ID NO:28);
RISGSGDRTDYADSVKG (SEQ ID NO:29);
SITWSTGNTHYADSVKG (SEQ ID NO:30);
VISSSGDSTHYSDFVKG (SEQ ID NO:31);
VITSSGDSTHYSDFVKG (SEQ ID NO:32);
QITWSDASIYYAGSVKG (SEQ ID NO:33);
QITWSDTSIYYAGSVKG (SEQ ID NO:34);
QITWSDGTTYPPGSVKG (SEQ ID NO:35);
QIRWSDDSTYYPGSVKG (SEQ ID NO:36);
QISWSDDSTYYADSVKG (SEQ ID NO:37);
TVSWGCVTYADSVKG (SEQ ID NO:38);
SIGSGGGYPSYTDVEG (SEQ ID NO:39);
SIGSGGGYPSYTGVEG (SEQ ID NO:40);
HIGSGGGYPSYTDVQG (SEQ ID NO:41);
HIGSGGGHATYTDVEG (SEQ ID NO:42); or
TIGSGGGITSYADSVKG (SEQ ID NO:43).

[0025] In exemplary embodiments, the CDR3 sequence is selected from:

VALSAEY (SEQ ID NO:44);
VALKAEY (SEQ ID NO:45);
VGLKAEY (SEQ ID NO:46);
KTKSAVLFGGMDY (SEQ ID NO:47);
YIRGEDY (SEQ ID NO:48);
KHYASNY (SEQ ID NO:49);
QDFGSPSF (SEQ ID NO:50);
QDFRSPDF (SEQ ID NO:51);
QIFGSPNF (SEQ ID NO:52);
LAIHGDY (SEQ ID NO:53);
NQIRQWP (SEQ ID NO:54);
NSIRQWP (SEQ ID NO:55);
NAIRQWP (SEQ ID NO:56);
RKVGGPDY (SEQ ID NO:57);
NTFGNVY (SEQ ID NO:58);
LGR; or
VIK.

[0026] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:2, SEQ ID NO:22, and SEQ ID NO:44.

[0027] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:3, SEQ ID NO:23, and SEQ ID NO:45.

[0028] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:4, SEQ ID NO:24, and SEQ ID NO:45.

- [0029] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:2, SEQ ID NO:25, and SEQ ID NO:46.
- [0030] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:5, SEQ ID NO:26, and SEQ ID NO:47.
- [0031] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:6, SEQ ID NO:27, and SEQ ID NO:48.
- [0032] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:7, SEQ ID NO:28, and SEQ ID NO:49.
- [0033] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:8, SEQ ID NO:29, and SEQ ID NO:50.
- [0034] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:8, SEQ ID NO:29, and SEQ ID NO:51.
- [0035] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:8, SEQ ID NO:29, and SEQ ID NO:52.
- [0036] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:9, SEQ ID NO:30, and SEQ ID NO:53.
- [0037] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:10, SEQ ID NO:31, and SEQ ID NO:54.
- [0038] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:10, SEQ ID NO:31, and SEQ ID NO:55.
- [0039] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:11, SEQ ID NO:32, and SEQ ID NO:56.
- [0040] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:12, SEQ ID NO:33, and SEQ ID NO:57.
- [0041] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:13, SEQ ID NO:34, and SEQ ID NO:57.
- [0042] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:14, SEQ ID NO:35, and SEQ ID NO:57.
- [0043] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:15, SEQ ID NO:36, and SEQ ID NO:57.
- [0044] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:16, SEQ ID NO:37, and SEQ ID NO:57.
- [0045] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:17, SEQ ID NO:37, and SEQ ID NO:57.
- [0046] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:18, SEQ ID NO:38, and SEQ ID NO:58.
- [0047] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:19, SEQ ID NO:39, and LGR.
- [0048] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:19, SEQ ID NO:40, and LGR.
- [0049] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:19, SEQ ID NO:41, and LGR.
- [0050] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:20, SEQ ID NO:42, and LGR.
- [0051] In an exemplary embodiment, the Clec9A binding agent comprises SEQ ID NO:21, SEQ ID NO:43, and VIK.
- [0052] In various exemplary embodiments, the Clec9A binding agent comprises an amino acid sequence selected from the following sequences:

R2CHCL8
QVQLVESGGGLVHPGGSLRLSCAASGSISSINVMGWYRQAPGKERELVAR
ITNLGLPNYADWLKDRFTISRDNAKNTVYLMNSLKPEDTAVYYCYLVALS
AEYWGGGTQVTVSS (SEQ ID NO:59);

R1 CHCL50
QVQLVESGGGLVHPGGSLRLSCAASGSFSSINVMGWYRQAPGKERELVA
RITNLGLPNYADSVTGRFTISRDNAKNTVYLMNSLKPEDTAVYYCYLVALK

AEYWGGGTQVTVSS (SEQ ID NO:60);

R1 CHCL21
QVQLVESGGGLVHRGGSRLRLSCAASGSISSINIMGWYRQAPGKERELVARI
TNIGLPNYADSVKGRFTISRDNAKSTVYLMNSLNAEDTAVYYCYLVALK
EYWGGGTQVTVSS (SEQ ID NO:61);

R2CHCL87
QVQLVESGGGLVQPGGSLRLSCAASGSISSINVMGWYRQAPGKERELVA
RITNLGLPNYADSVEGRFTISRDKIDENTVYLEMNTLKPEDTAVYYCYLVGLK
AEYWGGGTQVTVSS (SEQ ID NO:62);

R2CHCL24
QVQLVESGGGLVQPGGSLRLSCAASGSSDSINAMGWYRQAPGKERELVA
AITSGGRWYSDSVKGRGTISRDNAKNTVYLQIASLKPEDTAVYYCINVKTK
SAVLFGGMDYWGGGTQVTVSS (SEQ ID NO:63);

R2CHCL38
QVQLVESGGGLVQPGGSLRLSCAASVSIFINAMGWYRQAPGKERELVAA
ITSGGRTAYADSVKGRFTISRDNASKNTVYLMQDSLKPEDTDVYYKAYIRG
EDYWGGGTQVTVSS (SEQ ID NO:64);

R1 CHCL16
DVQLVESGGGLVQPGGSLRLSCAASGSIFSLNAMGWYRQAPGKERELVA
HITSDGRIVYADPVKGRFTISRVDGKNMVTLQMNSLKPEDTAVYYCNAKHY
ASNYWGQGTQVTVSS (SEQ ID NO:65);

R2CHCL10
QVQLVESGGGSVQAGGSLRLSCAASGRTISNYDMAWSRQAPGKEREFVA
RISGSGDRTDYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTAIYYCQIQD
FGSPSFSGQGTQVTVSS (SEQ ID NO:66);

R1 CHCL34
DVQLVESGGGSVQAGGSLRLSCAASGRTISNYDMAWSRQAPGKEREFVA
RISGSGDRTDYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTAIYYCQIQD

FRSPDFWSQGTQVTVSS (SEQ ID NO:67);

R1 CHCL82
QVQLVESGGESVQAGGSLRLSCAASGRTISNYDMAWSRQAPGKEREFVA
RISGSGDRTDYADSVKGRFTISRDNAKNTVY LQMNSLKPEDTAIYNCGTQI
FGSPNFSGQGTQVTVSS (SEQ ID NO:68);

R2CHCL3
QVQLVESGGGLVQAGDSLRLSCAASGRTFTTSLMQWHRQAPGKEREFVA
SITWSTGNTHYADSVKGRFTISRDNARN TVY LQMNSLKPEDTAIYTCRVLAI
HGDYWGQGTQVTVSS (SEQ ID NO:69);

R2CHCL69
DVQLVESGGGLVQAGDSLRLSCAASERNLRIYDMAWYRQAPGKEREYVA
VISSSGDSTHYSD FVKGRFTISRDNAKNTVSLQMDSLKPEDTAFYYCNV NQ
IRQWPWGQGTQVTVSS (SEQ ID NO:70);

R1 CHCL56
QVQLVESGGGLVQAGDSLRLSCAASERNLRIYDMAWYRQAPGKEREYVA
VISSSGDSTHYSD FVKGRFTISRDNAKNTVSLQMDSLKPEDTAFYYCNVNS
IRQWPWGQGTQVTVSS (SEQ ID NO:71);

R2CHCL32
QVQLVESGGGLVQAGDSLRLSCTASERNLRSYDMAWWRQAPGKEREYV
AVITSSGDSTHYSD FVKGRFTISRDNAKNTVSLQMDSLKPEDTASY YCNVN
AIRQWPWGQGTQVTVSS (SEQ ID NO:72);

R2CHCL49
DVQLVESGGGSVQAGGSLRLSCAISCLTF SNYHMGWYRQAPGREREFVA
QITWSDASIYYAGSVKGRFTISRDNVKNIVYLQIDNLKPEDTAIYYCDARKVG
GPDYWGQGTQVTVSS (SEQ ID NO:73);

R2CHCL53
QVQLVESGGGLVQAGGSLT LSCAISGLTFSSYHMGWYRQAPGREREFVA
QITWSDTSIYYAGSVKGRFTISRDNVKNIVYLQIDNLKPEDTAIYYCDARKVG
GPDYWGQGTQVTVSS (SEQ ID NO:74);

R2CHCL22
DVQLVESGGGLVQAGGSLRLSCAISGLTF SRYHMGWYRQAPGREREFVA
QITWSDGTTYYPG SVKGRFTISRDNARN TVY LQIDNLKPEDTAIYYCDARKV
GGPDYWGQGTQVTVSS (SEQ ID NO:75);

R2CHCL25
QVQLVESGGGLVQAGGSLRLSCATSGLTLSSYYIAWYRQAPGREREFVAQ
IRWSDDSTYYPGSVKGRFTISRDNARN TVY L RMDNLKPEDTARIYYCDARK
VGGPDYWGQGTQVTVSS (SEQ ID NO:76);

R2CHCL18
DVQLVESGGGLVQAGGSLRLSCATSGLTFSSYYTGWYRQAPGREREFVA
QISWSDDSTYYADSVKGRFTISRDNARN TVY LQMN NLKPGDTAIYYCDARK
VGGPDYWGQGTQVTVSS (SEQ ID NO:77);

R1 CHCL23
DVQLVESGGGLVQAGGSLRLSCATSGLTLSSYHMGWYRQAPGREREFVA
QISWSDDSTYYADSVKGRFTISRDNARN TVY LQMN NLKPEDTAIYYCDARK
VGGPDYWGQGTQVTVSS (SEQ ID NO:78);

R1 CHCL27
DVQLVESGGGLVQAGGSLRLSCAASGRTSSPYVTGWYRQTPGKEREPVA
TVSWGGVTYYADSVKGRFTISRDNAKNTVY LQMN ALKPEDTAIYYC NVN TF
GNVYWGQGTQVTVSS (SEQ ID NO:79);

R2CHCL13
QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYVMSWVRQAPGKGLEWV
ASIGSGGGYPSYTD SVEGRFTISRDNAKNTLYLLMDNLKPDDTAVYYCEML
GRRQQGTQVTVSS (SEQ ID NO:80);

R2CHCL14
QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYVMSWVRQAPGKGLEWV
ASIGSGGGYPSYTD SVEGRFTISRDNAKNTLYLQMN NLKPDDTAVYYCEM
.....

LGRRGQGTQVTVSS (SEQ ID NO:81);

R2CHCL42

QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYVMSWVRQAPGKGLEWV
ASIGSGGGYPSTYTGSGVEGRFTISRDNAKNTLYLLMNNLKPDdTAVYYCEML
GRRGQGTQVTVSS (SEQ ID NO:82);

R2CHCL41

QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYVMSWVRQAPGKGLEWV
AHIGSGGGYPSTYDTSVQGRFTISRDNAKNTLYLQMNNLKPEDTAVYYCEM
LGRRGQGTQVTVSS (SEQ ID NO:83);

R2CHCL94

QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYVMTWVRQAPGKGLEWV
AHIGSGGGHATYDTSVEGRFTISRDNAKNTLYLQMNNLKAEDTAVYYCEFL
GRRGQGTQVTVSS (SEQ ID NO:84); or

R2CHCL27

QVQLVESGGGLVQPGGSLRLSCAASGFTFSGYLMWVRQAPCKGLEWV
ATJGSGGGITSYADSVKGRFTISRDNAKNTLYLQMNNLKHEDTAVYYCETVI
KRQGTQVTVSS (SEQ ID NO:85).

[0053] In various embodiments, the Clec9A binding agent comprises a targeting moiety comprising a sequence that is at least 60% identical to any one of the sequences disclosed herein. For example, the Clec9A binding agent may comprise a targeting moiety comprising a sequence that is at least about 60%, at least about 61 %, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71 %, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81 %, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the sequences disclosed herein (e.g. about 60%, or about 61 %, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71 %, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81 %, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91 %, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity to any one of the sequences disclosed herein)

[0054] In various embodiments, the Clec9A binding agent comprises a targeting moiety comprising an amino acid sequence having one or more amino acid mutations with respect to any one of the sequences disclosed herein. In various embodiments, the Clec9A binding agent comprises a targeting moiety comprising an amino acid sequence having one, or two, or three, or four, or five, or six, or seven, or eight, or nine, or ten, or fifteen, or twenty amino acid mutations with respect to any one of the sequences disclosed herein. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations.

[0055] In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions.

[0056] "Conservative substitutions" may be made, for instance, on the basis of similarity in polarity, charge, size, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the amino acid residues involved. The 20 naturally occurring amino acids can be grouped into the following six standard amino acid groups: (1) hydrophobic: Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe.

[0057] As used herein, "conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed within the same group of the six standard amino acid groups shown above. For example, the exchange of Asp by Glu retains one negative charge in the so modified polypeptide. In addition, glycine and proline may be substituted for one another based on their ability to disrupt α -helices.

[0058] As used herein, "non-conservative substitutions" are defined as exchanges of an amino acid by another amino acid listed in a different group of the six standard amino acid groups (1) to (6) shown above.

[0059] In various embodiments, the substitutions may also include non-classical amino acids. Exemplary non-classical amino acids include, but are not limited to, selenocysteine, pyrrolysine, *N*-formylmethionine β -alanine, GABA and δ -Aminolevulinic acid, 4-aminobenzoic acid (PABA), D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteine acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β methyl amino acids, C α -methyl amino acids, N α -methyl amino acids, and amino acid analogs in general.

[0060] In various embodiments, the amino acid mutation may be in the CDRs of the targeting moiety (e.g., the CDR1, CDR2 or CDR3 regions). In another embodiment, amino acid alteration may be in the framework regions (FRs) of the targeting moiety (e.g., the FR1, FR2, FR3, or FR4 regions). Modification of the amino acid sequences may be achieved using any known technique in the art e.g., site- directed mutagenesis or PCR based mutagenesis. Such techniques are described, for example, in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., 1989 and Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y., 1989.

[0061] In various embodiments, the mutations do not substantially reduce the present Clec9A binding agent's capability to specifically bind to Clec9A. In various embodiments, the mutations do not substantially reduce the present Clec9A binding agent's capability to specifically bind to Clec9A and without functionally modulating (e.g., partially or fully neutralizing) Clec9A.

[0062] In various embodiments, the binding affinity of the Clec9A binding agent of the invention for the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or monomeric and/or dimeric forms and/or any other naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human Clec9A may be described by the equilibrium dissociation constant (KD). In various embodiments, the Clec9A binding agent comprises a targeting moiety that binds to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other

naturally occurring or synthetic analogs, variants, or mutants (including monomeric and/or dimeric forms) of human Clec9A with a KD of less than about 1 μ M, about 900 nM, about 800 nM, about 700 nM, about 600 nM, about 500 nM, about 400 nM, about 300 nM, about 200 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 60 nM, about 50 nM, about 40 nM, about 30 nM, about 20 nM, about 10 nM, or about 5 nM, or about 1 nM.

[0063] In various embodiments, the Clec9A binding agent comprises a targeting moiety that binds but does not functionally modulate (*e.g.*, partially or fully neutralize) the antigen of interest, *i.e.*, Clec9A. For instance, in various embodiments, the targeting moiety of the Clec9A binding agent simply targets the antigen but does not substantially functionally modulate (*e.g.* partially or fully inhibit, reduce or neutralize) a biological effect that the antigen has. In various embodiments, the targeting moiety of the Clec9A binding agent binds an epitope that is physically separate from an antigen site that is important for its biological activity (*e.g.* an antigen's active site).

[0064] Such binding without significant function modulation finds use in various embodiments of the present invention, including methods in which the present Clec9A binding agent is used to directly or indirectly recruit active immune cells to a site of need via an effector antigen. For example, in various embodiments, the present Clec9A binding agent may be used to directly or indirectly recruit dendritic cells via Clec9A to a tumor cell in a method of reducing or eliminating a tumor (*e.g.* the Clec9A binding agent may comprise a targeting moiety having an anti- Clec9A antigen recognition domain and a targeting moiety having a recognition domain (*e.g.* antigen recognition domain) directed against a tumor antigen or receptor). In such embodiments, it is desirable to directly or indirectly recruit dendritic cells but not to functionally modulate or neutralize the Clec9A activity. In these embodiments, Clec9A signaling is an important piece of the tumor reducing or eliminating effect.

[0065] In some embodiments, the Clec9A binding agent enhances antigen-presentation by dendritic cells. For example, in various embodiments, the present Clec9A binding agent directly or indirectly recruits dendritic cells via Clec9A to a tumor cell, where tumor antigens are subsequently endocytosed and presented on the dendritic cell for induction of potent humoral and cytotoxic T cell responses.

[0066] In other embodiments (for example, related to treating autoimmune or neurodegenerative disease), the Clec9A binding agent comprises a targeting moiety that binds and neutralizes the antigen of interest, *i.e.*, Clec9A. For instance, in various embodiments, the present methods may inhibit or reduce Clec9A signaling or expression, *e.g.* to cause a reduction in an immune response.

Therapeutic Agents Comprising the Present Clec9A Binding Agents

Chimeras and Fusions with Signaling Agents

[0067] The Clec9A binding agent of the invention is part of a chimera or fusion with one or more signaling agents. Accordingly, the present invention provides for chimeric or fusion proteins that include, for example, a targeting moiety against Clec9A and one or more signaling agents.

[0068] The signaling agent is modified to have reduced affinity or activity for one or more of its receptors, which allows for attenuation of activity (inclusive of agonism or antagonism) and/or prevents nonspecific signaling or undesirable sequestration of the chimeric or fusion protein. In various embodiments, the signaling agent is antagonistic in its wild type form and bears one or more mutations that attenuate its antagonistic activity. In various embodiments, the signaling agent is antagonistic due to one or more mutations, *e.g.* an agonistic signaling agent is converted to an antagonistic signaling agent and, such a converted signaling agent, optionally, also bears one or more mutations that attenuate its antagonistic activity (*e.g.* as described in WO 2015/007520).

[0069] The signaling agent is a modified (*e.g.* mutant) form of the signaling agent having one or more mutations. In various embodiments, the modifications (*e.g.* mutations) allow for the modified signaling agent to have one or more of attenuated activity such as one or more of reduced binding affinity, reduced endogenous activity, and reduced specific bioactivity relative to unmodified or unmutated, *i.e.* the wild type form of the signaling agent (*e.g.* comparing the same signaling agent in a wild type form versus a modified or mutant form). In some embodiments, the mutations which attenuate or reduce binding or affinity include those mutations which substantially reduce or ablate binding or activity. In some embodiments, the mutations which attenuate or reduce binding or affinity are different than those mutations which substantially reduce or ablate binding or activity. Consequentially, in various embodiments, the mutations allow for the signaling agent to have improved safety, *e.g.* reduced systemic toxicity, reduced side effects, and reduced off-target effects relative to unmutated, *i.e.* wild type, signaling agent (*e.g.* comparing the same signaling agent in a wild type form versus a modified (*e.g.* mutant) form).

[0070] As described herein, the agent may have improved safety due to one of more modifications, *e.g.* mutations. In various embodiments, improved safety means that the present chimeric protein provides lower toxicity (*e.g.* systemic toxicity and/or tissue/organ-associated toxicities); and/or lessened or substantially eliminated side effects; and/or increased tolerability, lessened or substantially eliminated adverse events; and/or reduced or substantially eliminated off-target effects; and/or an increased therapeutic window.

[0071] In various embodiments, the signaling agent is modified to have one or more mutations that reduce its binding affinity or activity for one or more of its receptors. In some embodiments, the signaling agent is modified to have one or more mutations that substantially reduce or ablate binding affinity or activity for the receptors. In some embodiments, the activity provided by the wild type signaling agent is agonism at the receptor (*e.g.* activation of a cellular effect at a site of therapy). For example, the wild type signaling agent may activate its receptor. In such embodiments, the mutations result in the modified signaling agent to have reduced or ablated activating activity at the receptor. For example, the mutations may result in the modified signaling agent to deliver a reduced activating signal to a target cell or the activating signal could be ablated. In some embodiments, the activity provided by the wild type signaling agent is antagonism at the receptor (*e.g.* blocking or dampening of a cellular effect at a site of therapy). For example, the wild type signaling agent may antagonize or inhibit the receptor. In these embodiments, the mutations result in the modified signaling agent to have a reduced or ablated antagonizing activity at the receptor. For example, the mutations may result in the modified signaling agent to deliver a reduced inhibitory signal to a target cell or the inhibitory signal could be ablated. In various embodiments, the signaling agent is antagonistic due to one or more mutations, *e.g.* an agonistic signaling agent is converted to an antagonistic signaling agent (*e.g.* as described in WO 2015/007520) and, such a converted signaling agent, optionally, also bears one or more mutations that reduce its binding affinity or activity for one or more of its receptors or that substantially reduce or ablate binding affinity or activity for one or more of its receptors.

[0072] The reduced affinity or activity at the receptor is restorable by attachment with one or more of the targeting moieties as described herein (*e.g.*, targeting moiety against Clec9A or any other targeting moiety described herein).

[0073] In various embodiments, the chimeric proteins of the present invention reduce off-target effects because their signaling agents have mutations that weaken or ablate binding affinity or activity at a receptor. In various embodiments, this reduction in side effects is observed relative with, for example, the wild type signaling agents. In various embodiments, the signaling agent is active on target cells because the targeting moiety(ies) compensates for the missing/insufficient binding (*e.g.*, without limitation and/or avidity) required for substantial activation. In various embodiments, the modified signaling agent is substantially inactive en

route to the site of therapeutic activity and has its effect substantially on specifically targeted cell types which greatly reduces undesired side effects.

[0074] In some embodiments, the signaling agent may include one or more mutations that attenuate or reduce binding or affinity for one receptor (*i.e.*, a therapeutic receptor) and one or more mutations that substantially reduce or ablate binding or activity at a second receptor. In such embodiments, these mutations may be at the same or at different positions (*i.e.*, the same mutation or multiple mutations). In some embodiments, the mutation(s) that reduce binding and/or activity at one receptor is different than the mutation(s) that substantially reduce or ablate at another receptor. In some embodiments, the mutation(s) that reduce binding and/or activity at one receptor is the same as the mutation(s) that substantially reduce or ablate at another receptor. In some embodiments, the present chimeric proteins have a modified signaling agent that has both mutations that attenuate binding and/or activity at a therapeutic receptor and therefore allow for a more controlled, on-target therapeutic effect (*e.g.* relative wild type signaling agent) and mutations that substantially reduce or ablate binding and/or activity at another receptor and therefore reduce side effects (*e.g.* relative to wild type signaling agent).

[0075] In some embodiments, the substantial reduction or ablation of binding or activity is restorable with a targeting moiety. In various embodiments, substantially reducing or ablating binding or activity at a second receptor also may prevent deleterious effects that are mediated by the other receptor. Alternatively, or in addition, substantially reducing or ablating binding or activity at the other receptor causes the therapeutic effect to improve as there is a reduced or eliminated sequestration of the therapeutic chimeric proteins away from the site of therapeutic action. For instance, in some embodiments, this obviates the need of high doses of the present chimeric proteins that compensate for loss at the other receptor. Such ability to reduce dose further provides a lower likelihood of side effects.

[0076] The modified signaling agent comprises one or more mutations that cause the signaling agent to have reduced, substantially reduced, or ablated affinity, *e.g.* binding (*e.g.* KD) and/or activation (for instance, when the modified signaling agent is an agonist of its receptor, measurable as, for example, KA and/or EC50) and/or inhibition (for instance, when the modified signaling agent is an antagonist of its receptor, measurable as, for example, Ki and/or IC50), for one or more of its receptors. In various embodiments, the reduced affinity at the immunomodulating agent's receptor allows for attenuation of activity (inclusive of agonism or antagonism). In such embodiments, the modified signaling agent has about 1 %, or about 3%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 10%-20%, about 20%-40%, about 50%, about 40%-60%, about 60%-80%, about 80%-100% of the affinity for the receptor relative to the wild type signaling agent. In some embodiments, the binding affinity is at least about 2-fold lower, about 3-fold lower, about 4-fold lower, about 5-fold lower, about 6-fold lower, about 7-fold lower, about 8-fold lower, about 9-fold lower, at least about 10-fold lower, at least about 15-fold lower, at least about 20-fold lower, at least about 25-fold lower, at least about 30-fold lower, at least about 35-fold lower, at least about 40-fold lower, at least about 45-fold lower, at least about 50-fold lower, at least about 100-fold lower, at least about 150-fold lower, or about 10-50-fold lower, about 50-100-fold lower, about 100-150-fold lower, about 150-200-fold lower, or more than 200-fold lower relative to the wild type signaling agent. In embodiments wherein the chimeric protein has mutations that reduce binding at one receptor and substantially reduce or ablate binding at a second receptor, the attenuation or reduction in binding affinity of a modified signaling agent for one receptor is less than the substantial reduction or ablation in affinity for the other receptor. In some embodiments, the attenuation or reduction in binding affinity of a modified signaling agent for one receptor is less than the substantial reduction or ablation in affinity for the other receptor by about 1%, or about 3%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In various embodiments, substantial reduction or ablation refers to a greater reduction in binding affinity and/or activity than attenuation or reduction.

[0077] In various embodiments, the modified signaling agent comprises one or more mutations that reduce the endogenous activity of the signaling agent to about 75%, or about 70%, or about 60%, or about 50%, or about 40%, or about 30%, or about 25%, or about 20%, or about 10%, or about 5%, or about 3%, or about 1%, *e.g.*, relative to the wild type signaling agent.

[0078] In some embodiments, the modified signaling agent comprises one or more mutations that cause the signaling agent to have reduced affinity for its receptor that is lower than the binding affinity of the targeting moiety(ies) for its(their) receptor(s). In some embodiments, this binding affinity differential is between signaling agent/receptor and targeting moiety/receptor on the same cell. In some embodiments, this binding affinity differential allows for the signaling agent, *e.g.* mutated signaling agent, to have localized, on-target effects and to minimize off-target effects that underlie side effects that are observed with wild type signaling agent. In some embodiments, this binding affinity is at least about 2-fold, or at least about 5-fold, or at least about 10-fold, or at least about 15-fold lower, or at least about 25-fold, or at least about 50-fold lower, or at least about 100-fold, or at least about 150-fold.

[0079] Receptor binding activity may be measured using methods known in the art. For example, affinity and/or binding activity may be assessed by Scatchard plot analysis and computer-fitting of binding data (*e.g.* Scatchard, 1949) or by reflectometric interference spectroscopy under flow through conditions, as described by Brecht *et al.* (1993).

[0080] The signaling agent is a modified version of human interferon alpha 2.

[0081] The amino acid sequences of the wild type signaling agents described herein are well known in the art. Accordingly, in various embodiments the modified signaling agent comprises an amino acid sequence that has at least 98%, or at least about 99% sequence identity with SEQ ID NO:86 or 87 (*e.g.* 98%, or about 99% sequence identity).

[0082] The modified signaling agent comprises an amino acid sequence having one or more amino acid mutations. In some embodiments, the one or more amino acid mutations may be independently selected from substitutions, insertions, deletions, and truncations. In some embodiments, the amino acid mutations are amino acid substitutions, and may include conservative and/or non-conservative substitutions, as described elsewhere herein.

[0083] In various embodiments, the substitutions may also include non-classical amino acids as described elsewhere herein.

[0084] As described herein, the modified signaling agents bear mutations that affect affinity and/or activity at one or more receptors. The receptors of any signaling agents, as described herein, are known in the art.

[0085] Illustrative mutations which provide reduced affinity and/or activity (*e.g.* agonistic) at a receptor are found in WO 2013/107791 (*e.g.* with regard to interferons).

[0086] The modified IFN- α agent has reduced affinity and/or activity for the IFN- α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains. In some embodiments, the modified IFN- α agent has substantially reduced or ablated affinity and/or activity for the IFN- α/β receptor (IFNAR), *i.e.*, IFNAR1 and/or IFNAR2 chains.

[0087] Mutant forms of interferon α are known to the person skilled in the art. In an illustrative embodiment, the modified signaling agent is the allelic form IFN- α 2a having the amino acid sequence of:

IFN-α2a:
CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLH
EMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDEACVIQGGVGTETPLMKED
SILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE (SEQ ID
NO:86)

[0088] In an illustrative embodiment, the modified signaling agent is the allelic form IFN-α2b having the amino acid sequence of (which differs from IFN-α2a at amino acid position 23):

IFN-α2b:
CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLH
EMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDEACVIQGGVGTETPLMKED
SILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE (SEQ ID
NO:87)

[0089] Said IFN-α2 mutant (IFN-α2a or IFN-α2b) is mutated at one or more amino acids at positions 148, 149 and/or 153. In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from L153A, R149A, and M148A. Such mutants are described, for example, in WO2013/107791 and Piehler et al., (2000) J. Biol. Chem, 275:40425-33.

[0090] In some embodiments, the IFN-α2 mutants have reduced affinity and/or activity for IFNAR1. In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from F64A, N65A, T69A, L80A, Y85A, and Y89A, as described in WO2010/030671.

[0091] In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from K133A, R144A, R149A, and L153A as described in WO2008/124086.

[0092] In some embodiments, the IFN-α2 mutant comprises one or more mutations selected from R120E and R120E/K121 E, as described in WO2015/007520 and WO2010/030671. In such embodiments, said IFN-α2 mutant antagonizes wildtype IFN-α2 activity. In such embodiments, said mutant IFN-α2 has reduced affinity and/or activity for IFNAR1 while affinity and/or activity of IFNR2 is retained.

[0093] In some embodiments, the human IFN-α2 mutant comprises (1) one or more mutations selected from R120E and R120E/K121E, which, without wishing to be bound by theory, create an antagonistic effect and (2) one or more mutations selected from K133A, R144A, R149A, and L153A, which, without wishing to be bound by theory, allow for an attenuated effect at, for example, IFNAR2. In an embodiment, the human IFN-α2 mutant comprises R120E and L153A.

[0094] In some embodiments, the human IFN-α2 mutant comprises one or more mutations selected from, L15A, A19W, R22A, R23A, L26A, F27A, L30A, L30V, K31A, D32A, R33K, R33A, R33Q, H34A, D35A, Q40A, D114R, L117A, R120A, R125A, K134A, R144A, A145G, A145M, M148A, R149A, S152A, L153A, and N156A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or L30A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or R33A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or M148A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations H57Y, E58N, Q61S, and/or L153A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations N65A, L80A, Y85A, and/or Y89A as disclosed in WO 2013/059885. In some embodiments, the human IFN-α2 mutant comprises the mutations N65A, L80A, Y85A, Y89A, and/or D114A as disclosed in WO 2013/059885.

[0095] In one embodiment, the present chimeric protein has (i) a targeting moiety against Clec9A and (ii) a targeting moiety which is directed against a tumor cell, along with any of the modified or mutant signaling agents described herein. In an embodiment, the present chimeric protein has a targeting moiety directed against Clec9A on dendritic cells and a second targeting moiety directed against PD-L1 or PD-L2 on tumor cells.

[0096] In one embodiment, the present chimeric protein has (i) a targeting moiety against Clec9A and (ii) a targeting moiety which is directed against a checkpoint inhibitor marker, along with any of the modified or mutant interferons described herein. In an embodiment, the present chimeric protein has a targeting moiety directed against Clec9A on dendritic cells and a second targeting moiety directed against PD-1.

Multi-Specific Chimeras and Fusions with Signaling Agents

[0097] In various embodiments, the Clec9A binding agent of the invention is part of a chimera or fusion with one or more signaling agents as described herein and one or more additional targeting moieties. Accordingly, the present invention provides for chimeric or fusion proteins that include one or more signaling agents and a targeting moiety against Clec9A and one or more additional targeting moieties. Accordingly, in various embodiments, the term "Clec9A binding agent" encompasses such chimeras or fusion proteins with one or more signaling agents and one or more additional targeting moieties.

[0098] In various embodiments, the chimeric proteins of the present invention have targeting moieties which target two different cells (e.g. to make a synapse) or the same cell (e.g. to get a more concentrated signaling agent effect).

[0099] In various embodiments, the Clec9A binding agent of the invention is multispecific, *i.e.*, the Clec9A binding agent comprises two or more targeting moieties having recognition domains (e.g. antigen recognition domains) that recognize and bind two or more targets (e.g. antigens, or receptors, or epitopes). In such embodiments, the Clec9A binding agent of the invention may comprises two more targeting moieties having recognition domains that recognize and bind two or more epitopes on the same antigen or on different antigens or on different receptors. In various embodiments, such multi-specific Clec9A binding agents exhibit advantageous properties such as increased avidity and/or improved selectivity. In an embodiment, the Clec9A binding agent of the invention comprises two targeting moieties and is bispecific, *i.e.*, binds and recognizes two epitopes on the same antigen or on different antigens or different receptors. Accordingly, in various embodiments, the term "Clec9A binding agent" encompasses such multi-specific Clec9A binding agents comprising two or more targeting moieties.

[0100] In various embodiments, the multispecific Clec9A binding agent of the invention comprises two or more targeting moieties with each targeting moiety being an antibody or an antibody derivative as described herein. In an embodiment, the multispecific Clec9A binding agent of the invention comprises at least one VHH comprising an antigen recognition domain against Clec9A and one antibody or antibody derivative comprising a recognition domain against a tumor antigen and/or an immune cell marker.

[0101] In various embodiments, the present multispecific Clec9A binding agents have two or more targeting moieties that target different antigens or receptors,

and one targeting moiety may be attenuated for its antigen or receptor, e.g. the targeting moiety binds its antigen or receptor with a low affinity or avidity (including, for example, at an affinity or avidity that is less than the affinity or avidity the other targeting moiety has for its antigen or receptor, for instance the difference between the binding affinities may be about 10-fold, or 25-fold, or 50-fold, or 100-fold, or 300-fold, or 500-fold, or 1000-fold, or 5000-fold; for instance the lower affinity or avidity targeting moiety may bind its antigen or receptor at a KD in the mid- to high-nM or low- to mid-μM range while the higher affinity or avidity targeting moiety may bind its antigen or receptor at a KD in the mid- to high-pM or low- to mid-nM range). For instance, in some embodiments, the present multispecific Clec9A binding agent comprises an attenuated targeting moiety that is directed against a promiscuous antigen or receptor, which may improve targeting to a cell of interest (e.g. via the other targeting moiety) and prevent effects across multiple types of cells, including those not being targeted for therapy (e.g. by binding promiscuous antigen or receptor at a higher affinity than what is provided in these embodiments).

[0102] The multispecific Clec9A binding agent of the invention may be constructed using methods known in the art, see for example, U.S. Patent No. 9,067,991, U.S. Patent Publication No. 20110262348 and WO 2004/041862. In an illustrative embodiment, the multispecific Clec9A binding agent of the invention comprising two or more targeting moieties may be constructed by chemical crosslinking, for example, by reacting amino acid residues with an organic derivatizing agent as described by Blattler *et al.*, Biochemistry 24,1517-1524 and EP294703. In another illustrative embodiment, the multispecific Clec9A binding agent comprising two or more targeting moieties is constructed by genetic fusion, i.e., constructing a single polypeptide which includes the polypeptides of the individual targeting moieties. For example, a single polypeptide construct may be formed which encodes a first VHH with an antigen recognition domain against Clec9A and a second antibody or antibody derivative with an antigen recognition domain against e.g., a tumor antigen or a checkpoint inhibitor. A method for producing bivalent or multivalent VHH polypeptide constructs is disclosed in PCT patent application WO 96/34103. In a further illustrative embodiment, the multispecific Clec9A binding agent of the invention may be constructed by using linkers. For example, the carboxy-terminus of a first VHH with an antigen recognition domain against Clec9A may be linked to the amino- terminus of a second antibody or antibody derivative with an antigen recognition domain against e.g., a tumor antigen or a checkpoint inhibitor (or vice versa). Illustrative linkers that may be used are described herein. In some embodiments, the components of the multispecific Clec9A binding agent of the invention are directly linked to each other without the use of linkers.

[0103] In various embodiments, the multi-specific Clec9A binding agent of the invention recognizes and binds to Clec9A and one or more antigens found on one or more immune cells, which can include, without limitation, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, natural killer cells, T lymphocytes (e.g., cytotoxic T lymphocytes, T helper cells, natural killer T cells), B lymphocytes, plasma cells, dendritic cells, or subsets thereof. In some embodiments, the CLEC9A binding agent specifically binds to an antigen of interest and effectively directly or indirectly recruits one of more immune cells.

[0104] In various embodiments, the multi-specific Clec9A binding agent of the invention recognizes and binds to Clec9A and one or more antigens found on tumor cells. In these embodiments, the present Clec9A binding agents may directly or indirectly recruit an immune cell to a tumor cell or the tumor microenvironment. In some embodiments, the present Clec9A binding agents may directly or indirectly recruit an immune cell, e.g. a dendritic cell, to a site of action (such as, by way of non-limiting example, the tumor microenvironment). In some embodiments, the present Clec9A binding agent enhances antigen presentation (e.g. tumor antigen presentation) by dendritic cells for the induction of a potent humoral and cytotoxic T cell response. In some embodiments, the present Clec9A binding agents are capable of, or find use in methods involving, shifting the balance of immune cells in favor of immune attack of a tumor. For instance, the present Clec9A binding agents can shift the ratio of immune cells at a site of clinical importance in favor of cells that can kill and/or suppress a tumor (e.g. T cells, cytotoxic T lymphocytes, T helper cells, natural killer (NK) cells, natural killer T (NKT) cells, anti-tumor macrophages (e.g. M1 macrophages), B cells, and dendritic cells and in opposition to cells that protect tumors (e.g. myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs); tumor associated neutrophils (TANs), M2 macrophages, tumor associated macrophages (TAMs), or subsets thereof). In some embodiments, the present Clec9A binding agent is capable of increasing a ratio of effector T cells to regulatory T cells.

[0105] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. antigen or receptor) associated with tumor cells. In some embodiments, the targeting moiety directly or indirectly recruits tumor cells. For instance, in some embodiments, the recruitment of the tumor cell is to one or more effector cell (e.g. an immune cell as described herein) that can kill and/or suppress the tumor cell.

[0106] Tumor cells, or cancer cells refer to an uncontrolled growth of cells or tissues and/or an abnormal increased in cell survival and/or inhibition of apoptosis which interferes with the normal functioning of bodily organs and systems. For example, tumor cells include benign and malignant cancers, polyps, hyperplasia, as well as dormant tumors or micro metastases. Illustrative tumor cells include, but are not limited to cells of: basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intraepithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblasts leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (e.g. that associated with brain tumors), and Meigs' syndrome. Tumor cells, or cancer cells also include, but are not limited to, carcinomas, e.g. various subtypes, including, for example, adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma), sarcomas (including, for example, bone and soft tissue), leukemias (including, for example, acute myeloid, acute lymphoblastic, chronic myeloid, chronic lymphocytic, and hairy cell), lymphomas and myelomas (including, for example, Hodgkin and non-Hodgkin lymphomas, light chain, non-secretory, MGUS, and plasmacytomas), and central nervous system cancers (including, for example, brain (e.g. gliomas (e.g. astrocytoma, oligodendroglioma, and ependymoma), meningioma, pituitary adenoma, and neuromas, and spinal cord tumors (e.g. meningiomas and neurofibroma).

[0107] Illustrative tumor antigens include, but are not limited to, MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADAbp), cyclophilin b, Colorectal associated antigen (CRC)-0017-1A/GA733, Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3, prostate-specific membrane antigen (PSMA), T-cell receptor/CD3-zeta chain, MAGE-family of tumor antigens (e.g., MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4), MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (e.g., GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21 ras, RCAS1, a-fetoprotein, E-cadherin, a-catenin, β-catenin and γ-catenin, p120ctn, gp100 Pmel117, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig-idiotypic, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papilloma virus proteins, Smad family of tumor antigens, Imp-1, NA, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen

phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 CT-7, c-erbB-2, CD19, CD20, CD22, CD30, CD33, CD37, CD56, CD70, CD74, CD138, AGS16, MUC1, GPNMB, Ep-CAM, PD-L1, PD- L2, PMSA, and BCMA (TNFRSF17). In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these tumor antigens.

[0108] In some embodiments, the present multi-specific Clec9A binding agent recognizes and binds to Clec9A as well as an antigen on a tumor cell. In some embodiments, the multi-specific Clec9A binding agent directly or indirectly recruits dendritic cells to the tumor cell or tumor microenvironment.

[0109] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with T cells. In some embodiments, the targeting moiety directly or indirectly recruits T cells. In an embodiment, the antigen recognition domains specifically bind to effector T cells. In some embodiments, the antigen recognition domain directly or indirectly recruits effector T cells, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative effector T cells include cytotoxic T cells (e.g. $\alpha\beta$ TCR, CD3⁺, CD8⁺, CD45RO⁺); CD4⁺ effector T cells (e.g. $\alpha\beta$ TCR, CD3⁺, CD4⁺, CCR7⁺, CD62L^{hi}, IL-7R/CD127⁺); CD8⁺ effector T cells (e.g. $\alpha\beta$ TCR, CD3⁺, CD8⁺, CCR7⁺, CD62L^{hi}, IL7R/CD127⁺); effector memory T cells (e.g. CD62L^{low}, CD44⁺, TCR, CD3⁺, IL7R/CD127⁺, IL-15R⁺, CCR7^{low}); central memory T cells (e.g. CCR7⁺, CD62L⁺, CD27⁺; or CCR7^{hi}, CD44⁺, CD62L^{hi}, TCR, CD3⁺, IL-7R/CD127⁺, IL-15R⁺); CD62L⁺ effector T cells; CD8⁺ effector memory T cells (TEM) including early effector memory T cells (CD27⁺CD62L⁻) and late effector memory T cells (CD27⁻CD62L⁻) (TemE and TemL, respectively); CD127(+) CD25(low/-) effector T cells; CD127(-)CD25(-) effector T cells; CD8⁺ stem cell memory effector cells (TSCM) (e.g. CD44(low)CD62L(high)CD122(high)sca(+)); TH1 effector T-cells (e.g. CXCR3⁺, CXCR6⁺ and CCR5⁺; or $\alpha\beta$ TCR, CD3⁺, CD4⁺, IL-12R⁺, IFN γ R⁺, CXCR3⁺), TH2 effector T cells (e.g. CCR3⁺, CCR4⁺ and CCR8⁺; or $\alpha\beta$ TCR, CD3⁺, CD4⁺, IL-4R⁺, IL-33R⁺, CCR4⁺, IL-17RB⁺, CRTH2⁺); TH9 effector T cells (e.g. $\alpha\beta$ TCR, CD3⁺, CD4⁺); TH17 effector T cells (e.g. $\alpha\beta$ TCR, CD3⁺, CD4⁺, IL-23R⁺, CCR6⁺, IL-1R⁺); CD4⁺ CD45RO⁺ CCR7⁺ effector T cells, ICOS⁺ effector T cells; CD4⁺ CD45RO⁺ CCR7(-) effector T cells; and effector T cells secreting IL-2, IL-4 and/or IFN- γ .

[0110] Illustrative T cell antigens of interest include, for example (and inclusive of the extracellular domains, where applicable): CD8, CD3, SLAMF4, IL-2R α , 4-1 BB/TNFRSF9, IL-2R β , ALCAM, B7-1, IL-4R, B7-H3, BLAME/SLAMFS, CEACAM1, IL-6R, CCR3, IL-7R α , CCR4, CXCR1/IL-8 RA, CCR5, CCR6, IL-10R α , CCR 7, IL-10 R β , CCRS, IL-12 R β 1, CCR9, IL-12 R β 2, CD2, IL-13 R α 1, IL-13, CD3, CD4, ILT2/CDS5j, ILT3/CDS5k, ILT4/CDS5d, ILT5/CDS5a, Integrin α 4/CD49d, CDS, Integrin α E/CD103, CD6, Integrin α M/CD 11 b, CDS, Integrin α X/CD11 c, Integrin β 2/CDIS, KIR/CD15S, CD27/TNFRSF7, KIR2DL1, CD2S, KIR2DL3, CD30/TNFRSFS, KIR2DL4/CD15Sd, CD31/PECAM-1, KIR2DS4, CD40 Ligand/TNFSF5, LAG-3, CD43, LAIR1, CD45, LAIR2, CDS3, Leukotriene B4-R1, CDS4/SLAMF5, NCAM-L1, CD94, NKG2A, CD97, NKG2C, CD229/SLAMF3, NKG2D, CD2F-10/SLAMF9, NT-4, CD69, NTB-A/SLAMF6, Common γ Chain/IL-2 R γ , Osteopontin, CRACC/SLAMF7, PD-1, CRTAM, PSGL-1, CTLA-4, RANK/TNFRSF11A, CX3CR1, CX3CL1, L-Selectin, CXCR3, SIRP β 1, CXCR4, SLAM, CXCR6, TCCR/WSX-1, DNAM-1, Thymopoietin, EMMPRIN/CD147, TIM-1, EphB6, TIM-2, Fas/TNFRSF6, TIM-3, Fas Ligand/TNFSF6, TIM-4, Fey RIII/CD16, TIM-6, TNFR1/TNFRSF1A, Granulysin, TNF RIII/TNFRSF1 B, TRAIL R1/TNFRSF10A, ICAM-1/CD54, TRAIL R2/TNFRSF10B, ICAM-2/CD102, TRAILR3/TNFRSF10C, IFN- γ R1, TRAILR4/TNFRSF10D, IFN- γ R2, TSLP, IL-1 R1 and TSLP R. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative T cell antigens.

[0111] By way of non-limiting example, in various embodiments, the present chimeric protein has a targeting moiety directed against a checkpoint marker expressed on a T cell, e.g. one or more of PD-1, CD28, CTLA4, ICOS, BTLA, KIR, LAG 3, CD137, OX40, CD27, CD40L, TIM3, and A2aR.

[0112] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with B cells. In some embodiments, the targeting moiety directly or indirectly recruits B cells, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative B cell antigens of interest include, for example, CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD37, CD38, CD39, CD40, CD72, CD73, CD74, CDw75, CDw76, CD77, CD78, CD79a/b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD89, CD98, CD126, CD127, CDw130, CD138, CDw150, and B-cell maturation antigen (BCMA). In various embodiments, the Clec9A binding agent comprises a targeting moiety that binds one or more of these illustrative B cell antigens.

[0113] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with Natural Killer cells. In some embodiments, the targeting moiety directly or indirectly recruits Natural Killer cells, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative Natural Killer cell antigens of interest include, for example TIGIT, 2B4/SLAMF4, KIR2DS4, CD155/PVR, KIR3DL1, CD94, LMIR1/CD300A, CD69, LMIR2/CD300c, CRACC/SLAMF7, LMIR3/CD300LF, KIR α , DNAM-1, LMIR5/CD300LB, Fc- ϵ RII, LMIR6/CD300LE, Fc- γ RI/CD64, MICA, Fc- γ RIIb/CD32b, MICB, Fc- γ RIIC/CD32c, MULT-1, Fc- γ RIIA/CD32a, Nectin-2/CD112, Fc- γ RIII/CD16, NKG2A, FcRH1/IRTA5, NKG2C, FcRH2/IRTA4, NKG2D, FcRH4/IRTA1, NKp30, FcRH5/IRTA2, NKp44, Fc-Receptor-like 3/CD16-2, NKp46/NCR1, NKp80/KLRF1, NTB-A/SLAMF6, Rae-1, Rae-1 a, Rae-1 β , Rae-1 delta, H60, Rae-1 epsilon, ILT2/CD85j, Rae-1 γ , ILT3/CD85k, TREM-1, ILT4/CD85d, TREM-2, ILT5/CD85a, TREM-3, KIR/CD158, TREML1/TLT-1, KIR2DL1, ULBP-1, KIR2DL3, ULBP-2, KIR2DL4/CD158d and ULBP-3. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative NK cell antigens.

[0114] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with macrophages/monocytes. In some embodiments, the targeting moiety directly or indirectly directly or indirectly recruits macrophages/monocytes, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative macrophages/monocyte antigens of interest include, for example SIRP α , B7-1/CD80, ILT4/CD85d, B7-H1, ILT5/CD85a, Common β Chain, Integrin α 4/CD49d, BLAME/SLAMF8, Integrin α X/CD11c, CCL6/C10, Integrin β 2/CD18, CD155/PVR, Integrin β 3/CD61, CD31/PECAM-1, Latexin, CD36/SR-B3, Leukotriene B4 R1, CD40/TNFRSF5, LIMP α SR-B2, CD43, LMIR1/CD300A, CD45, LMIR2/CD300c, CD68, LMIR3/CD300LF, CD84/SLAMF5, LMIR5/CD300LB, CD97, LMIR6/CD300LE, CD163, LRP-1, CD2F-10/SLAMF9, MARCO, CRACC/SLAMF7, MD-1, ECF-L, MD-2, EMMPRIN/CD147, MGL2, Endoglin/CD105, Osteoactivin/GPNMB, Fc- γ RI/CD64, Osteopontin, Fc- γ RIIb/CD32b, PD-L2, Fc- γ RIIC/CD32c, Siglec-3/CD33, Fc- γ RIIA/CD32a, SIGNR1/CD209, Fc- γ RIII/CD16, SLAM, GM-CSF R a, TCCR/WSX-1, ICAM-2/CD102, TLR3, IFN- γ RI, TLR4, IFN- γ R2, TREM-I, IL-1 RII, TREM-2, ILT2/CD85j, TREM-3, ILT3/CD85k, TREML1/TLT-1, 2B4/SLAMF 4, IL-10 R α , ALCAM, IL-10 R β , AminopeptidaseN/ANPEP, ILT2/CD85j, Common β Chain, ILT3/CD85k, C1q R1/CD93, ILT4/CD85d, CCR1, ILT5/CD85a, CCR2, CD206, Integrin α 4/CD49d, CCR5, Integrin α M/CD11 b, CCR8, Integrin α X/CD11c, CD155/PVR, Integrin β 2/CD18, CD14, Integrin β 3/CD61, CD36/SR-B3, LAIR1, CD43, LAIR2, CD45, Leukotriene B4-R1, CD68, LIMP α SR-B2, CD84/SLAMF5, LMIR1/CD300A, CD97, LMIR2/CD300c, CD163, LMIR3/CD300LF, Coagulation Factor III/Tissue Factor, LMIR5/CD300LB, CX3CR1, CX3CL1, LMIR6/CD300LE, CXCR4, LRP-1, CXCR6, M-CSF R, DEP-1/CD148, MD-1, DNAM-1, MD-2, EMMPRIN/CD147, MMR, Endoglin/CD105, NCAM-L1, Fc- γ RI/CD64, PSGL-1, Fc- γ RIIICD16, RP105, G-CSF R, L-Selectin, GM-CSF R a, Siglec-3/CD33, HVEM/TNFRSF14, SLAM, ICAM-1/CD54, TCCR/WSX-1, ICAM-2/CD102, TREM-I, IL-6 R, TREM-2, CXCR1/IL-8 RA, TREM-3 and TREML1/TLT-1. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative macrophage/monocyte antigens.

[0115] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically

binds to a target (e.g. an antigen or receptor) associated with dendritic cells. In some embodiments, the targeting moiety directly or indirectly recruits dendritic cells, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect). Illustrative dendritic cell antigens of interest include, for example, CLEC9A, XCR1, RANK, CD36/SRB3, L0X-1/SR-E1, CD68, MARCO, CD163, SR-A1/MSR, CD5L, SREC-1, CL-PI/C0LEC12, SREC-II, LIMP1IISRB2, RP105, TLR4, TLR1, TLR5, TLR2, TLR6, TLR3, TLR9, 4-IBB Ligand/TNFSF9, IL-12/IL-23 p40, 4-Amino-1,8-naphthalimide, ILT2/CD85j, CCL21/6Ckine, ILT3/CD85k, 8-oxo-dG, ILT4/CD85d, 8D6A, ILT5/CD85a, A2B5, lutegrin a 4/CD49d, Aag, Integrin β 2/CD18, AMICA, Langerin, B7-2/CD86, Leukotriene B4 RI, B7-H3, LMIR1/CD300A, BLAME/SLAMF8, LMIR2/CD300c, Clq R1/CD93, LMIR3/CD300LF, CCR6, LMIR5/CD300LB CCR7, LMIR6/CD300LE, CD40/TNFRSF5, MAG/Siglec-4-a, CD43, MCAM, CD45, MD-1, CD68, MD-2, CD83, MDL-1/CLEC5A, CD84/SLAMF5, MMR, CD97, N CAM LI, CD2F-10/SLAMF9, Osteoactivin GPNMB, Chern 23, PD-L2, CLEC-1, RP105, CLEC-2, CLEC-8, Siglec-2/CD22, CRACC/SLAMF7, Siglec-3/CD33, DC-SIGN, DCE205, Siglec-5, DC-SIGNR/CD299, Siglec-6, DCAR, Siglec-7, DCIR/CLEC4A, Siglec-9, DEC-205, Siglec-10, Dectin-1/CLEC7A, Siglec-F, Dectin-2/CLEC6A, SIGNR1/CD209, DEP-1/CD148, SIGNR4, DLEC, SLAM, EMMPRIN/CD147, TCCR/WSX-1, Fc-γ R1/CD64, TLR3, Fc-γ RIIB/CD32b, TREM-1, Fc-γ RIIC/CD32c, TREM-2, Fc-Y RIIA/CD32a, TREM-3, Fc-γ RIII/CD16, TREML1/TLT-1, ICAM-2/CD102 and Vanilloid R1. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative DC antigens.

[0116] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with immune cells selected from, but not limited to, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, or subsets thereof. In some embodiments, the antigen recognition domains directly or indirectly recruit megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, or subsets thereof, e.g., in some embodiments, to a therapeutic site (e.g. a locus with one or more disease cell or cell to be modulated for a therapeutic effect).

[0117] In some embodiments, the multi-specific CLEC9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with megakaryocytes and/or thrombocytes. Illustrative megakaryocyte and/or thrombocyte antigens of interest include, for example, GP IIb/IIIa, GPIb, vWF, PF4, and TSP. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative megakaryocyte and/or thrombocyte antigens.

[0118] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with erythrocytes. Illustrative erythrocyte antigens of interest include, for example, CD34, CD36, CD38, CD41a (platelet glycoprotein IIb/IIIa), CD41 b (GPIIb), CD71 (transferrin receptor), CD105, glycophorin A, glycophorin C, c-kit, HLA-DR, H2 (MHC-II), and Rhesus antigens. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these illustrative erythrocyte antigens.

[0119] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with mast cells. Illustrative mast cells antigens of interest include, for example, SCFR/CD117, FcεRI, CD2, CD25, CD35, CD88, CD203c, C5R1, CMAI, FCERIA, FCER2, TPSAB1. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these mast cell antigens.

[0120] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with basophils. Illustrative basophils antigens of interest include, for example, FcεRI, CD203c, CD123, CD13, CD107a, CD107b, and CD164. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these basophil antigens.

[0121] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with neutrophils. Illustrative neutrophils antigens of interest include, for example, 7D5, CD10/CALLA, CD13, CD16 (FcRIII), CD18 proteins (LFA-1, CR3, and p150, 95), CD45, CD67, and CD177. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these neutrophil antigens.

[0122] In some embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to a target (e.g. an antigen or receptor) associated with eosinophils. Illustrative eosinophils antigens of interest include, for example, CD35, CD44 and CD69. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these eosinophil antigens.

[0123] In various embodiments, the multi-specific Clec9A binding agent of the invention comprises a targeting moiety having a recognition domain that specifically binds to an appropriate antigen or cell surface marker known by the skilled artisan. In some embodiments, the antigen or cell surface marker is a tissue-specific marker. Illustrative tissue-specific markers include, but are not limited to, endothelial cell surface markers such as ACE, CD14, CD34, CDH5, ENG, ICAM2, MCAM, NOS3, PECAMI, PROCR, SELE, SELP, TEK, THBD, VCAMI, VWF; smooth muscle cell surface markers such as ACTA2, MYH10, MYH1 1, MYH9, MYOCD; fibroblast (stromal) cell surface markers such as ALCAM, CD34, COLIAI, C0L1A2, C0L3A1, FAP, PH-4; epithelial cell surface markers such as CDID, K6IRS2, KRTIO, KRT13, KRT17, KRT18, KRT19, KRT4, KRT5, KRT8, MUCI, TACSTD1; neovasculature markers such as CD13, TFNA, Alpha-v beta-3 (αvβ3), E-selectin; and adipocyte surface markers such as ADIPOQ, FABP4, and RETN. In various embodiments, the CLEC9A binding agent comprises a targeting moiety that binds one or more of these antigens. In various embodiments, a targeting moiety of the chimeric protein binds one or more of cells having these antigens.

[0124] In various embodiments, the multi-specific Clec9A binding agent of the invention has one or more targeting moieties directed against a checkpoint marker, e.g. one or more of PD-1/PD-L1 or PD-L2, CD28/CD80 or CD86, CTLA4/ CD80 or CD86, ICOS/ICOSL or B7RP1, BTLA/HVEM, KIR, LAG3, CD137/CD137L, OX40/OX40L, CD27, CD40L, TIM3/Gal9, and A2aR. In some embodiments, the multispecific Clec9A binding agent of the invention may comprise an antibody or antibody format, e.g. VHH, against a checkpoint inhibitor marker selected from one of CTLA-4, PD-L1, PD-L2, and PD-1.

[0125] By way of non-limiting example, in various embodiments, the present multispecific Clec9A binding agent has a targeting moiety directed against (i) a checkpoint marker expressed on a T cell, e.g. one or more of PD-1, CD28, CTLA4, ICOS, BTLA, KIR, LAG3, CD137, OX40, Cd27, CD40L, TIM3, and A2aR and (ii) a targeting moiety is directed against a tumor cell, along with any of the modified (e.g. mutant) signaling agents described herein.

[0126] In various embodiments, the present multi-specific Clec9A binding agent has one or more targeting moieties directed against PD-1. In some embodiments, the Clec9A binding agent has one or more targeting moieties which selectively bind a PD-1 polypeptide. In some embodiments, the Clec9A binding agent comprises one or more antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind a PD-1 polypeptide.

[0127] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody pembrolizumab (aka MK-3475, KEYTRUDA), or fragments thereof. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, et al. (2013) New England Journal of Medicine 369 (2): 134-44, US 8,354,509, and WO 2009/114335. In illustrative embodiments, pembrolizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of:
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPNSNGGTNF
NEKFKNRVTLTDSSTTTAYMELKSLQFDDTAVVYVCARRDYRFDMGFEDYWGQGTTVTVSS

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQFPREFQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHREALHNHYTQKSLSLGLGK (SEQ ID NO:98);
and/or a light chain comprising the amino acid sequence of
EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLA
SYLES
GVPARFSGSGSGTDFTLTITSSLEPEDFAVYYCQHSRDLP
LTFGGGTKEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYLSLS
STLTLSKADYEKHKVYACEVTHQGLSSEVTKSFNRGEC (SEQ ID NO:99) .

[0128] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody, nivolumab (aka BMS-936558, MDX- 1 106, ONO-4538, OPDIVO), or fragments thereof. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO 2006/121 168. In illustrative embodiments, nivolumab or an antigen- binding fragment thereof comprises a heavy chain comprising the amino acid sequence of:

QVQLVESGCGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWDGSKRYY
ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGT
LVT VSSASTKGPS
VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS
VVTVPSSSLG TKTYTCNVDH KPSNTKVDKRVESKYGPCCP PCPAPEFLGG PSVFLFPPKP
KDTLMISRTPEVTCVVDVVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT
VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC
LVKGFYPSDI AVEWESNGQP ENNYKTTPFV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
MHREALHNHYT QKSLSLGLGK (SEQ ID NO: 100);

and/or a light chain comprising the amino acid sequence of:
EIVLTQSPATLSLSPGERATLSCRASQSVSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTITSSLEPEDFAVYYCQSSNWPRTEFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSLS
STLTLSKADYEKHKVYACEVTHQGLSSEVTKSFNRGEC (SEQ ID NO: 101).

[0129] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody pidilizumab (aka CT-01 1, hBAT or hBAT-1), or fragments thereof. Pidilizumab and other humanized anti-PD-I monoclonal antibodies are disclosed in US 2008/0025980 and WO 2009/101611. In illustrative embodiments, the anti-PD-1 antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a light chain variable regions comprising an amino acid sequence selected from SEQ ID NOS: 15-18 of US 2008/0025980:

SEQ ID NO: 15 of US 2008/0025980 (SEQ ID NO:102):

EIVLTQSPFSSLSASVGDRTITCSARSSVSYMHWYQQKPGKAPKLLIYRTSNLASGVPSR
FSGSGSGTDFTLTINSLQPEDFATYYCQQRSSFFLTFGGGTKEIK;

SEQ ID NO: 16 of US 2008/0025980 (SEQ ID NO:103):

EIVLTQSPFSSLSASVGDRTITCSARSSVSYMHWYQQKPGKAPKLWIYRTSNLASGVPSR
FSGSGSGTDYTLTINSLQPEDFATYYCQQRSSFFLTFGGGTKEIK;

SEQ ID NO: 17 of US 2008/0025980 (SEQ ID NO:104):

EIVLTQSPFSSLSASVGDRTITCSARSSVSYMHWYQQKPGKAPKLWIYRTSNLASGVPSR
FSGSGSGTDYCLTINSLQPEDFATYYCQQRSSFFLTFGGGTKEIK;

SEQ ID NO: 18 of US 2008/0025980 (SEQ ID NO:105):

EIVLTQSPFSSLSASVGDRTITCSARSSVSYMHWYQQKPGKAPKLWIYRTSNLASGVPSR
FSGSGSGTSYCLTINSLQPEDFATYYCQQRSSFFLTFGGGTKEIK;

and/or a heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 20-24 of US 2008/0025980:
SEQ ID NO: 20 of US 2008/0025980 (SEQ ID NO:106):

QVQLVQSGSEELKKPGASVKISCKASGYSPFTNYGMNWVRQAPGQGLQWMGWINTDSGESTY
AEEFKGRFVFSLDTSVSTAYLQITSLTAEDTGMVFCARVGYDALDYWGQGLVTVSS;

SEQ ID NO: 21 of US 2008/0025980 (SEQ ID NO:107):

QVQLVQSGSEELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMGWINTDSGESTY
AEEFKGRFVFSLDTSVSTAYLQITSLTAEDTGMVFCARVGYDALDYWGQGLVTVSS;

SEQ ID NO: 22 of US 2008/0025980 (SEQ ID NO:108):

QVQLVQSGSEELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMGWINTDSGESTY
AEEFKGRFVFSLDTSVNTAYLQITSLTAEDTGMVFCVRVGYDALDYWGQGLVTVSS;

SEQ ID NO: 23 of US 2008/0025980 (SEQ ID NO:109):

QIQLVQSGSEELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMGWINTDSGESTY
AEEFKGRFVFSLDTSVNTAYLQITSLTAEDTGMVFCVRVGYDALDYWGQGLVTVSS;

SEQ ID NO: 24 of US 2008/0025980 (SEQ ID NO:110):

QIQLVQSGSEELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMGWINTDSGESTY
AEEFKGRFAFSLDTSVNTAYLQITSLNAEDTGMVFCVRVGYDALDYWGQGLVTVSS .

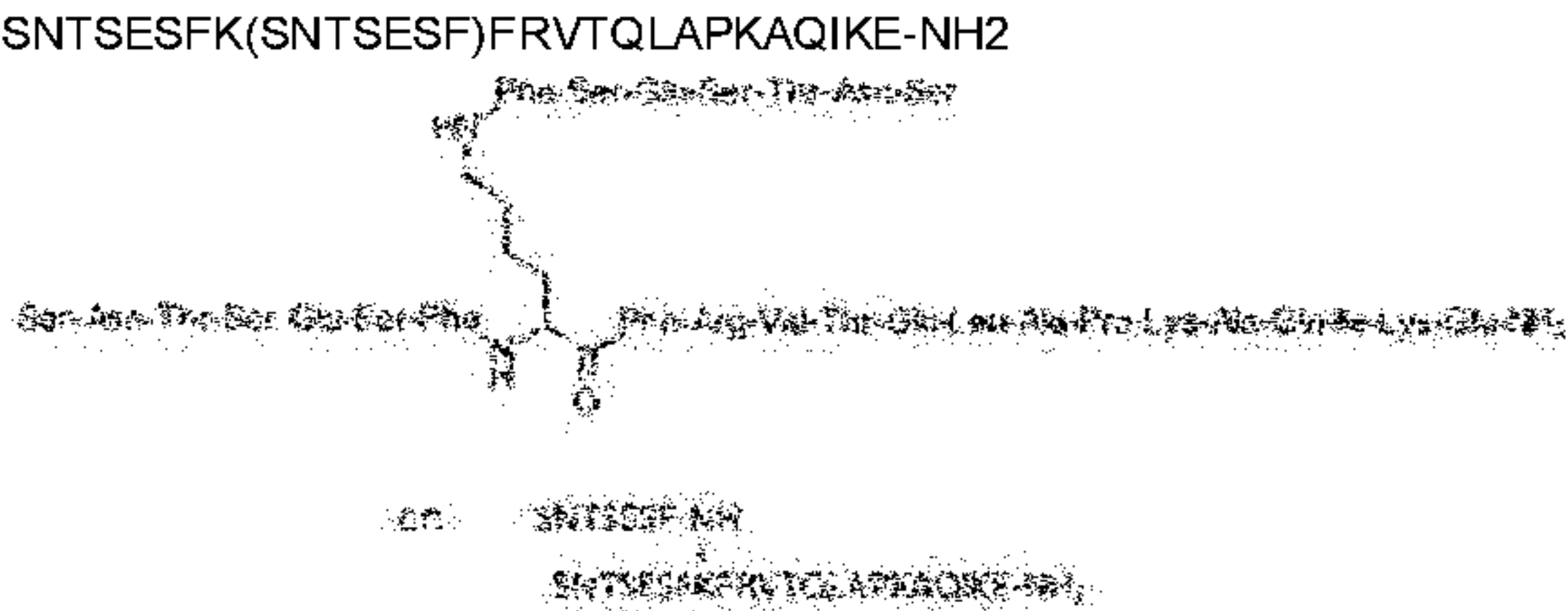
[0130] In an embodiment, the targeting moiety comprises a light chain comprising SEQ ID NO:18 of US 2008/0025980 and a heavy chain comprising SEQ ID NO:22 of US 2008/0025980.

[0131] In an embodiment, the targeting moiety comprises AMP-514 (aka MEDI-0680).

[0132] In an embodiment, the targeting moiety comprises the PD-L2-Fc fusion protein AMP-224, which is disclosed in WO2010/027827 and WO 2011/066342. In such an embodiment, the targeting moiety may include a targeting domain which comprises SEQ ID NO:4 of WO2010/027827 (SEQ ID NO:111):

LFTVTVPKELYLIEHGSNVTLECNFDTGSHVNLGAITASLQKVENDTSPHRERATLLEEQLPLGKASFHIPQVQVRDEGQYQCIIITYGVAWDYKYLTLKVKASYRKINTHILKVPETDEV
ELTCQATGYPLAEVSWPNVSVPANTSHSRTPEGLYQVTSVLRLKPPFGRNFSCVFWNTHV
RELTLASIDLQSQMEFRTHPTWLLHIFIFPCIIAFIFIATVIALRKQLCQKLYSSKDTTK
RPVTTTKREVNSAI
and/or the B7-DC fusion protein which comprises SEQ ID NO:83 of WO2010/027827 (SEQ ID NO:112):
MIFLLMLSLLELQLHQIAALFTVTVPKELYLIEHGSNVTLECNFDTGSHVNLGAITASLQ
KVENDTSPHRERATLLEEQLPLGKASFHIPQVQVRDEGQYQCIIITYGVAWDYKYLTLKVK
ASYRKINTHILKVPETDEVELTCQATGYPLAEVSWPNVSVPANTSHSRTPEGLYQVTSVL
RLKPPPGGRNFSCVFWNTHVRELTLASIDLQSQMEFRTHPTWEPKSCDKTHTCPCPAPEL
LGGPSVFLFPKPKDTLMISRTP EVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYR VVS VLT V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S
R D E L T K N Q V S L P C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

[0133] In an embodiment, the targeting moiety comprises the peptide AUNP 12 or any of the other peptides disclosed in US 2011/0318373 or 8,907,053. For example, the targeting moiety may comprise AUNP 12 (i.e., Compound 8 or SEQ ID NO:49 of US 2011/0318373) which has the sequence of SEQ ID NO:113:



[0134] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody 1 E3, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 1 E3 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:

EVQLQQSGPV LVKPGASVKM SCKASGYTFT DYIMNWVKQS HGKSLEWIGN
INPYNGGTTY NQKFKGKATL TVDKSSRTAY MEINSLTSED SAVYYCARGR
IYDGSLDYWG QGTALT VSS (SEQ ID NO:114);

and/or a light chain variable region comprising the amino acid sequence of:

DIQMTQFPSS LCASQGGKVT VTCKASQDIN NYMAWYQHKE GKGPRLLIHY
TSTLLSGIPS RFSGSGSGRD YSFSISNLEP EDIATYYCLQ YDNLWTFGGG
TKLEIK (SEQ ID NO:115).

[0135] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody 1 E8, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 1 E8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:

QVQLQQSGAE LAKPGASVRL SCKASGYTFT NYWMHWVKQR PGQGLEWIGH
INPSSGFTTY NQNEFKDKATL TADKSSNTAY MQLSSLTYED SAVYFCARED
YDVDYWGQGT TLT VSS (SEQ ID NO: 116);

and/or a light chain variable region comprising the amino acid sequence of:

DIVMTQSQKF MSTSVGDRVS VTCKASQSVD TNVAWYQQKP GQSPKALIFS
ASYRYSVGPD RFTGSGSGTD FTLTINSVQS EDLAEYFCQQ YNSYPYTFGS
GTKLEIK (SEQ ID NO: 117).

[0136] In an embodiment, the targeting moiety comprises the anti-PD-1 antibody 1 H3, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 1 H3 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:

EVQLVESGGG LVKPGGSLKL SCAASGFTFS DYGMHWVRQA PEKGLEWVAY
ISSGSYTIYY TDTVKGRFTI SRDNAKNTLF IQMTSLRSED TAMYYCARRG
YGSFYEYYFD YWGQGTTLTV SS (SEQ ID NO: 118);

and/or light chain variable region comprising the amino acid sequence of:

QIVLTQSPAL MSASFGEKVT MTCGASSVS YMYWYQQKPR SSPKPWIIYL
SNLASGVPAR FSGSGSGTSY SLTISSMEAE DAATYYCQQW SNNPFTFGSG
TKLEIK (SEQ ID NO: 119).

[0137] In an embodiment, the targeting moiety comprises a VHH directed against PD-1 as disclosed, for example, in US 8,907,065 and WO 2008/071447. In illustrative embodiments, the VHHs against PD-1 comprise SEQ ID NOS: 347-351 of US 8,907,065:

SEQ ID NO: 347 of US 8,907,065 (SEQ ID NO:120):
EVQLVESGGGLVQAGKSLRLSCAASGSI FSIHAMGWFRQAPGKEREFVAA
ITWSSGITYYEDSVKGRFTISRDNAKNTVY LQMNSLKPEDTAIYYCAADR
AESSWYDYWGQGTQVTVSS;

SEQ ID NO: 348 of US 8,907,065 (SEQ ID NO:121):

EVQLVESGGGLVQAGGSLRLSCAASGSIASIHAMGWFRQAPGKEREFVAV

ITWSSGGITYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAIYYCAGDK
HQSSWYDYWGQGTQVTVSS;

SEQ ID NO: 349 of US 8,907,065 (SEQ ID NO:122);

EVQLVESGGGLVQAGGSLRLSCAASGSISSIHAMGWFRQAPGKEREFVAA
ITWSSGGITYYADSLKGRFTISRDNAKNTGYLQMNSLKPEDTAIYYCAADR
AQSSWYDYWGQGTQVTVSS;

SEQ ID NO: 350 of US 8,907,065 (SEQ ID NO:123);

EVQLVESGGGLVQAGGSLGLSCAASGSIFSINAMAWFRQAPGKEREFVAL
ISWSSGGSTIYEDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAIYYCAADR
VDSNWDYWGQGTQVTVSS;

SEQ ID NO: 351 of US 8,907,065 (SEQ ID NO:124);

EVQLVESGGGLVQAGGSLRLSCAASGRAFS3SGTMGWFRRAPGKEREFVA
SIPWSSGGRIYYADSVKGRFTISRDNAQNTVYLQMNSLKPEDTAVYYCAVK
ERSTGWDFASWGQCTQVTVSS.

[0138] In an embodiment, the targeting moiety comprises any one of the anti-PD-1 antibodies, or fragments thereof, as disclosed in US2011/0271358 and WO2010/036959. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID NOS: 25-29 of US2011/0271358:
SEQ ID NO: 25 of US2011/0271358 (SEQ ID NO:125);

QVQLVQSGAELKQPGASVKMSCKASGYSTSSWIHWVKQAPGGLEWIGYIYPSTGFTEY
NQKFKDRATLTADKSTSTAYMELSSLRSEDSAVYYCARWRDSSGYHAMDYWGQGTSVTVS
S;

SEQ ID NO: 26 of US2011/0271358 (SEQ ID NO:126);

QVQLVQSGAEVKQPGASVKMSCKASGYSTSSWIHWVKQAPGGLEWIGYIYPSTGFTEY
NQKFKDRATLTADKSTSTAYMELSSLRSEDTAVYY3/d10CARWRDSSGYHAMDYWGQGTSVTVS
S;

SEQ ID NO: 27 of US2011/0271358 (SEQ ID NO:127);

QVQLVQSGHEVKQPGASVKMSCKASGYSTSSWIHWVKQAPGGLEWIGYIYPSTGFTEY
NQKFKDRATLTADKSTSTAYMELSSLRSEDTAVYYCARWRDSSGYHAMDYWGQGLVTVS
S;

SEQ ID NO: 28 of US2011/0271358 (SEQ ID NO:128);

QVQLVQSGHEVKQPGASVKMSCKASGYSTSSWIHWVRQAPGGLEWIGYIYPSTGFTEY
NQKFKDRATLTADKSTSTAYMELSSLRSEDTAVYYCARWRDSSGYHAMDYWGQGLVTVS
S;

SEQ ID NO: 29 of US2011/0271358 (SEQ ID NO:129);

QVQLVQSGHEVKQPGASVKVSKASGYSTSSWIHWVRQAPGGLEWIGYIYPSTGFTEY
NQKFKDRATITADKSTSTAYMELSSLRSEDTAVYYCARWRDSSGYHAMDYWGQGLVTVS
S;

and/or a light chain comprising an amino acid sequence selected from SEQ ID NOS: 30-33 of US2011/0271358:
SEQ ID NO: 30 of US2011/0271358 (SEQ ID NO:130);

DIVLTQSPFASLTLSFGQRLTISCRASQSVSTSGYSYMHWYQQKPDQSPKLLIKFGSNLES
GIPARFSGSGSGTDFTLTISLEEEDFATYYCQHSWEI PYTFGQGTKLEIK;

SEQ ID NO: 31 of US2011/0271358 (SEQ ID NO:131);

DIVLTQSPATLSLSPGQRLTISCRASQSVSTSGYSYMHWYQQKPDQSPKLLIKFGSNLES
GIPARFSGSGSGTDFTLTISSELEPEDFATYYCQHSWEIPYTFGQGTKLEIK;

SEQ ID NO: 32 of US2011/0271358 (SEQ ID NO:132);

EIVLTQSPATLSLSPGQRLTISCRASQSVSTSGYSYMHWYQQKPDQSPKLLIKFGSNLES
GIPARFSGSGSGTDFTLTISSELEPEDFATYYCQHSWEIPYTFGQGTKLEIK;

SEQ ID NO: 33 of US2011/0271358 (SEQ ID NO:133);

DIVLTQSPATLSLSPGQRLTISCRASQSVSTSGYSYMHWYQQKPDQSPKLLIKFGSNLES
GIPARFSGSGSGTDFTLTISSELEPEDFAVYYCQHSWEIPYTFGQGTKLEIK.

[0139] In various embodiments, the present multi-specific Clec9A binding agent comprises one or more antibodies directed against PD-1, or antibody fragments thereof, selected from TSR-042 (Tesaro, Inc.), REGN2810 (Regeneron Pharmaceuticals, Inc.), PDR001 (Novartis Pharmaceuticals), and BGB-A317 (BeiGene Ltd.)

[0140] In an exemplary embodiment, the present multi-specific Clec9A binding agent comprises a targeting moiety directed against PD-1, such as SEQ ID NO:134:
EVQLVESGGGLVQAGKSLRLSCAASGSIFSIHAMGWFRQAPGKEREFVAAITWSSGGITYYEDSVKGRFTISRDN
AKNTVYLQMNSLKPEDTAIYYCAADRAESSWYDYWGQGTQVTVSS.

[0141] In various embodiments, the present multi-specific Clec9A binding agent has one or more targeting moieties directed against PD-L1. In some embodiments, the Clec9A binding agent has one or more targeting moieties which selectively bind a PD-L1 polypeptide. In some embodiments, the Clec9A binding agent comprises one or more antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind a PD-L1 polypeptide.

[0142] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody MEDI4736 (aka durvalumab), or fragments thereof. MEDI4736 is selective for PD-L1 and blocks the binding of PD-L1 to the PD-1 and CD80 receptors. MEDI4736 and antigen-binding fragments thereof for use in the methods provided herein comprises a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. The sequence of MEDI4736 is disclosed in WO/2016/06272. In illustrative embodiments, MEDI4736 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of:

EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN
IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG
GWFGELAFDY WQGGLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV WNSGALTSG VHTFFAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKHTC PCPAPPEFEG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQV
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPASIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTTP
VLDS DGSFFL YSKLTVDKSR WQGNVFSCS VMHEALHNHY TQKSLSLSPG
K (SEQ ID NO: 135);

and/or a light chain comprising the amino acid sequence of:
EIVLTQSPGT LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY
DASSRATGIP DRFGSGSGT DFTLTISRLE PEDFAVYYCQ QYGS LPWTFG
QGTKVEIKRT VAAPSVFIEP ESDEQLKSGT ASVVCLLNNF YPREAKVQWK
VDNALQSGNS QESVTEQDSK DSTYSLSTL TLSKADYEKH KVIACEVTHQ
GLSSPVTKSF NRGEC (SEQ ID NO: 136).

[0143] In illustrative embodiments, the MEDI4736 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:4 of WO/2016/06272 (SEQ ID NO: 137):

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYY
VDSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWQGGLVTVS
S;
and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:3 of WO/2016/06272 (SEQ ID NO: 138):
EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIP
DRFGSGSGTDFTLTISRLEPEDFAVYYCQYGS LPWTFGQGTKVEIK

[0144] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody atezolizumab (aka MPDL3280A, RG7446), or fragments thereof. In illustrative embodiments, atezolizumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVANISPYGGSTYYADSVKGRF
TISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGLTVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVN HKPSNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKENWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
IAVEWESNGQPENNYKTTTPVLDS DGSFFLY SKLTVDKSRWQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 139);
and/or a light chain comprising the amino acid sequence of:
DIQMTQSPFSSLSASVGRVTITCRASQDVTAVAWYQQKPGKAPKLLIYGASFLYSGVPSRFRSGSGSG
TDFTLTISSLQPEDFATYYCQYLYHPATEFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTLTLSKADYEKKVIACEVTHQGLSSP
VTKSFNRGEC (SEQ ID NO:140).

[0145] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody avelumab (aka MSB0010718C), or fragments thereof. In illustrative embodiments, avelumab or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising the amino acid sequence of:

EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS
IYPSGGITFY ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK
LGTVTTVLYW QGGLTVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK
DYFPEPVTVS WNSGALTSGV HTFFAVLQSS GLYSLSSVVT VPSSSLGTQT
YICNVNHKPS NTKVDKKVEP KSCDKHTCTP PCPAPPELLGG PSVFLFPPKP
KDTLMISRTPEVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ
VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPEV
LDS DGSFFLY SKLTVDKSRW QGNVFSCSV MHEALHNHYT QKSLSLSPGK
(SEQ ID NO:141);

and/or a light chain comprising the amino acid sequence of:
QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ
HPGKAPKLM IYDVSNRPSGV SNRFGSKSG NTASLTISGL
QAEDEADYYC SSYTSSSTRV FGTGTVTVL GQPKANPTVT
LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADGSPVK
AGVETTKPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT
HEGSTVEKTV APTECS (SEQ ID NO:142).

[0146] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody BMS-936559 (aka 12A4, MDX-1105), or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, BMS-936559 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGSSVKVSKTSGDTFSTYATSWVRQAPGQGLEWMGGIIPIFGKAHY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMDVWGQGTTVT
VSS (SEQ ID NO: 143);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISLSEPEDFAVYYCQQRSNWPTFGQGTKVEIK (SEQ ID NO:144);

[0147] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 3G10, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 3G10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSKASGYTFTDYGFSVVVRQAPGQGLEWMGWITAYNGNTNY
AQKLQGRVTMTTDTSTSTVYMELRSLRSDDTAVYYCARDYFYGMDVWGQGTITVTVSS (SEQ ID NO: 145);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLVWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISLSEPEDFAVYYCQQRSNWPRTFGQGTKVEIK (SEQ ID NO:146);

[0148] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 10A5, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 10A5 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSKASGYTFTSYDVHWVRQAPGQRLEWMGWLHADTGITKF
SQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARERIQLWFDYWGQGTITVTVSS
(SEQ ID NO: 147);
and/or a light chain variable region comprising the amino acid sequence of:
DIQMTQSPSSLSASVGDRTVITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK (SEQ ID NO:148);

[0149] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 5F8, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 5F8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGSSVKVSKVSGGIFSTYAINWVRQAPGQGLEWMGGIIPIFGTANH
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDQGIAAALFDYWGQGTITVTVSS
(SEQ IDNO: 149);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK (SEQ ID NO:150);

[0150] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 10H10, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 10H10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVQLVESGGGLVQPGRSLRLSCAVSGFTFDYVVHWVRQAPGKGLEWVSGISGNSGNIGY
ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAVPFDYWGQGTITVTVSS (SEQ ID NO: 151);
and/or a light chain variable region comprising the amino acid sequence of:
DIQMTQSPSSLSASVGDRTVITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGTKLEIK (SEQ ID NO:152);

[0151] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 1 B12, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 1 B12 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGSSVKVSKTSGDTFSSYATSWVRQAPGQGLEWMGGIIPIFGRAHY
AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYFCARKFHFVSGSPFGMDVWGQGTTVT
VSS (SEQ ID NO: 153);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISLSEPEDFAVYYCQQRSNWPTFGQGTKVEIK (SEQ ID NO:154);

[0152] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 7H1, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 7H1 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGSSVKVSKTSGGTFFSSYATSWVRQAPGQGLEWMGGIIPIFGKAHY
AQKFQGRVTITADESTTTAYMELSSLRSEDTAVYYCARKYDYVSGSPFGMDVWGQGTTVT
VSS (SEQ ID NO: 155);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISLSEPEDFAVYYCQQRSNWPTFGQGTKVEIK (SEQ ID NO:156);

[0153] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 11 E6, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 11 E6 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKKPGSSVKVSKASGCTFSSYAINWVRQAPGQGLEWMGGIIPIFGSANY
AQKFQGRVTITADESTSAAYWPTESITDSFNTAVYYCARDSGSSPYMDRWGQGTITVTVS

AQATQGRVTITTADESTTAAIMEDSSSRSEEDTAVTTCARDSSGWRITMDVWQGSITVTVS
S (SEQ ID NO: 157);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSFGLTSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPFGGGTKVEIK (SEQ ID NO:158).

[0154] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 12B7, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 12B7 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
QVQLVQSGAEVKEFGSSVKVSCRASGGTFNSYAIISWVRQAPGQGLEWMGGIIPFGIAHY
AQKFQGRVTITADESTNTAYMDLSSLRSEDTAVYYCARKYSYVSGSPFGMDVWGQGTTVT
VSS (SEQ ID NO: 159);
and/or a light chain variable region comprising the amino acid sequence of:
EIVLTQSFATLTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYDASNRATGIPA
RFSGSGSGTDFTLTISSELEPEDFAVYYCQQRSNWPTFGQGTREIK (SEQ ID NO:160).

[0155] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 13G4, or fragments thereof, as disclosed in US 2013/0309250 and WO2007/005874. In illustrative embodiments, 13G4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVQLVESGGGLVQPGRSLRLSCAASGITFDDYGMHWVRQAPGKGLEWVSGISWNRGRIEY
ADSVKGRFTISRDNAKNSLIYLQMNSLRAEDTALYYCAKGRFRIYEDWELDYWGQGTILVTVS
S (SEQ ID NO:161);
and/or a light chain variable region comprising the amino acid sequence of:
AIQLTQSPSSLSASVGDRAVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESQVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPFTFGPGTKVDIK (SEQ ID NO:162).

[0156] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 1E12, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 1E12 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVKLQESGPS LVKPSQTLSL TCSVTGYSIT SDYWNWIRKF PGNKLEYVGY
ISYTGSTYYN PSLKSRISIT RDTSKNQYYL QLNVTSEDT ATYYCARYGG
WLSPFEDYWGQ GTTILTVSS (SEQ ID NO:163);
and/or a light chain variable region comprising the amino acid sequence of:
DIVMTQSHKL MSTSVGDRVS ITCKASQDVG TAVAWYQQKP GQSPKLLIYW
ASTRHTGVPD RFTGSGSGTD FTLTISNVQS EDLADYFCQQ DSSYPITFGA
GTKVELK (SEQ ID NO:164).

[0157] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 1 F4, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 1 F4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVQLQESGPG LVAPSQSLSI TCTVSGFSLT TYSINWIRQP PGKGLEWLGV
MWAGGGTNSN SVLKSRLLIS KDNSKSQVEL KMNSLQTDDE ARYYCARYYG
NSPIYAIDYW GQGTSTVTVSS (SEQ ID NO:165);
and/or a light chain variable region comprising the amino acid sequence of:
DIVTTQSHKL MSTSVGDRVS ITCKASQDVG TAVAWYQQKP GQSPKLLIYW
ASTRHTGVPD RFTGSGSGTD FTLTISNVQS EDLADYFCQQ DSSYPITFGA
GTKVELK (SEQ ID NO:166).

[0158] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2G11, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 2G11 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVKLQESGPS LVKPSQTLSL TCSVTGYSII SDYWNWIRKF PGNKLEYLGY
ISYTGSTYYN PSLKSRISIT RDTSKNQYYL QLNVTTEDT ATYYCARRGG
WLLPFEDYWGQ GTTILTVSS (SEQ ID NO:167);
and/or a light chain variable region comprising the amino acid sequence of:
DIVMTQSPSS LAVSVGEKVS MGCKSSQSLI YSSNQKNSLA WYQQKPGQSP
KLLIDWASTR ESGVDRFTG SGSGTDFTLT ISSVKAEDLA VYYCQQYYGY
PLTFGAGTKL ELK (SEQ ID NO:168).

[0159] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 3B6, or fragments thereof, as disclosed in US 2014/0044738. In illustrative embodiments, 3B6 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVKLQESGPS LVKPGASVKL SCKASGYTFT SYDINWVKQR PGQGLEWIGW
IFPRDNNTKY NENFKGKATL TVDTSSTAY MELHSLTSED SAVYFCTKEN
WVGDFDYWGQ GTTILTLSS (SEQ ID NO:169);
and/or a light chain variable region comprising the amino acid sequence of:
DIVMTQSPAI MSASPGKVMT MTCASASSIR YMHWYQQKPG TSPKRWISDT
SKLTSGVFAR FSGSGSGTSY ALTISSMEAE DAATYYCHQR SSYPWTFGGG
TKLEIK (SEQ ID NO:170).

[0160] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 3D10, or fragments thereof, as disclosed in US 2014/0044738 and WO2012/145493. In illustrative embodiments, 3D10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
EVQLQQSGPD LVTPGASVRI SCQASGYTFP DYIMNWVKQS HGKSLIEWIGD

IDPNYGGTTY NQKFKGKAIL TVDRSSSTAY MELRSLTSED SAVYYCARGA
LTDWQGQTS� TVSS (SEQ ID NO:171);
and/or a light chain variable region comprising the amino acid sequence of:
QIVLSQSPAI LSASFGKVT MTCRASSSVS YIWFQQKPG SSPKPWIYAT
ENLASGVPAR FSGSGSGTSY SLTISRVEŦ DAATYYCQQW SNNPLTFGAG
TKLELK (SEQ ID NO:172).

[0161] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in US2011/0271358 and WO2010/036959. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 34-38 of US2011/0271358:
SEQ ID NO: 34 of US2011/0271358 (SEQ ID NO:173);

EVQLVQSGPELKKPGASVKMSCKASGYTFTSYVMHWVKQAPGQRLEWIGYVNPENDGTKY
NEMFKGRATLTSĐKSTSTAYMELSSLSRSEDSAVYYCARQAWGYPWGQGTILVTVSS;

SEQ ID NO: 35 of US2011/0271358 (SEQ ID NO:174);

EVQLVQSGAEVKKPGASVKMSCKASGYTFTSYVMHWVKQAPGQRLEWIGYVNPENDGTKY
NEMFKGRATLTSĐKSTSTAYMELSSLSRSEDTAVYYCARQAWGYPWGQGTILVTVSS;

SEQ ID NO: 36 of US2011/0271358 (SEQ ID NO:175);

EVQLVQSGAEVKKPGASVKMSCKASGYTFTSYVMHWVRQAPGQRLEWIGYVNPENDGTKY
NEMFKGRATLTSĐKSTSTAYMELSSLSRSEDTAVYYCARQAWGYPWGQGTILVTVSS;

SEQ ID NO: 37 of US2011/0271358 (SEQ ID NO:176);

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYVNPENDGTKY
NEMFKGRATLTSĐKSTSTAYMELSSLSRSEDTAVYYCARQAWGYPWGQGTILVTVSS;

SEQ ID NO: 38 of US2011/0271358 (SEQ ID NO:177);

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVMHWVRQAPGQRLEWIGYVNPENDGTKY
NEMFKGRATITSĐKSTSTAYMELSSLSRSEDTAVYYCARQAWGYPWGQGTILVTVSS;

and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 39-42 of US2011/0271358:
SEQ ID NO: 39 of US2011/0271358 (SEQ ID NO:178);

DIVLTQSPFASIALSPGERATLSCRATESVEYYGTSLSLVQWYQQKPGQPPKLLIYAASSVDS
GVPSRFSGSGSGTDFTLTINSLEEEDAAMYFCQQSRRVPYTFGQGTKLEIK;

SEQ ID NO: 40 of US2011/0271358 (SEQ ID NO:179);

DIVLTQSPFATLSLSĐPERATLSCRATESVEYYGSLVQWYQQKPGQPPKLLIYAASSVDS
GVPSRFSGSGSGTDFTLTINSLEAEDAAMYFCQQSRRVPYTFGQGTKLEIK;

SEQ ID NO: 41 of US2011/0271358 (SEQ ID NO:180);

EIVLTQSPATLSLSĐPERATLSCRATESVEYYGTSLSLVQWYQQKPGQPPKLLIYAASSVDS
GVPSRFSGSGSGTDFTLTINSLEAEDAAMYFCQQSRRVPYTFGQGTKLEIK;

SEQ ID NO: 42 of US2011/0271358 (SEQ ID NO:181);

DIVLTQSPATLSLSĐPERATLSCRATESVEYYGTSLSLVQWYQQKPGQPPKLLIYAASSVDS
GVPSRFSGSGSGTDFTLTINSLEAEDAATYFCQQSRRVPYTFGQGTKLEIK.

[0162] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.7A4, or fragments thereof, as disclosed in WO 2011/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 2.7A4 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 2 of WO 2011/066389 (SEQ ID NO:182);

EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYSMNWVRQAPGKGLEWVSSISSGDIYY
ADSVKGRFTISRĐNAKNSLFLQMNSLKAEDTAVYYCARDLVTSMVAFDYGQGTILVTVSS;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 7 of WO 2011/066389 (SEQ ID NO:183):
SYELTQPPSVSVSPGQAARITCSGDALPQKYVFWYQQKSGQAPVLVIYEDSKRPSGIPER
FSGSSSGTMATLTISGAQVEADYYCYSTDRSĐNHRVFGGTRLTVL.

[0163] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.9Đ10, or fragments thereof, as disclosed in WO 2011/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 2.9Đ10 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 12 of WO 2011/066389 (SEQ ID NO:184);

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGGEQYY
VDSVKGRFTISRĐNAKNSLYLQMNSLRAEDTAVYYCARDWNYGYDMDVWGQGTITVTVSS;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 17 of WO 2011/066389 (SEQ ID NO:185):
EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWFQQKPGQAPRLIFGTSSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQYGSSTFTFGPGTKVDIK.

[0164] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.14H9, or fragments thereof, as disclosed in WO 2011/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 2.14H9 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of: SEQ ID NO: 22 of WO 201 1/066389 (SEQ ID NO:186)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYY

VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTILVTVS
S;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 27 of WO 201 1/066389 (SEQ ID NO:187):
EIVLTQSEGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTEVEIK.

[0165] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.20A8, or fragments thereof, as disclosed in WO 201 1/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 2.20A8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 32 of WO 201 1/066389 (SEQ ID NO:188):

EVQLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAIRGSGGSTYY
ADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDLHYDSSGYLDYWGQGTILVTVS
S;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 37 of WO 201 1/066389 (SEQ ID NO:189):
DIQMTQSPSSVSASVGDRTITCRASQGIRSWLAWYQQKPGKAPKLLIY AISR LQSGVPS
RFSGSGSGTDFTLTIS SLQPEDFATYYCQQANSFPLTFGGGTKVEIK.

[0166] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 3.15G8, or fragments thereof, as disclosed in WO 201 1/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 3.15G8 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 42 of WO 201 1/066389 (SEQ ID NO:190):

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQDGGEKYY
VDSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARVQLYSDYFDYWGQGTILVTVSS;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 47 of WO 201 1/066389 (SEQ ID NO:191):
DIQMTQSPFSSVSASVGDRTITCRASQGISSWLAWYQQKSGKAPKLLIYAASGLQSGVPS
RFSGSGSGTDFTLTIS SLQPEDLATYYCQQSHSLPPTFGQGTKVEIK.

[0167] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 3.18G1, or fragments thereof, as disclosed in WO 2011/066389, US8,779,108, and US2014/0356353. In illustrative embodiments, 3.18G1 or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 52 of WO 201 1/066389 (SEQ ID NO:192):

EVQLESGGDLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEWVSTISGSGGFTFS
ADSVKGRFTISRDN SKNTLFLQMNSLRVEDSAVYSCAKVLVGFNNGCWDYWGQGTILVTVS
S;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 57 of WO 201 1/066389 (SEQ ID NO:193):
SYVLTQPPSVSVAPGQTARITCGGN NIGSKSVHWYQQKPGQAPVLWYDDSDRPSGIPER
FSGSNSGNTAILTISRVEAGDEADY YCQVWDSNDHWFGGGTKLTVL.

[0168] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.7A40PT, or fragments thereof, as disclosed in WO 201 1/066389, US8.779.108, and US2014/0356353, and US2014/0356353. In illustrative embodiments, 2.7A40PT or an antigen- binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 62 of WO 201 1/066389 (SEQ ID NO:194):

EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYSMNWVRQAPGKGLEWVSSISSGDIYY
ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLVTSMVAFDYWGQGTILVTVSS;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 67 of WO 201 1/066389 (SEQ ID NO:195):
SYELTQPPSVSVSPGQTARITCSGDALPQKYVFWYQQKSGQAPVLVIYEDSKRPSGIPER
FSGSSSGTMATL I3GAQVEDEADYCYSTDRSGNHRVFGGGTKLTVL.

[0169] In an embodiment, the targeting moiety comprises the anti-PD-L1 antibody 2.14H90PT, or fragments thereof, as disclosed in WO 201 1/066389, US8.779.108, and US2014/0356353. In illustrative embodiments, 2.14H90PT or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain variable region comprising the amino acid sequence of:
SEQ ID NO: 72 of WO 201 1/066389 (SEQ ID NO:196):

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYY
VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTILVTVS
S;

and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 77 of WO 2011/066389 (SEQ ID NO:197):
EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIP
DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK.

[0170] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2016/061142. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 18, 30, 38, 46, 50, 54, 62, 70, and 78 of WO2016/061142:
SEQ ID NO: 18 of WO2016/061142 (SEQ ID NO:198):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQGTITVTVSS;
SEQ ID NO: 30 of WO2016/061142 (SEQ ID NO:199):

EVQLVQSGAEVKKPGATVKISKVSGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKY
NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQGTITVTVSS;

SEQ ID NO: 38 of WO2016/061142 (SEQ ID NO:200);

EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWYWVRQAPGGGLEWLMGRIDPNSGSTKY
NEKFKNRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 46 of WO2016/061142 (SEQ ID NO:201);

EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWYWIRQSPSRGLEWLGRIDPNSGSTKY
NEKFKNRLTISKDTSKNQVVLTMTNMDPVDATYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 50 of WO2016/061142 (SEQ ID NO:202);

EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWYWIRQPPGKGLEWIGRIDPNSGSTKY
NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 54 of WO2016/061142 (SEQ ID NO:203);

QVQLVQSGAEVKKPGASVKVSKASGYTFTSYWYWIRQSPSRGLEWLGRIDPNSGSTKY
NEKFKNRFTISRDDSKNTAYLQMNSLKTEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 62 of WO2016/061142 (SEQ ID NO:204);

EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWYWVRQARQRLEWIGRIDPNSGSTKY
NEKFKNRLTISKDTSKNQVVLTMTNMDPVDATYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 70 of WO2016/061142 (SEQ ID NO:205);

QITLKESGPTLVKPTQTTLTCTFSGYTFTSYWYWVRQAPGKGLEWVSRIDPNSGSTKY
NEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS;

SEQ ID NO: 78 of WO2016/061142 (SEQ ID NO:206);

EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWYWVRQARQRLEWIGRIDPNSGSTKY
NEKFKNRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS;

and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 22, 26, 34, 42, 58, 66, 74, 82, and 86 of WO2016/061142:

SEQ ID NO: 22 of WO2016/061142 (SEQ ID NO:207);

DI VMTQTPLSLPVTPGEPASISCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGIPA
RFGSGSGSTEFTLTIS SLQSEDFAVYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 26 of WO2016/061142 (SEQ ID NO:208);

DIQMTQSPSSLSASVGDRVTITCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGVPS
RFGSGSGSTDFTLTIS SLQPEDFATYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 34 of WO2016/061142 (SEQ ID NO:209);

EIVLTQSPDFQSVTPKEKVTITCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGVPD
RFGSGSGSTDFTLKISRVEAEDVGVYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 42 of WO2016/061142 (SEQ ID NO:210);

EIVLTQSPDFQSVTPKEKVTITCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGVPS
RFGSGSGSTDFTFTIS SLQPEDIATYYCQQYNSYPLTFGQGTKVEIK.

SEQ ID NO: 58 of WO2016/061142 (SEQ ID NO:211);

EIVLTQSPATLSLSPGERATLSCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGIPP
RFGSGSGYGTDFTLTINNIESEDAAYYFCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 66 of WO2016/061142 (SEQ ID NO:212);

DWMTQSPSLSLPVTLGQPASISCKASQDVGTA VAWYQQKPGQAPRLLIYWASTRHTGVPS
RFGSGSGSTEFTLTIS SLQPDDFATYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 74 of WO2016/061142 (SEQ ID NO:213);

DIQMTQSPSSLSASVGDRVTITCKASQDVGTA VAWYQQKPGQAPRLLIYWASTRHTGVPS
RFGSGSGSTDFTFTIS SLQPEDIATYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 82 of WO2016/061142 (SEQ ID NO:214);

AIQLTQSPSSLSASVGDRVTITCKASQDVGTA VAWY LQKPGQSPQLLIYWASTRHTGVPS
RFGSGSGSTDFTFTIS SLQAEDAATYYCQQYNSYPLTFGQGTKVEIK;

SEQ ID NO: 86 of WO2016/061142 (SEQ ID NO:215);

EIVLTQSPDFQSVTPKEKVTITCKASQDVGTA VAWYQQKPGQAPRLLIYWASTRHTGVPS
RFGSGSGSTEFTLTIS SLQPDDFATYYCQQYNSYPLTFGQGTKVEIK.

[0171] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2016/022630. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, and 46 of WO2016/022630:

SEQ ID NO: 2 of WO2016/022630 (SEQ ID NO:216);

EVKLVESGGGLVKPGGSLKLSCAASGFI FRSYGMSWVRQTPEKRL EWVASISSGGSTYYP
DSVKGRFTISRDNARNILY LQMS SLRSED TAMYDCARGYDSGFAYWGQGLTVTVSE;

SEQ ID NO: 6 of WO2016/022630 (SEQ ID NO:217);

EVKLVESGGGLVKPGGSLKLSCAASGFTFRSYGMSWVRQTPEKRLEWVASISSGGTTYYP
DSVKGRFTIISRDNARNILYLQMSLRS EDTAMYYCAKGYDSGFAYWCGGTLVIVSA;

SEQ ID NO: 10 of WO2016/022630 (SEQ ID NO:218);

QVQLKQSGPGLVQPSSLSITCTVSGFSLTTYGVHWVRQSPGKGLEWLGVIWRGVTTDYN
AAFMSRLTITKDNSKSQVFFKMNSLQANDTAIYYCARLGFYAMDYWGQGTSVTVSS;

SEQ ID NO: 14 of WO2016/022630 (SEQ ID NO:219);

QVQLKQSGPGLVQPSSLSITCTVSGFSLTSYGVHWVRQSPGKGLEWLGVIWSGGVTDYN
AAFISRLSISKDNSKSQVFFKMNSLQANDTAIYYCARLGFYAMDYWGQGTSVTVSS;

SEQ ID NO: 18 of WO2016/022630 (SEQ ID NO:220);

EVKLFESGGGLVQPGGSLKLS CVASGFDFSTYWMHWVRQAPGQGLEWIGQINPDSTTINY
APSLKDRFTIISRDNAKNTLFLQMSKVRSEDTALYYCAKPGDYGDFDCWGGGTLTVSS;

SEQ ID NO: 22 of WO2016/022630 (SEQ ID NO:221);

EVQLQESGSPSLVKPSQTL SLTCSVTGDSITSGYWNWIRKFPGNKLEYMGYISYSGSTYYN
PSLKSRI SITRDT SKNQYYLQLNSVTTEDTATYYCARSLLEWSTGFAYWCGGTLVTVSA;

SEQ ID NO: 26 of WO2016/022630 (SEQ ID NO:222);

QVQLKQSGPGLVQPSSLSITCTVSGFSLTSYGVHWVRQSPGKGLEWLGVIWSGGITDYN
AAFKSRLSI SKDNSKSQVFFKMNSLQANDTAIYFCARLGFYAMDYWGQGTSVTVSS;

SEQ ID NO: 30 of WO2016/022630 (SEQ ID NO:223);

EVKLVESGGGLVKPGGSLKLSCAASGFTFRSYGMSWARQIPEKRLEWVASISSGGTTYYL
GSVQGRFTIISRDNARNILYLQMSLRS EDTAMYYCARGYDAGFAYWCGGTLVSVSE;

SEQ ID NO: 34 of WO2016/022630 (SEQ ID NO:224);

EVQLQESGSPSLVKPSQTL SLTCSVTGDSITSGYWTWIRKFPGNKLEYMGYISYTGSTYYNPSLKSRI
SISRDTSKSQYYLQLNSVTTEDTATYYCARQRDWLGFAYWCGGTLVTVSA;

SEQ ID NO: 38 of WO2016/022630 (SEQ ID NO:225);

EEKLVESGGGLVKPGGSLKLSCAASGFSSSYGMSWVRQTPEKRLEWVASISSGGSIYYP
DSVKGRFTIISRDNARNILYLQMSLRS EDTAMYYCARGYDAGFAFWCGGTLVTASA;

SEQ ID NO: 42 of WO2016/022630 (SEQ ID NO:226);

QITLKESGPTLVKPTQTTLTCTVSGFSLSTYGVHWIRQPPGKALEWLGVIWRGVTTDYN
AAFMSRLTITKDNSKNQWLTMNNMDPVDTATYYCARLGFYAMDYWGQGTLVTVSS;

SEQ ID NO: 46 of WO2016/022630 (SEQ ID NO:227);

EVQLVESGGGLVKPGGSLRLSCAASGFI FRSYGMSWVRQAPGKGLEWVASISSGGSTIYP
DSVKGRFTIISRDNAKNSLYLQMNSLRAEDTAVYDCARGYDSGFAYWCGGTLVTVSS;

and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 of WO2016/022630:

SEQ ID NO: 4 of WO2016/022630 (SEQ ID NO:228);

DIVLTQSPASLAVSLGQRATISCRASQSVSTSSSSFMHWYQQKPGQPPKLLIKYASNLES
GVPARFSGSGSGTDFTLNIHPVEEEDTATYYCQHSWEIPTYTFGGGTKLEIK;

SEQ ID NO: 8 of WO2016/022630 (SEQ ID NO:229);

DIVLTQSPFSLAVSLGQRATISCRASQSVSTSSSSYMHWYQQKPGQPPKLLIKYASNLES
GVPARFSGSGSGTDFTLNIHPVEEEDTATYYCQHSWEIPTYTFGGGTKLEIK;

SEQ ID NO: 12 of WO2016/022630 (SEQ ID NO:230);

SIVMTQTPKFLLVSAGDRVITCKASQSVSNDVAWYQQKPGQSPKLLIYYAANRYTGVPD
RFTGSGYGTDFFTTISIVQAEDLAVYFCQQDYTSPTYTFGGGTKLEIK;

SEQ ID NO: 16 of WO2016/022630 (SEQ ID NO:231);

SIVMTQTPKFLLVSAGDRVITCKASQSVSNDVGWYQQKPGQSPKLLIYYASNRYSGVPD
RFTGSGYGTDFFTISTVQAEDLAVYFCQQDYTSPTYTFGGGTKLEIK;

SEQ ID NO: 20 of WO2016/022630 (SEQ ID NO:232);

DVIMTQTPLYLPVSLGDQASISCRSSQIIVHSNANTYLEWFLQKPGQSPKLLIYKVSNRF
SGVPDRFSGSGSGTDFTLTKISRVEAEDLGVIYCFQGSHVPTYTFGGGTKLEIK;

SEQ ID NO: 24 of WO2016/022630 (SEQ ID NO:233);

QIVLTQSPAIMASAPGEKVTLTCSASSSVSSSYLYWNQKPGSSPKVWIYNTSNLASGVP
ARFSGSGSGTSYSLTISMEADAASYFCHQWRSYPPTLGAGTKLELK;

SEQ ID NO: 28 of WO2016/022630 (SEQ ID NO:234);

QIVLTQSPAIMASAPGEKVTMTCSANSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPAR
FSGSGSGTSYSLTISMEADAATVYCCQWSNPEFTFGGGTKLEIK.

LSGGGSLTDLTGGFRLDNLITQQKQDNTLGGGRLDNL,

SEQ ID NO: 32 of WO2016/022630 (SEQ ID NO:235):

DIVLTQSPASLAVSLGQRATISCRASQSVSTSSYSYMHWYQQKPGQPPKLLIKYASNLES
GVPARFSGSGSGTDFTLNHPVEEEDTATYYCQNSWEIPYTFGGGTKLEIK;

SEQ ID NO: 36 of WO2016/022630 (SEQ ID NO:236):

DIVMTQTFSSSLAVSLGEKVTMSCKSSQSLLYSSNQKNSLAWYQQKPGQSPKLLIYWASNR
ESGVPRDRTGSSSGTDFTLTISSVKAEDLAVYYCQQYYSYPLTFGAGTKLELK;

SEQ ID NO: 40 of WO2016/022630 (SEQ ID NO:237):

DIVLTQSPASLAVSLGQRATISCRASQSVSTSSYSYVHWYQQKPGQPPKLLIKYASNLES
GVPARFSGSGSGTDFTLNHPVEEEDTATYYCQHSWEIPYTFGGGTKLEIK;

SEQ ID NO: 44 of WO2016/022630 (SEQ ID NO:238):

DIQMTQSPSSLSASVGDRTVITCKASQSVSNDVAWYQQKPGKAPKLLIYYAANRYTGVDP
RFSGSGYGTDFTFITSSLPEDIATYFCQQDYTSPYTFGQGTKLEIK;

SEQ ID NO: 48 of WO2016/022630 (SEQ ID NO:239):

DIVLTQSPASLAVSPGQRATITCRASQSVSTSSSSFMHWYQQKPGQPPKLLIKYASNLES
GVPARFSGSGSGTDFTLTIPVEANDTANYYCQHSWEIPYTFGQGTKLEIK.

[0172] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO2015/112900. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 38, 50, 82, and 86 of WO 2015/112900:

SEQ ID NO: 38 of WO2015/112900 (SEQ ID NO:240):

EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQATGQGLEWMGNIYPGTGGSNF
DEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCTRWTGTGAYWGQGTTVTVSS;

SEQ ID NO: 50 of WO 2015/112900 (SEQ ID NO:241):

EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWIRQSPSRGLEWLGNIYPGTGGSNF
DEKFKNRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTRWTGTGAYWGQGTTVTVSS;

SEQ ID NO: 82 of WO 2015/112900 (SEQ ID NO:242):

QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYWMHWIRQSPSRGLEWLGNIYPGTGGSNF
DEKFKNRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTRWTGTGAYWGQGTTVTVSS;

SEQ ID NO: 86 of WO 2015/112900 (SEQ ID NO:243):

EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQAPGQGLEWMGNIYPGTGGSNF
DEKFKNRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTRWTGTGAYWGQGTTVTVSS;

and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 42, 46, 54, 58, 62, 66, 70, 74, and 78 of WO 2015/112900:

SEQ ID NO: 42 of WO2015/112900 (SEQ ID NO:244):

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFRSGSGSGTEFTLTISSLQPDDEATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 46 of WO 2015/112900 (SEQ ID NO:245):

DIQMTQSPSSLSASVGDRTVITCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGIPPRFRSGSGYGTDFTLTINNIESEDAAYYFCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 54 of WO 2015/112900 (SEQ ID NO:246):

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGKAPKLLIYWASTR
ESGVPSRFRSGSGSGTDFTFTISSLPEDIATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 58 of WO 2015/112900 (SEQ ID NO:247):

DIVMTQTFPLSLPVTGEPASISCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFRSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 62 of WO 2015/112900 (SEQ ID NO:248):

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGKAPKLLIYWASTR
ESGVPSRFRSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 66 of WO 2015/112900 (SEQ ID NO:249):

EIVLTQSPDFQSVTPKEKVTITCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFRSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 70 of WO 2015/112900 (SEQ ID NO:250):

EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQKPGQAPRLLIYWASTR
ESGVPSRFRSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 74 of WO 2015/112900 (SEQ ID NO:251):

DIQMTQSPSSLSASVGDRTVITCKSSQSLLDSGNQKNFLTWYLQKPGQSPQLLIYWASTR

ESGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK;

SEQ ID NO: 78 of WO 2015/112900 (SEQ ID NO:252):

DWMTPQSPLSLSPVTLGQPASISCKSSQSLLDSGNQKNFLTWYQQKPGKAPKLLIYWASTR
ESGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQNDYSYPYTFGQGTKVEIK.

[0173] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies disclosed in WO 2010/077634 and US 8,217,149. In illustrative embodiments, the anti-PD-L1 antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain region comprising the amino acid sequence of:
SEQ ID NO: 20 of WO 2010/077634 (SEQ ID NO:253):

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAVISPYGGSTYY
ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGGGTLLVTVSA;
and/or a light chain variable region comprising the amino acid sequence of: SEQ ID NO: 21 of WO 2010/077634 (SEQ ID NO:254):
DIQMTQSPSSLSASVGDVITITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS
RFSGSGSGTDFTLTITSSLPEDFATYYCQQYLYHPATFGQGTKVELKR.

[0174] In an embodiment, the targeting moiety comprises any one of the anti-PD-L1 antibodies obtainable from the hybridoma accessible under CNCM deposit numbers CNCM 1-4122, CNCM I-4080 and CNCM 1-4081 as disclosed in US 20120039906.

[0175] In an embodiment, the targeting moiety comprises a VHH directed against PD-L1 as disclosed, for example, in US 8,907,065 and WO 2008/071447. In illustrative embodiments, the VHHs against PD-L1 comprise SEQ ID NOS: 394-399 of US 8,907,065:
SEQ ID NO: 394 of US 8,907,065 (SEQ ID NO:255):

EVQLVESGGGLVQPGGSLRLSCAASGFTLDYYAIGWFRQAPGKEREWASS
ISSSDGSTYYADSVKGRFTISRDNAKNTVFLQMNSLKPEDTAVYSCAASQ
APITTIATMMKPEYDYWGQGTQVTVSS;

SEQ ID NO: 395 of US 8,907,065 (SEQ ID NO:256):

EVQLVESGGGLVQPGGSLRLSCAASGFTLDYYAKCWFQRQAPGKEREWVSC
ISSSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYFCAARH
GGPLTVEYFFDYWGQGTQVTVSS;

SEQ ID NO: 396 of US 8,907,065 (SEQ ID NO:257):

EVQLVESGGGLVQPGGSLRLSCAASGFTFDYYAIGWFRQAPGKAREGVSC
ISGGDNSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCATGG
WKYCSGYDPEYIYWGGGTQVTVSS;

SEQ ID NO: 397 of US 8,907,065 (SEQ ID NO:258):

EVQLVESGGGLVQAGGSLRLSCAASGSTFSQYDVGWYRQAPGKQRELVA
FSSSGGRTIYPDSVKGRFTFSRDNTKNTVYLQMTSLKPEDTAVYYCKIDW
YLNSYWGQGTQVTVSS;

SEQ ID NO: 398 of US 8,907,065 (SEQ ID NO:259):

EVQLVESGGGLVQAGGSLRLSCAASGVDA SNSAMGWYRQAPGKQREWVAR
ITGGGLIAYTDSVKGRFTISRDNAKSTVYLQMNSLEPEDTAVYYCNTINS
RDGWGQGTQVTVSS;

SEQ ID NO: 399 of US 8,907,065 (SEQ ID NO:260):

EVQLVESGGGLVQAGGSLTISCAASGITFSDSIVSWYRRARGKQREWVAG
ISNGGTTKYAESVLGRFTISRDNAKNNVYLQMNGLNPEDTAVYLCVKVRQY
WGQGTQVTVSS.

[0176] In an exemplary embodiment, the present multi-specific Clec9A binding agent comprises a targeting moiety directed against PDL-1, such as SEQ ID NO:261:
EVQLVESGGGLVQPGGSLRLSCAASGFTLDYYAKCWFQRQAPGKEREWVSCISSDGSTYYADSVKGRF
TISRDNAKNTVYLQMNSLKPEDTAVYFCAARHGGPLTVEYFFDYWGQGTQVTVSS

[0177] In various embodiments, the present multi-specific Clec9A binding agent has one or more targeting moieties directed against PD-L2. In some embodiments, the Clec9A binding agent has one or more targeting moieties which selectively bind a PD-L2 polypeptide. In some embodiments, the Clec9A binding agent comprises one or more antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind a PD-L2 polypeptide.

[0178] In an embodiment, the targeting moiety comprises a VHH directed against PD-L2 as disclosed, for example, in US 8,907,065 and WO 2008/071447. In illustrative embodiments, the VHHs against PD-1 comprise SEQ ID Nos: 449-455 of US 8,907,065:
SEQ ID NO: 449 of US 8,907,065 (SEQ ID NO:262):

EVQLVESGGGLVQAGGSLRLSCAASESTVLINAMGWYRQAPGKQRELVAS
ISSGGSTNYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCNADV
PQDYGLGYVEGKVYYGHDYWGTCGLVTVSS;

SEQ ID NO: 450 of US 8,907,065 (SEQ ID NO:263):

EVQLVESGGGLVQAGGSLRLSCAASGSTFSNYVSNYAMGWGRQAPGTQ

RELVASISNGDTTNYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYY
CFEHQVAGLTWGGTQVTVSS;

SEQ ID NO: 451 of US 8,907,065 (SEQ ID NO:264);

EVQLVESGGGLVQAGGSLRLSCVASGXALKIXVMGWYRQAPGKQRELV
AAITSGGRITNYSDSVKGRFTISGDNAXNTVYLQMNSLKSEDTAVYYCRE
WNSGYPPVDYWGGTQVTVSS;

SEQ ID NO: 452 of US 8,907,065 (SEQ ID NO:265);

EVQLVESGGGLVQAGGSLRLSCAASGRTFSSGTMGWFRRAFGKEREFEV
ASIPWSGGRITYYADSVKDRFTISRDNAXNTVFLQMNSLKPEDTAVYYCAF
KERSTGWDFASWGQGIQVTVSS;

SEQ ID NO: 453 of US 8,907,065 (SEQ ID NO:266);

EVQLVESGGGLVQTGGSLRLSCAASGFTLDYYGIGWFRQAPGKEREGVS
FISGSDGSTYYAESVKGRFTISRDKAKNTVYLQMNSLKPEDTAVYYCAAD
PWGPPSIATMTSYEYKHWGGTQVTVSS;

SEQ ID NO: 454 of US 8,907,065 (SEQ ID NO:267);

EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYTMIWLRAPGKGFEEV
STIDKDGNTNYVDSVKGRFAVSRDNTKNTLYLQMNSLKPEDTAMYYCTK
HGSSARGQGTRVTVSS;

SEQ ID NO: 455 of US 8,907,065 (SEQ ID NO:268);

EVQLVESGGGLVEPGGSLRLSCVASGFTFSSYDMSWVRQAPGKGLE
WYSTINSGGGITYRGSVKGRFTISRDNAKNTLYLQMNSLKPEDTAVYY
CENGSSYRRGGTQVTVSS.

[0179] In an embodiment, the targeting moiety comprises any one of the anti-PD-L2 antibodies disclosed in US2011/0271358 and WO2010/036959. In illustrative embodiments, the antibody or an antigen-binding fragment thereof for use in the methods provided herein comprises a heavy chain comprising an amino acid sequence selected from SEQ ID Nos: 43-47 of US2011/0271358:

SEQ ID NO: 43 of US2011/0271358 (SEQ ID NO:269);

QVQLVQSGAELKKPGASVKMSCKASGYTFTGYTMHWVKQAPGQGLEWIGYINPRSGYTEY
NQKFKDRITTLTADKSTSTAYMELSSLRSEDSAVYYCARPWFAYWGQGTLLTVSS;

SEQ ID NO: 44 of US2011/0271358 (SEQ ID NO:270);

QVQLVQSGAEVKKPGASVKMSCKASGYTFTGYTMHWVKQAPGQGLEWIGYINPRSGYTEY
NQKFKDRITTLTADKSTSTAYMELSSLRSEDTAVYYCARPWFAYWGQGTLLTVSS;

SEQ ID NO: 45 of US201 1/0271358 (SEQ ID NO:271);

QVQLVQSGAEVKKPGASVKMSCKASGYTFTGYTMHWVRQAPGQGLEWIGYINPRSGYTEY
NQKFKDRITTLTADKSTSTAYMELSSLRSEDTAVYYCARPWFAYWGQGTLLTVSS;

SEQ ID NO: 46 of US2011/0271358 (SEQ ID NO:272);

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYTMHWVRQAPGQGLEWIGYINPRSGYTEY
NQKFKDRITTLTADKSTSTAYMELSSLRSEDTAVYYCARPWFAYWGQGTLLTVSS;

SEQ ID NO: 47 of US2011/0271358 (SEQ ID NO:273);

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYTMHWVRQAPGQGLEWIGYINPRSGYTEY
NQKFKDRITITADKSTSTAYMELSSLRSEDTAVYYCARPWFAYWGQGTLLTVSS;
and/or a light chain comprising an amino acid sequence selected from SEQ ID Nos: 48-51 of US201 1/0271358: SEQ ID NO: 48 of US2011/0271358 (SEQ ID NO:274):
DIVMTQSPASLTVPGEKVTITCKSSQSLNLSGNQKNYLTWYQQKPGQPPKLLIYWASTR
ESGVPDRFTGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPLTFGQGTKLEIK;

SEQ ID NO: 49 of US201 1/0271358 (SEQ ID NO:275);

DIVMTQSPASLSVTPGEKVTITCKSSQSLNLSGNQKNYLTWYQQKPGQPPKLLIYWASTR
ESGVPDRFTGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPLTFGQGTKLEIK;

SEQ ID NO: 50 of US2011/0271358 (SEQ ID NO:276);

DIVMTQSPAFLSVTPGEKVTITCKSSQSLNLSGNQKNYLTWYQQKPGQPPKLLIYWASTR
ESGVPDRFTGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPLTFGQGTKLEIK;

SEQ ID NO: 51 of US2011/0271358 (SEQ ID NO:277);

DIVMTQSPAFLSVTPGEKVTITCKSSQSLNLSGNQKNYLTWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYSYPLTFGQGTKLEIK.

[0180] In various embodiments, the targeting moieties of the invention may comprise a sequence that targets PD-1, PD-L1, and/or PD-L2, or any other targets described herein, which is at least about 60%, at least about 61 %, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71 %, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81 %, at least about

82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91 %, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to any of the sequences disclosed herein (e.g. about 60%, or about 61 %, or about 62%, or about 63%, or about 64%, or about 65%, or about 66%, or about 67%, or about 68%, or about 69%, or about 70%, or about 71 %, or about 72%, or about 73%, or about 74%, or about 75%, or about 76%, or about 77%, or about 78%, or about 79%, or about 80%, or about 81 %, or about 82%, or about 83%, or about 84%, or about 85%, or about 86%, or about 87%, or about 88%, or about 89%, or about 90%, or about 91 %, or about 92%, or about 93%, or about 94%, or about 95%, or about 96%, or about 97%, or about 98%, about 99% or about 100% sequence identity with any of the sequences disclosed herein).

[0181] In various embodiments, the targeting moieties of the invention may comprise any combination of heavy chain, light chain, heavy chain variable region, light chain variable region, complementarity determining region (CDR), and framework region sequences that target PD-1, PD-L1, and/or PD-L2 as disclosed herein.

[0182] Additional antibodies, antibody derivatives or formats, peptides or polypeptides, or fusion proteins that selectively bind or target PD-1, PD-L1 and/or PD-L2 are disclosed in WO 2011/066389, US 2008/0025980, US 2013/0034559, US 8,779,108, US 2014/0356353, US 8,609,089, US 2010/028330, US 2012/0114649, WO 2010/027827, WO 2011/066342, US 8,907,065, WO 2016/062722, WO 2009/101611, WO2010/027827, WO 2011/066342, WO 2007/005874, WO 2001/014556, US2011/0271358, WO 2010/036959, WO 2010/077634, US 8,217,149, US 2012/0039906, WO 2012/145493, US 2011/0318373, U.S. Patent No. 8,779,108, US 20140044738, WO 2009/089149, WO 2007/00587, WO 2016061142, WO 2016,02263, WO 2010/077634, and WO 2015/112900.

[0183] In various embodiments, the multi-specific Clec9A binding agent of the invention has one or more targeting moieties directed against XCR1 e.g. on dendritic cells. For instance, the targeting moiety, in some embodiments comprises all or part of XCL1 or an anti-XCR1 agent that does not functionally modulate (e.g. a non-neutralizing) XCR1.

[0184] In various embodiments, the multi-specific Clec9A binding agents have targeting moieties having recognition domains which specifically bind to a target (e.g. antigen, receptor) which is part of a non-cellular structure. In some embodiments, the antigen or receptor is not an integral component of an intact cell or cellular structure. In some embodiments, the antigen or receptor is an extracellular antigen or receptor. In some embodiments, the target is a non-proteinaceous, non-cellular marker, including, without limitation, nucleic acids, inclusive of DNA or RNA, such as, for example, DNA released from necrotic tumor cells or extracellular deposits such as cholesterol.

[0185] In some embodiments, the target (e.g. antigen, receptor) of interest is part of the non-cellular component of the stroma or the extracellular matrix (ECM) or the markers associated therewith. As used herein, stroma refers to the connective and supportive framework of a tissue or organ. Stroma may include a compilation of cells such as fibroblasts/myofibroblasts, glial, epithelia, fat, immune, vascular, smooth muscle, and immune cells along with the extracellular matrix (ECM) and extracellular molecules. In various embodiments, the target (e.g. antigen, receptor) of interest is part of the non-cellular component of the stroma such as the extracellular matrix and extracellular molecules. As used herein, the ECM refers to the non-cellular components present within all tissues and organs. The ECM is composed of a large collection of biochemically distinct components including, without limitation, proteins, glycoproteins, proteoglycans, and polysaccharides. These components of the ECM are usually produced by adjacent cells and secreted into the ECM via exocytosis. Once secreted, the ECM components often aggregate to form a complex network of macromolecules. In various embodiments, the chimeric protein of the invention comprises a targeting moiety that recognizes a target (e.g., an antigen or receptor or non-proteinaceous molecule) located on any component of the ECM. Illustrative components of the ECM include, without limitation, the proteoglycans, the non-proteoglycan polysaccharides, fibers, and other ECM proteins or ECM non-proteins, e.g. polysaccharides and/or lipids, or ECM associated molecules (e.g. proteins or non-proteins, e.g. polysaccharides, nucleic acids and/or lipids).

[0186] In some embodiments, the targeting moiety recognizes a target (e.g. antigen, receptor) on ECM proteoglycans. Proteoglycans are glycosylated proteins. The basic proteoglycan unit includes a core protein with one or more covalently attached glycosaminoglycan (GAG) chains. Proteoglycans have a net negative charge that attracts positively charged sodium ions (Na⁺), which attracts water molecules via osmosis, keeping the ECM and resident cells hydrated. Proteoglycans may also help to trap and store growth factors within the ECM. Illustrative proteoglycans that may be targeted by the chimeric proteins of the invention include, but are not limited to, heparan sulfate, chondroitin sulfate, and keratan sulfate. In an embodiment, the targeting moiety recognizes a target (e.g. antigen, receptor) on non-proteoglycan polysaccharides such as hyaluronic acid.

[0187] In some embodiments, the targeting moiety recognizes a target (e.g. antigen, receptor) on ECM fibers. ECM fibers include collagen fibers and elastin fibers. In some embodiments, the targeting moiety recognizes one or more epitopes on collagens or collagen fibers. Collagens are the most abundant proteins in the ECM. Collagens are present in the ECM as fibrillar proteins and provide structural support to resident cells. In one or more embodiments, the targeting moiety recognizes and binds to various types of collagens present within the ECM including, without limitation, fibrillar collagens (types I, II, III, V, XI), facit collagens (types IX, XII, XIV), short chain collagens (types VIII, X), basement membrane collagens (type IV), and/or collagen types VI, VII, or XIII. Elastin fibers provide elasticity to tissues, allowing them to stretch when needed and then return to their original state. In some embodiments, the target moiety recognizes one or more epitopes on elastins or elastin fibers.

[0188] In some embodiments, the targeting moiety recognizes one or more ECM proteins including, but not limited to, a tenascin, a fibronectin, a fibrin, a laminin, or a nidogen/entactin.

[0189] In an embodiment, the targeting moiety recognizes and binds to tenascin. The tenascin (TN) family of glycoproteins includes at least four members, tenascin-C, tenascin-R, tenascin-X, and tenascin W. The primary structures of tenascin proteins include several common motifs ordered in the same consecutive sequence: amino-terminal heptad repeats, epidermal growth factor (EGF)-like repeats, fibronectin type III domain repeats, and a carboxyl-terminal fibrinogen-like globular domain. Each protein member is associated with typical variations in the number and nature of EGF-like and fibronectin type III repeats. Isoform variants also exist particularly with respect to tenascin-C. Over 27 splice variants and/or isoforms of tenascin-C are known. In a particular embodiment, the targeting moiety recognizes and binds to tenascin-CA1. Similarly, tenascin-R also has various splice variants and isoforms. Tenascin-R usually exists as dimers or trimers. Tenascin-X is the largest member of the tenascin family and is known to exist as trimers. Tenascin-W exists as trimers. In some embodiments, the targeting moiety recognizes one or more epitopes on a tenascin protein. In some embodiments, the targeting moiety recognizes the monomeric and/or the dimeric and/or the trimeric and/or the hexameric forms of a tenascin protein.

[0190] In an embodiment, the targeting moieties recognize and bind to fibronectin. Fibronectins are glycoproteins that connect cells with collagen fibers in the ECM, allowing cells to move through the ECM. Upon binding to integrins, fibronectins unfolds to form functional dimers. In some embodiments, the targeting moiety recognizes the monomeric and/or the dimeric forms of fibronectin. In some embodiments, the targeting moiety recognizes one or more epitopes on fibronectin. In illustrative embodiments, the targeting moiety recognizes fibronectin extracellular domain A (EDA) or fibronectin extracellular domain B (EDB). Elevated levels of EDA are associated with various diseases and disorders including psoriasis, rheumatoid arthritis, diabetes, and cancer. In some embodiments, the targeting moiety recognizes fibronectin that contains the EDA isoform and may be utilized to target the chimeric protein to diseased cells including cancer cells. In some embodiments, the targeting moiety recognizes fibronectin that contains the EDB isoform. In various embodiments, such targeting moieties may be utilized

to target the chimeric protein to tumor cells including the tumor neovasculature.

[0191] In an embodiment, the targeting moiety recognizes and binds to fibrin. Fibrin is another protein substance often found in the matrix network of the ECM. Fibrin is formed by the action of the protease thrombin on fibrinogen which causes the fibrin to polymerize. In some embodiments, the targeting moiety recognizes one or more epitopes on fibrin. In some embodiments, the targeting moiety recognizes the monomeric as well as the polymerized forms of fibrin.

[0192] In an embodiment, the targeting moiety recognizes and binds to laminin. Laminin is a major component of the basal lamina, which is a protein network foundation for cells and organs. Laminins are heterotrimeric proteins that contain an α -chain, a β -chain, and a γ -chain. In some embodiments, the targeting moiety recognizes one or more epitopes on laminin. In some embodiments, the targeting moiety recognizes the monomeric, the dimeric as well as the trimeric forms of laminin.

[0193] In an embodiment, the targeting moiety recognizes and binds to a nidogen or entactin. Nidogens/entactins are a family of highly conserved, sulfated glycoproteins. They make up the major structural component of the basement membranes and function to link laminin and collagen IV networks in basement membranes. Members of this family include nidogen-1 and nidogen-2. In various embodiments, the targeting moiety recognizes an epitope on nidogen-1 and/or nidogen-2.

[0194] In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes an epitope present on any of the targets (*e.g.*, ECM proteins) described herein. In an embodiment, the antigen-recognition domain recognizes one or more linear epitopes present on the protein. As used herein, a linear epitope refers to any continuous sequence of amino acids present on the protein. In another embodiment, the antigen-recognition domain recognizes one or more conformational epitopes present on the protein. As used herein, a conformation epitope refers to one or more sections of amino acids (which may be discontinuous) which form a three-dimensional surface with features and/or shapes and/or tertiary structures capable of being recognized by an antigen recognition domain.

[0195] In various embodiments, the targeting moiety may bind to the full-length and/or mature forms and/or isoforms and/or splice variants and/or fragments and/or any other naturally occurring or synthetic analogs, variants, or mutants of any of the targets (*e.g.*, ECM proteins) described herein. In various embodiments, the targeting moiety may bind to any forms of the proteins described herein, including monomeric, dimeric, trimeric, tetrameric, heterodimeric, multimeric and associated forms. In various embodiments, the targeting moiety may bind to any post-translationally modified forms of the proteins described herein, such as glycosylated and/or phosphorylated forms.

[0196] In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes extracellular molecules such as DNA. In some embodiments, the targeting moiety comprises an antigen recognition domain that recognizes DNA. In an embodiment, the DNA is shed into the extracellular space from necrotic or apoptotic tumor cells or other diseased cells.

[0197] In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes one or more non-cellular structures associated with atherosclerotic plaques. Two types of atherosclerotic plaques are known. The fibro-lipid (fibro-fatty) plaque is characterized by an accumulation of lipid-laden cells underneath the intima of the arteries. Beneath the endothelium there is a fibrous cap covering the atheromatous core of the plaque. The core includes lipid-laden cells (macrophages and smooth muscle cells) with elevated tissue cholesterol and cholesterol ester content, fibrin, proteoglycans, collagen, elastin, and cellular debris. In advanced plaques, the central core of the plaque usually contains extracellular cholesterol deposits (released from dead cells), which form areas of cholesterol crystals with empty, needle-like clefts. At the periphery of the plaque are younger foamy cells and capillaries. A fibrous plaque is also localized under the intima, within the wall of the artery resulting in thickening and expansion of the wall and, sometimes, spotty localized narrowing of the lumen with some atrophy of the muscular layer. The fibrous plaque contains collagen fibers (eosinophilic), precipitates of calcium (hematoxylinophilic) and lipid-laden cells. In some embodiments, the targeting moiety recognizes and binds to one or more of the non-cellular components of these plaques such as the fibrin, proteoglycans, collagen, elastin, cellular debris, and calcium or other mineral deposits or precipitates. In some embodiments, the cellular debris is a nucleic acid, *e.g.* DNA or RNA, released from dead cells.

[0198] In various embodiments, the targeting moiety comprises an antigen recognition domain that recognizes one or more non-cellular structures found in the brain plaques associated with neurodegenerative diseases. In some embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures located in the amyloid plaques found in the brains of patients with Alzheimer's disease. For example, the targeting moiety may recognize and bind to the peptide amyloid beta, which is a major component of the amyloid plaques. In some embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures located in the brains plaques found in patients with Huntington's disease. In various embodiments, the targeting moiety recognizes and binds to one or more non-cellular structures found in plaques associated with other neurodegenerative or musculoskeletal diseases such as Lewy body dementia and inclusion body myositis.

Linkers and Functional Groups

[0199] In various embodiments, the Clec9A binding agent may include one or more functional groups, residues, or moieties. In various embodiments, the one or more functional groups, residues, or moieties are attached or genetically fused to any of the signaling agents or targeting moieties described herein. In some embodiments, such functional groups, residues or moieties confer one or more desired properties or functionalities to the Clec9A binding agent of the invention. Examples of such functional groups and of techniques for introducing them into the Clec9A binding agent are known in the art, for example, see Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Co., Easton, Pa. (1980).

[0200] In various embodiments, the Clec9A binding agent may be conjugated and/or fused with another agent to extend half-life or otherwise improve pharmacodynamic and pharmacokinetic properties. In some embodiments, the CD8 binding agent may be fused or conjugated with one or more of PEG, XTEN (*e.g.*, as rPEG), polysialic acid (POLYXEN), albumin (*e.g.*, human serum albumin or HAS), elastin-like protein (ELP), PAS, HAP, GLK, CTP, transferrin, and the like. In some embodiments, the CD8 binding agent may be fused or conjugated with an antibody or an antibody fragment such as an Fc fragment. For example, the chimeric protein may be fused to either the N-terminus or the C-terminus of the Fc domain of human immunoglobulin (Ig) G. In various embodiments, each of the individual chimeric proteins is fused to one or more of the agents described in BioDrugs (2015) 29:215-239.

[0201] In some embodiments, the functional groups, residues, or moieties comprise a suitable pharmacologically acceptable polymer, such as poly(ethyleneglycol) (PEG) or derivatives thereof (such as methoxypoly(ethyleneglycol) or mPEG). In some embodiments, attachment of the PEG moiety increases the half-life and/or reduces the immunogenicity of the Clec9A binding protein. Generally, any suitable form of pegylation can be used, such as the pegylation used in the art for antibodies and antibody fragments (including but not limited to single domain antibodies such as VHHs); see, for example, Chapman, Nat. Biotechnol., 54, 531-545 (2002); by Veronese and Harris, Adv. Drug Deliv. Rev. 54, 453-456 (2003), by Harris and Chess, Nat. Rev. Drug. Discov., 2, (2003) and in WO04060965. Various reagents for pegylation of proteins are also commercially available, for example, from Nektar Therapeutics, USA. In some

embodiments, site-directed pegylation is used, in particular via a cysteine-residue (see, for example, Yang et al., Protein Engineering, 16, 10, 761-770 (2003)). For example, for this purpose, PEG may be attached to a cysteine residue that naturally occurs in the Clec9A binding agent of the invention. In some embodiments, the Clec9A binding agent of the invention is modified so as to suitably introduce one or more cysteine residues for attachment of PEG, or an amino acid sequence comprising one or more cysteine residues for attachment of PEG may be fused to the amino- and/or carboxy-terminus of the Clec9A binding agent, using techniques known in the art.

[0202] In some embodiments, the functional groups, residues, or moieties comprise N-linked or O-linked glycosylation. In some embodiments, the N-linked or O-linked glycosylation is introduced as part of a co-translational and/or post-translational modification.

[0203] In some embodiments, the functional groups, residues, or moieties comprise one or more detectable labels or other signal-generating groups or moieties. Suitable labels and techniques for attaching, using and detecting them are known in the art and, include, but are not limited to, fluorescent labels (such as fluorescein, isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, and fluorescamine and fluorescent metals such as Eu or others metals from the lanthanide series), phosphorescent labels, chemiluminescent labels or bioluminescent labels (such as luminal, isoluminol, theromatic acridinium ester, imidazole, acridinium salts, oxalate ester, dioxetane or GFP and its analogs), radio-isotopes, metals, metals chelates or metallic cations or other metals or metallic cations that are particularly suited for use in in vivo, in vitro or in situ diagnosis and imaging, as well as chromophores and enzymes (such as malate dehydrogenase, staphylococcal nuclease, delta- V-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, biotinavidin peroxidase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-VI-phosphate dehydrogenase, glucoamylase and acetylcholine esterase). Other suitable labels include moieties that can be detected using NMR or ESR spectroscopy. Such labeled VHHs and polypeptides of the invention may, for example, be used for in vitro, in vivo or in situ assays (including immunoassays known per se such as ELISA, RIA, EIA and other "sandwich assays," etc.) as well as in vivo diagnostic and imaging purposes, depending on the choice of the specific label.

[0204] In some embodiments, the functional groups, residues, or moieties comprise a tag that is attached or genetically fused to the Clec9A binding agent. In some embodiments, the Clec9A binding agent may include a single tag or multiple tags. The tag for example is a peptide, sugar, or DNA molecule that does not inhibit or prevent binding of the Clec9A binding agent to Clec9A or any other antigen of interest such as tumor antigens. In various embodiments, the tag is at least about: three to five amino acids long, five to eight amino acids long, eight to twelve amino acids long, twelve to fifteen amino acids long, or fifteen to twenty amino acids long. Illustrative tags are described for example, in U.S. Patent Publication No. US2013/0058962. In some embodiment, the tag is an affinity tag such as glutathione-S-transferase (GST) and histidine (His) tag. In an embodiment, the Clec9A binding agent comprises a His tag. In some embodiments, the functional groups, residues, or moieties comprise a chelating group, for example, to chelate one of the metals or metallic cations. Suitable chelating groups, for example, include, without limitation, diethyl-enetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0205] In some embodiments, the functional groups, residues, or moieties comprise a functional group that is one part of a specific binding pair, such as the biotin-(strept)avidin binding pair. Such a functional group may be used to link the Clec9A binding agent of the invention to another protein, polypeptide or chemical compound that is bound to the other half of the binding pair, *i.e.*, through formation of the binding pair. For example, a Clec9A binding agent of the invention may be conjugated to biotin, and linked to another protein, polypeptide, compound or carrier conjugated to avidin or streptavidin. For example, such a conjugated Clec9A binding agent may be used as a reporter, for example, in a diagnostic system where a detectable signal-producing agent is conjugated to avidin or streptavidin. Such binding pairs may, for example, also be used to bind the Clec9A binding agent to a carrier, including carriers suitable for pharmaceutical purposes. One non-limiting example are the liposomal formulations described by Cao and Suresh, Journal of Drug Targeting, 8, 4, 257 (2000). Such binding pairs may also be used to link a therapeutically active agent to the Clec9A binding agent of the invention.

[0206] In some embodiments, the present Clec9A binding agent optionally comprises one or more linkers. In some embodiments, the Clec9A binding agent includes a linker that connects each binding region and/or targeting moieties. In some embodiments, the Clec9A binding agent includes a linker that connects each signaling agent and targeting moiety (or, if more than one targeting moiety, a signaling agent to one of the targeting moieties). In some embodiments, the linker may be utilized to link various functional groups, residues, or moieties as described herein to the Clec9A binding agent. In some embodiments, the linker is a single amino acid or a plurality of amino acids that does not affect or reduce the stability, orientation, binding, neutralization, and/or clearance characteristics of the binding regions and the binding protein. In various embodiments, the linker is selected from a peptide, a protein, a sugar, or a nucleic acid.

[0207] In some embodiments, the present Clec9A binding agent comprises a linker connecting the targeting moiety and the signaling agent. In some embodiments, the present chimeric protein comprises a linker within the signaling agent (*e.g.* in the case of single chain TNF, which can comprise two linkers to yield a trimer).

[0208] The invention contemplates the use of a variety of linker sequences. In various embodiments, the linker may be derived from naturally-occurring multi-domain proteins or are empirical linkers as described, for example, in Chichili et al., (2013), Protein Sci. 22(2):153-167, Chen et al., (2013), Adv Drug Deliv Rev. 65(10): 1357-1369. In some embodiments, the linker may be designed using linker designing databases and computer programs such as those described in Chen et al., (2013), Adv Drug Deliv Rev. 65(10):1357-1369 and Crasto et al., (2000), Protein Eng. 13(5):309-312. In various embodiments, the linker may be functional. For example, without limitation, the linker may function to improve the folding and/or stability, improve the expression, improve the pharmacokinetics, and/or improve the bioactivity of the present Clec9A binding agent. In some embodiments, the linker is a polypeptide. In some embodiments, the linker is less than about 100 amino acids long. For example, the linker may be less than about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids long. In some embodiments, the linker is a polypeptide. In some embodiments, the linker is greater than about 100 amino acids long. For example, the linker may be greater than about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids long. In some embodiments, the linker is flexible. In another embodiment, the linker is rigid.

[0209] In some embodiments, the linker length allows for efficient binding of a targeting moiety and the signaling agent to their receptors. For instance, in some embodiments, the linker length allows for efficient binding of one of the targeting moieties and the signaling agent to receptors on the same cell as well as the efficient binding of the other targeting moiety to another cell. Illustrative pairs of cells are provided elsewhere herein.

[0210] In some embodiments the linker length is at least equal to the minimum distance between the binding sites of one of the targeting moieties and the signaling agent to receptors on the same cell. In some embodiments the linker length is at least twice, or three times, or four times, or five times, or ten times, or twenty times, or 25 times, or 50 times, or one hundred times, or more the minimum distance between the binding sites of one of the targeting moieties and the signaling agent to receptors on the same cell.

[0211] In some embodiments, a linker connects the two targeting moieties to each other and this linker has a short length and a linker connects a targeting moiety

and a signaling agent this linker is longer than the linker connecting the two targeting moieties. For example, the difference in amino acid length between the linker connecting the two targeting moieties and the linker connecting a targeting moiety and a signaling agent may be about 100, about 95, about 90, about 85, about 80, about 75, about 70, about 65, about 60, about 55, about 50, about 45, about 40, about 35, about 30, about 25, about 20, about 19, about 18, about 17, about 16, about 15, about 14, about 13, about 12, about 11, about 10, about 9, about 8, about 7, about 6, about 5, about 4, about 3, or about 2 amino acids. In some embodiments, the linker is flexible. In another embodiment, the linker is rigid.

[0212] In various embodiments, the linker is substantially comprised of glycine and serine residues (*e.g.* about 30%, or about 40%, or about 50%, or about 60%, or about 70%, or about 80%, or about 90%, or about 95%, or about 97% glycines and serines). For example, in some embodiments, the linker is (Gly4Ser)*n*, where *n* is from about 1 to about 8, *e.g.* 1, 2, 3, 4, 5, 6, 7, or 8. In an embodiment, the linker sequence is GGSGSGGGGSGGGGS (SEQ ID NO:278). Additional illustrative linkers include, but are not limited to, linkers having the sequence LE, GGGGS (SEQ ID NO:279), (GGGS)" (*n*=1-4) (SEQ ID NO:280), (Gly)8(SEQ ID NO:281), (Gly)6(SEQ ID NO:282), (EAAAK)" (*n*=1-3) (SEQ ID NO:283);, A(EAAAK)"A (*n* = 2-5) (SEQ ID NO:284), AEA AAKEAAKA (SEQ ID NO:285), A(EAAAK)4ALEA(EAAAK)4A (SEQ ID NO:286), PAPAP (SEQ ID NO:287), KESGSVSSEQLAQFRSLD (SEQ ID NO:288), EGKSSGSGSESKST (SEQ ID NO:289), GSAGSAAGSGEF (SEQ ID NO:290), and (XP)*n*, with X designating any amino acid, *e.g.*, Ala, Lys, or Glu. In various embodiments, the linker is GGS.

[0213] In some embodiments, the linker is a hinge region of an antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). In various embodiments, the linker is a hinge region of an antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). The hinge region, found in IgG, IgA, IgD, and IgE class antibodies, acts as a flexible spacer, allowing the Fab portion to move freely in space. In contrast to the constant regions, the hinge domains are structurally diverse, varying in both sequence and length among immunoglobulin classes and subclasses. For example, the length and flexibility of the hinge region varies among the IgG subclasses. The hinge region of IgG1 encompasses amino acids 216-231 and, because it is freely flexible, the Fab fragments can rotate about their axes of symmetry and move within a sphere centered at the first of two inter-heavy chain disulfide bridges. IgG2 has a shorter hinge than IgG1, with 12 amino acid residues and four disulfide bridges. The hinge region of IgG2 lacks a glycine residue, is relatively short, and contains a rigid poly-proline double helix, stabilized by extra inter-heavy chain disulfide bridges. These properties restrict the flexibility of the IgG2 molecule. IgG3 differs from the other subclasses by its unique extended hinge region (about four times as long as the IgG1 hinge), containing 62 amino acids (including 21 prolines and 11 cysteines), forming an inflexible poly-proline double helix. In IgG3, the Fab fragments are relatively far away from the Fc fragment, giving the molecule a greater flexibility. The elongated hinge in IgG3 is also responsible for its higher molecular weight compared to the other subclasses. The hinge region of IgG4 is shorter than that of IgG1 and its flexibility is intermediate between that of IgG1 and IgG2. The flexibility of the hinge regions reportedly decreases in the order IgG3>IgG1 >IgG4>IgG2.

[0214] According to crystallographic studies, the immunoglobulin hinge region can be further subdivided functionally into three regions: the upper hinge region, the core region, and the lower hinge region. See Shin et al., 1992 Immunological Reviews 130:87. The upper hinge region includes amino acids from the carboxyl end of Cm to the first residue in the hinge that restricts motion, generally the first cysteine residue that forms an interchain disulfide bond between the two heavy chains. The length of the upper hinge region correlates with the segmental flexibility of the antibody. The core hinge region contains the inter-heavy chain disulfide bridges, and the lower hinge region joins the amino terminal end of the CH2 domain and includes residues in CH2. Id. The core hinge region of wild-type human IgG1 contains the sequence Cys-Pro-Pro-Cys which, when dimerized by disulfide bond formation, results in a cyclic octapeptide believed to act as a pivot, thus conferring flexibility. In various embodiments, the present linker comprises, one, or two, or three of the upper hinge region, the core region, and the lower hinge region of any antibody (*e.g.*, of IgG, IgA, IgD, and IgE, inclusive of subclasses (*e.g.* IgG1, IgG2, IgG3, and IgG4, and IgA1 and IgA2)). The hinge region may also contain one or more glycosylation sites, which include a number of structurally distinct types of sites for carbohydrate attachment. For example, IgA1 contains five glycosylation sites within a 17-amino-acid segment of the hinge region, conferring resistance of the hinge region polypeptide to intestinal proteases, considered an advantageous property for a secretory immunoglobulin. In various embodiments, the linker of the present invention comprises one or more glycosylation sites. In various embodiments, the linker is a hinge-CH2-CH3 domain of a human IgG4 antibody.

[0215] If desired, the present Clec9A binding agent can be linked to an antibody Fc region, comprising one or both of CH2 and CH3 domains, and optionally a hinge region. For example, vectors encoding the present Clec9A binding agents linked as a single nucleotide sequence to an Fc region can be used to prepare such polypeptides.

[0216] In some embodiments, the linker is a synthetic linker such as PEG.

[0217] In various embodiments, the linker may be functional. For example, without limitation, the linker may function to improve the folding and/or stability, improve the expression, improve the pharmacokinetics, and/or improve the bioactivity of the present Clec9A binding agent. In another example, the linker may function to target the Clec9A binding agent to a particular cell type or location.

Modifications and Production of Clec9A binding agents

[0218] The Clec9A binding agent comprises a targeting moiety that is a VHH. In various embodiments, the VHH is not limited to a specific biological source or to a specific method of preparation. For example, the VHH can generally be obtained: (1) by isolating the VHH domain of a naturally occurring heavy chain antibody; (2) by expression of a nucleotide sequence encoding a naturally occurring VHH domain; (3) by "humanization" of a naturally occurring VHH domain or by expression of a nucleic acid encoding a such humanized VHH domain; (4) by "camelization" of a naturally occurring VH domain from any animal species, such as from a mammalian species, such as from a human being, or by expression of a nucleic acid encoding such a camelized VH domain; (5) by "camelization" of a "domain antibody" or "Dab" as described in the art, or by expression of a nucleic acid encoding such a camelized VH domain; (6) by using synthetic or semi-synthetic techniques for preparing proteins, polypeptides or other amino acid sequences known in the art; (7) by preparing a nucleic acid encoding a VHH using techniques for nucleic acid synthesis known in the art, followed by expression of the nucleic acid thus obtained; and/or (8) by any combination of one or more of the foregoing.

[0219] In an embodiment, the Clec9A binding agent comprises a VHH that corresponds to the VHH domains of naturally occurring heavy chain antibodies directed against human Clec9A. In some embodiments, such VHH sequences can generally be generated or obtained by suitably immunizing a species of Camelid with a Clec9A molecule, (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against Clec9A), by obtaining a suitable biological sample from the Camelid (such as a blood sample, or any sample of B-cells), and by generating VHH sequences directed against Clec9A, starting from the sample, using any suitable known techniques. In some embodiments, naturally occurring VHH domains against Clec9A can be obtained from naive libraries of Camelid VHH sequences, for example, by screening such a library using Clec9A or at least one part, fragment, antigenic determinant or epitope thereof using one or more screening techniques known in the art. Such libraries and techniques are, for example, described in WO9937681, WO0190190, WO03025020 and WO03035694. In some embodiments, improved synthetic or semi-synthetic libraries derived from naive VHH libraries may be used, such as VHH libraries obtained from naive VHH libraries by techniques such as random mutagenesis and/or CDR shuffling, as for example, described in WO0043507. In some embodiments, another technique for obtaining VHH sequences directed against a Clec9A involves suitably immunizing a transgenic mammal that is capable of expressing heavy chain antibodies (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against Clec9A), obtaining a suitable biological sample from the

transgenic mammal (such as a blood sample, or any sample of B-cells), and then generating VHH sequences directed against Clec9A starting from the sample, using any suitable known techniques. For example, for this purpose, the heavy chain antibody-expressing mice and the further methods and techniques described in WO02085945 and in WO04049794 can be used.

[0220] In an embodiment, the Clec9A binding agent comprises a VHH that has been "humanized" *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of the naturally occurring VHH sequence (and in particular in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being. This can be performed using humanization techniques known in the art. In some embodiments, possible humanizing substitutions or combinations of humanizing substitutions may be determined by methods known in the art, for example, by a comparison between the sequence of a VHH and the sequence of a naturally occurring human VH domain. In some embodiments, the humanizing substitutions are chosen such that the resulting humanized VHHs still retain advantageous functional properties. Generally, as a result of humanization, the VHHs of the invention may become more "human-like," while still retaining favorable properties such as a reduced immunogenicity, compared to the corresponding naturally occurring VHH domains. In various embodiments, the humanized VHHs of the invention can be obtained in any suitable manner known in the art and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VHH domain as a starting material.

[0221] In an embodiment, the Clec9A binding agent comprises a VHH that has been "camelized," *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring VH domain from a conventional 4-chain antibody by one or more of the amino acid residues that occur at the corresponding position(s) in a VHH domain of a heavy chain antibody of a camelid. In some embodiments, such "camelizing" substitutions are inserted at amino acid positions that form and/or are present at the VH-VL interface, and/or at the so-called Camelidae hallmark residues (see, for example, WO9404678). In some embodiments, the VH sequence that is used as a starting material or starting point for generating or designing the camelized VHH is a VH sequence from a mammal, for example, the VH sequence of a human being, such as a VH3 sequence. In various embodiments, the camelized VHHs can be obtained in any suitable manner known in the art (*i.e.*, as indicated under points (1)-(8) above) and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VH domain as a starting material.

[0222] In various embodiments, both "humanization" and "camelization" can be performed by providing a nucleotide sequence that encodes a naturally occurring VHH domain or VH domain, respectively, and then changing, in a manner known in the art, one or more codons in the nucleotide sequence in such a way that the new nucleotide sequence encodes a "humanized" or "camelized" VHH, respectively. This nucleic acid can then be expressed in a manner known in the art, so as to provide the desired VHH of the invention. Alternatively, based on the amino acid sequence of a naturally occurring VHH domain or VH domain, respectively, the amino acid sequence of the desired humanized or camelized VHH of the invention, respectively, can be designed and then synthesized *de novo* using techniques for peptide synthesis known in the art. Also, based on the amino acid sequence or nucleotide sequence of a naturally occurring VHH domain or VH domain, respectively, a nucleotide sequence encoding the desired humanized or camelized VHH, respectively, can be designed and then synthesized *de novo* using techniques for nucleic acid synthesis known in the art, after which the nucleic acid thus obtained can be expressed in a manner known in the art, so as to provide the desired VHH of the invention. Other suitable methods and techniques for obtaining the VHHs of the invention and/or nucleic acids encoding the same, starting from naturally occurring VH sequences or VHH sequences, are known in the art, and may, for example, comprise combining one or more parts of one or more naturally occurring VH sequences (such as one or more FR sequences and/or CDR sequences), one or more parts of one or more naturally occurring VHH sequences (such as one or more FR sequences or CDR sequences), and/or one or more synthetic or semi-synthetic sequences, in a suitable manner, so as to provide a VHH of the invention or a nucleotide sequence or nucleic acid encoding the same.

[0223] Methods for producing the Clec9A binding agents of the invention are described herein. For example, DNA sequences encoding the Clec9A binding agents of the invention can be chemically synthesized using methods known in the art. Synthetic DNA sequences can be ligated to other appropriate nucleotide sequences, including, *e.g.*, expression control sequences, to produce gene expression constructs encoding the desired Clec9A binding agents. Accordingly, in various embodiments, the present invention provides for isolated nucleic acids comprising a nucleotide sequence encoding the Clec9A binding agent of the invention.

[0224] Nucleic acids encoding the Clec9A binding agent of the invention can be incorporated (ligated) into expression vectors, which can be introduced into host cells through transfection, transformation, or transduction techniques. For example, nucleic acids encoding the Clec9A binding agent of the invention can be introduced into host cells by retroviral transduction. Illustrative host cells are E.coli cells, Chinese hamster ovary (CHO) cells, human embryonic kidney 293 (HEK 293) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and myeloma cells. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the Clec9A binding agent of the invention. Accordingly, in various embodiments, the present invention provides expression vectors comprising nucleic acids that encode the Clec9A binding agent of the invention. In various embodiments, the present invention additionally provides host cells comprising such expression vectors.

[0225] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in E. coli, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, *e.g.*, Trp or Tac, and a prokaryotic signal sequence. In another example, if the engineered gene is to be expressed in eukaryotic host cells, *e.g.*, CHO cells, it is first inserted into an expression vector containing for example, a suitable eukaryotic promoter, a secretion signal, enhancers, and various introns. The gene construct can be introduced into the host cells using transfection, transformation, or transduction techniques.

[0226] The Clec9A binding agent of the invention can be produced by growing a host cell transfected with an expression vector encoding the Clec9A binding agent under conditions that permit expression of the protein. Following expression, the protein can be harvested and purified using techniques well known in the art, *e.g.*, affinity tags such as glutathione-S-transferase (GST) and histidine (His) tags or by chromatography. In an embodiment, the Clec9A binding agent comprises a His tag. In an embodiment, the Clec9A binding agent comprises a His tag and a proteolytic site to allow cleavage of the His tag.

[0227] Accordingly, in various embodiments, the present invention provides for a nucleic acid encoding a Clec9A binding agent of the present invention. In various embodiments, the present invention provides for a host cell comprising a nucleic acid encoding a Clec9A binding agent of the present invention.

[0228] In various embodiments, the methods of modifying and producing the Clec9A binding agents as described herein can be easily adapted for the modification and production of any multi-specific binding agents or chimeras comprising two or more targeting moieties and/or signaling agents. For example, the methods may be adapted for production of a multi-specific Clec9A binding agent comprising a targeting moiety against a checkpoint inhibitor antigen.

Pharmaceutically Acceptable Salts and Excipients

[0229] The Clec9A binding agents (and/or any other therapeutic agents) described herein can possess a sufficiently basic functional group, which can react with an inorganic or organic acid, or a carboxyl group, which can react with an inorganic or organic base, to form a pharmaceutically acceptable salt. A

pharmaceutically acceptable acid addition salt is formed from a pharmaceutically acceptable acid, as is well known in the art. Such salts include the pharmaceutically acceptable salts listed in, for example, Journal of Pharmaceutical Science, 66, 2-19 (1977) and The Handbook of Pharmaceutical Salts; Properties, Selection, and Use. P. H. Stahl and C. G. Wermuth (eds.), Verlag, Zurich (Switzerland) 2002.

[0230] Pharmaceutically acceptable salts include, by way of non-limiting example, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, camphorsulfonate, pamoate, phenylacetate, trifluoroacetate, acrylate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, isobutyrate, phenylbutyrate, a-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate, cinnamate, glycollate, heptanoate, hippurate, malate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, phthalate, teraphthalate, propiolate, propionate, phenylpropionate, sebacate, suberate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, xylenesulfonate, and tartarate salts.

[0231] The term "pharmaceutically acceptable salt" also refers to a salt of the compositions of the present invention having an acidic functional group, such as a carboxylic acid functional group, and a base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-lower alkylamines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxyl-lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

[0232] In some embodiments, the compositions described herein are in the form of a pharmaceutically acceptable salt.

Pharmaceutical Compositions and Formulations

[0233] In various embodiments, the present invention pertains to pharmaceutical compositions comprising the Clec9A binding agents (and/or any other therapeutic agents) described herein and a pharmaceutically acceptable carrier or excipient. In some embodiments, the present invention pertains to pharmaceutical compositions comprising the present Clec9A binding agents. In another embodiment, the present invention pertains to pharmaceutical compositions comprising any other therapeutic agents described herein. In a further embodiment, the present invention pertains to pharmaceutical compositions comprising a combination of the present Clec9A binding agents and any other therapeutic agents described herein. Any pharmaceutical compositions described herein can be administered to a subject as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. Such compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration.

[0234] In various embodiments, pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be, for example, saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to a subject. Water is a useful excipient when any agent described herein is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, specifically for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Any agent described herein, if desired, can also comprise minor amounts of wetting or emulsifying agents, or pH buffering agents. Other examples of suitable pharmaceutical excipients are described in Remington's Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995).

[0235] The present invention includes the described pharmaceutical compositions (and/or additional therapeutic agents) in various formulations. Any inventive pharmaceutical composition (and/or additional therapeutic agents) described herein can take the form of solutions, suspensions, emulsion, drops, tablets, pills, pellets, capsules, capsules containing liquids, gelatin capsules, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, lyophilized powder, frozen suspension, desiccated powder, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule. In another embodiment, the composition is in the form of a tablet. In yet another embodiment, the pharmaceutical composition is formulated in the form of a soft-gel capsule. In a further embodiment, the pharmaceutical composition is formulated in the form of a gelatin capsule. In yet another embodiment, the pharmaceutical composition is formulated as a liquid.

[0236] Where necessary, the inventive pharmaceutical compositions (and/or additional agents) can also include a solubilizing agent. Also, the agents can be delivered with a suitable vehicle or delivery device as known in the art. Combination therapies outlined herein can be co-delivered in a single delivery vehicle or delivery device.

[0237] The formulations comprising the inventive pharmaceutical compositions (and/or additional agents) of the present invention may conveniently be presented in unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods generally include the step of bringing the therapeutic agents into association with a carrier, which constitutes one or more accessory ingredients. Typically, the formulations are prepared by uniformly and intimately bringing the therapeutic agent into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into dosage forms of the desired formulation (e.g., wet or dry granulation, powder blends, etc., followed by tableting using conventional methods known in the art).

[0238] In various embodiments, any pharmaceutical compositions (and/or additional agents) described herein is formulated in accordance with routine procedures as a composition adapted for a mode of administration described herein.

[0239] Routes of administration include, for example: oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically. Administration can be local or systemic. In some embodiments, the administering is effected orally. In another embodiment, the administration is by parenteral injection. The mode of administration can be left to the discretion of the practitioner, and depends in-part upon the site of the medical condition. In most instances, administration results in the release of any agent described herein into the bloodstream.

[0240] In one embodiment, the Clec9A binding agent described herein is formulated in accordance with routine procedures as a composition adapted for oral administration. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can comprise one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable

preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving any Clec9A binding agents described herein are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be useful. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade. Suspensions, in addition to the active compounds, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, etc., and mixtures thereof.

[0241] Dosage forms suitable for parenteral administration (e.g. intravenous, intramuscular, intraperitoneal, subcutaneous and intra-articular injection and infusion) include, for example, solutions, suspensions, dispersions, emulsions, and the like. They may also be manufactured in the form of sterile solid compositions (e.g. lyophilized composition), which can be dissolved or suspended in sterile injectable medium immediately before use. They may contain, for example, suspending or dispersing agents known in the art. Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.

[0242] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The compositions provided herein, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0243] Any inventive pharmaceutical compositions (and/or additional agents) described herein can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,556. Such dosage forms can be useful for providing controlled- or sustained-release of one or more active ingredients using, for example, hydropropyl cellulose, hydropropylmethyl cellulose, polyvinylpyrrolidone, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those skilled in the art, including those described herein, can be readily selected for use with the active ingredients of the agents described herein. The invention thus provides single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

[0244] Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, stimulation by an appropriate wavelength of light, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0245] In another embodiment, a controlled-release system can be placed in proximity of the target area to be treated, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, Science 249:1527-1533) may be used.

[0246] Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

Administration and Dosage

[0247] It will be appreciated that the actual dose of the Clec9A binding agent and/or any therapeutic agents described herein to be administered will vary according to the particular dosage form, and the mode of administration. Many factors that may modify the action of the Clec9A binding agent (e.g., body weight, gender, diet, time of administration, route of administration, rate of excretion, condition of the subject, drug combinations, genetic disposition and reaction sensitivities) can be taken into account by those skilled in the art. Administration can be carried out continuously or in one or more discrete doses within the maximum tolerated dose. Optimal administration rates for a given set of conditions can be ascertained by those skilled in the art using conventional dosage administration tests.

[0248] In some embodiments, a suitable dosage of the Clec9A binding agent and/or any therapeutic agents described herein is in a range of about 0.01 mg/kg to about 10 g/kg of body weight of the subject, about 0.01 mg/kg to about 1 g/kg of body weight of the subject, about 0.01 mg/kg to about 100 mg/kg of body weight of the subject, about 0.01 mg/kg to about 10 mg/kg of body weight of the subject, for example, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, 1.9 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg body weight, about 100 mg/kg body weight, about 1 g/kg of body weight, about 10 g/kg of body weight, inclusive of all values and ranges therebetween.

[0249] Individual doses of the Clec9A binding agent and/or any therapeutic agents described herein can be administered in unit dosage forms containing, for example, from about 0.01 mg to about 100 g, from about 0.01 mg to about 75 g, from about 0.01 mg to about 50 g, from about 0.01 mg to about 25 g, about 0.01 mg to about 10 g, about 0.01 mg to about 7.5 g, about 0.01 mg to about 5 g, about 0.01 mg to about 2.5 g, about 0.01 mg to about 1 g, about 0.01 mg to about 100 mg, from about 0.1 mg to about 100 mg, from about 0.1 mg to about 90 mg, from about 0.1 mg to about 80 mg, from about 0.1 mg to about 70 mg, from about 0.1 mg to about 60 mg, from about 0.1 mg to about 50 mg, from about 0.1 mg to about 40 mg active ingredient, from about 0.1 mg to about 30 mg, from about 0.1 mg to about 20 mg, from about 0.1 mg to about 10 mg, from about 0.1 mg to about 5 mg, from about 0.1 mg to about 3 mg, from about 0.1 mg to about 1 mg per unit dosage form, or from about 5 mg to about 80 mg per unit dosage form. For example, a unit dosage form can be about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg,

about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 200 mg, about 500 mg, about 1 g, about 2.5 g, about 5 g, about 10 g, about 25 g, about 50 g, about 75 g, about 100 g, inclusive of all values and ranges therebetween.

[0250] In one embodiment, the Clec9A binding agent and/or any therapeutic agents described herein can be administered at an amount of from about 0.01 mg to about 100 g daily, from about 0.01 mg to about 75 g daily, from about 0.01 mg to about 50 g daily, from about 0.01 mg to about 25 g daily, from about 0.01 mg to about 10 g daily, from about 0.01 mg to about 7.5 g daily, from about 0.01 mg to about 5 g daily, from about 0.01 mg to about 2.5 g daily, from about 0.01 mg to about 1 g daily, from about 0.01 mg to about 100 mg daily, from about 0.1 mg to about 100 mg daily, from about 0.1 mg to about 95 mg daily, from about 0.1 mg to about 90 mg daily, from about 0.1 mg to about 85 mg daily, from about 0.1 mg to about 80 mg daily, from about 0.1 mg to about 75 mg daily, from about 0.1 mg to about 70 mg daily, from about 0.1 mg to about 65 mg daily, from about 0.1 mg to about 60 mg daily, from about 0.1 mg to about 55 mg daily, from about 0.1 mg to about 50 mg daily, from about 0.1 mg to about 45 mg daily, from about 0.1 mg to about 40 mg daily, from about 0.1 mg to about 35 mg daily, from about 0.1 mg to about 30 mg daily, from about 0.1 mg to about 25 mg daily, from about 0.1 mg to about 20 mg daily, from about 0.1 mg to about 15 mg daily, from about 0.1 mg to about 10 mg daily, from about 0.1 mg to about 5 mg daily, from about 0.1 mg to about 3 mg daily, from about 0.1 mg to about 1 mg daily, or from about 5 mg to about 80 mg daily. In various embodiments, the Clec9A binding agent is administered at a daily dose of about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 200 mg, about 500 mg, about 1 g, about 2.5 g, about 5 g, about 7.5 g, about 10 g, about 25 g, about 50 g, about 75 g, about 100 g, inclusive of all values and ranges therebetween.

[0251] The pharmaceutical composition comprising the Clec9A binding agent and/or any therapeutic agents described herein may be administered, for example, more than once daily (e.g., about two times, about three times, about four times, about five times, about six times, about seven times, about eight times, about nine times, or about ten times daily), about once per day, about every other day, about every third day, about once a week, about once every two weeks, about once every month, about once every two months, about once every three months, about once every six months, or about once every year.

Combination Therapy and Additional Therapeutic Agents

[0252] The pharmaceutical composition of the present invention can be co-administered in conjunction with additional therapeutic agent(s). Co-administration can be simultaneous or sequential.

[0253] The additional therapeutic agent and the Clec9A binding agent of the present invention can be administered to a subject simultaneously. The term "simultaneously" as used herein, means that the additional therapeutic agent and the Clec9A binding agent are administered with a time separation of no more than about 60 minutes, such as no more than about 30 minutes, no more than about 20 minutes, no more than about 10 minutes, no more than about 5 minutes, or no more than about 1 minute. Administration of the additional therapeutic agent and the Clec9A binding agent can be by simultaneous administration of a single formulation (e.g., a formulation comprising the additional therapeutic agent and the Clec9A binding agent) or of separate formulations (e.g., a first formulation including the additional therapeutic agent and a second formulation including the Clec9A binding agent).

[0254] Co-administration does not require the therapeutic agents to be administered simultaneously, if the timing of their administration is such that the pharmacological activities of the additional therapeutic agent and the Clec9A binding agent overlap in time, thereby exerting a combined therapeutic effect. For example, the additional therapeutic agent and the Clec9A binding agent can be administered sequentially. The term "sequentially" as used herein means that the additional therapeutic agent and the Clec9A binding agent are administered with a time separation of more than about 60 minutes. For example, the time between the sequential administration of the additional therapeutic agent and the Clec9A binding agent can be more than about 60 minutes, more than about 2 hours, more than about 5 hours, more than about 10 hours, more than about 1 day, more than about 2 days, more than about 3 days, more than about 1 week, or more than about 2 weeks, or more than about one month apart. The optimal administration times will depend on the rates of metabolism, excretion, and/or the pharmacodynamic activity of the additional therapeutic agent and the Clec9A binding agent being administered. Either the additional therapeutic agent or the Clec9A binding agent cell may be administered first.

[0255] Co-administration also does not require the therapeutic agents to be administered to the subject by the same route of administration. Rather, each therapeutic agent can be administered by any appropriate route, for example, parenterally or non-parenterally.

[0256] The Clec9A binding agent described herein may act synergistically when co-administered with another therapeutic agent. The Clec9A binding agent and the additional therapeutic agent may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy.

[0257] In some embodiments, the present invention pertains to chemotherapeutic agents as additional therapeutic agents. For example, without limitation, such combination of the present Clec9A binding agents and chemotherapeutic agent find use in the treatment of cancers, as described elsewhere herein. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and CYTOXAN cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; acetogenins (e.g., bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; cally statin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (e.g., cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB 1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Agnew, Chem. Intl. Ed. Engl., 33: 183-186 (1994))); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxy doxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitiostane, testolactone; anti-adrenals such as minogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet;

pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (e.g., T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepea; taxoids, e.g., TAXOL paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumburg, 111.), and TAXOTERE doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE. vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-11) (including the treatment regimen of irinotecan with 5-FU and leucovorin); topoisoemrase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; combretastatin; leucovorin (LV); oxaliplatin, including the oxaliplatin treatment regimen (FOLFOX); lapatinib (Tykerb); inhibitors of PKC-a, Raf, H-Ras, EGFR (e.g., erlotinib (Tarceva)) and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above. In addition, the methods of treatment can further include the use of radiation. In addition, the methods of treatment can further include the use of photodynamic therapy. Accordingly, disclosed are combination therapies using the Clec9A binding agent and a chemotherapeutic agent. Disclosed is the administration of the Clec9A binding agent to a patient undergoing treatment with a chemotherapeutic agent. The chemotherapeutic agent may be a DNA-intercalating agent such as, without limitation, doxorubicin, cisplatin, daunorubicin, and epirubicin. The DNA-intercalating agent may be doxorubicin.

[0258] The Clec9A binding agent may act synergistically when co-administered with doxorubicin. The Clec9A binding agent may act synergistically when co-administered with doxorubicin for use in treating tumor or cancer. For example, co-administration of the Clec9A binding agent and doxorubicin may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. The combination of the Clec9A binding agent and doxorubicin may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. The Clec9A binding agent and doxorubicin may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy.

[0259] Disclosed is a combination therapy with one or more immune- modulating agents, for example, without limitation, agents that modulate immune checkpoint. The immune-modulating agent may target one or more of PD-1, PD-L1, and PD-L2. The immune-modulating agent may be PD-1 inhibitor. The immune-modulating agent may be an antibody specific for one or more of PD-1, PD-L1, and PD-L2. For instance, in some embodiments, the immune-modulating agent is an antibody such as, by way of non-limitation, nivolumab, (ONO-4538/BMS- 936558, MDX1106, OPDIVO, BRISTOL MYERS SQUIBB), pembrolizumab (KEYTRUDA, MERCK), pidilizumab (CT-011, CURE TECH), MK-3475 (MERCK), BMS 936559 (BRISTOL MYERS SQUIBB), MPDL3280A (ROCHE). The immune-modulating agent may target one or more of CD137 or CD137L. The immune-modulating agent may be an antibody specific for one or more of CD137 or CD137L. For instance, the immune-modulating agent may be an antibody such as, by way of non-limitation, urelumab (also known as BMS-663513 and anti-4-1BB antibody). The present chimeric protein may be combined with urelumab (optionally with one or more of nivolumab, lirilumab, and urelumab) for the treatment of solid tumors and/or B-cell non-Hodgkins lymphoma and/or head and neck cancer and/or multiple myeloma. The immune-modulating agent may be an agent that targets one or more of CTLA-4, AP2M1, CD80, CD86, SHP-2, and PPP2R5A. The immune-modulating agent may be an antibody specific for one or more of CTLA-4, AP2M1, CD80, CD86, SHP-2, and PPP2R5A. For instance, the immune-modulating agent may be an antibody such as, by way of non-limitation, ipilimumab (MDX-010, MDX-101, Yervoy, BMS) and/or tremelimumab (Pfizer). The present chimeric protein may be combined with ipilimumab (optionally with bavituximab) for the treatment of one or more of melanoma, prostate cancer, and lung cancer. The immune-modulating agent may target CD20. The immune-modulating agent may be an antibody specific CD20. For instance, the immune-modulating agent may be an antibody such as, by way of non-limitation, Ofatumumab (GENMAB), obinutuzumab (GAZYVA), AME-133v (APPLIED MOLECULAR EVOLUTION), Ocrelizumab (GENENTECH), TRU-015 (TRUBION/EMERGENT), veltuzumab (IMMU-106).

[0260] Disclosed is a combination therapy using the Clec9A binding agent and a checkpoint inhibitor. Disclosed is the administration of the Clec9A binding agent to a patient undergoing treatment with a checkpoint inhibitor. The checkpoint inhibitor may be an agent that targets one or more of PD-1, PD-L1, PD-L2, and CTLA-4 (including any of the anti-PD-1, anti-PD-L1, anti-PD-L2, and anti-CTLA-4 agents described herein). The checkpoint inhibitor may be one or more of nivolumab, (ONO-4538/BMS-936558, MDX1106, OPDIVO, BRISTOL MYERS SQUIBB), pembrolizumab (KEYTRUDA, MERCK), pidilizumab (CT-011, CURE TECH), MK-3475 (MERCK), BMS 936559 (BRISTOL MYERS SQUIBB), MPDL3280A (ROCHE), ipilimumab (MDX-010, MDX-101, Yervoy, BMS) and tremelimumab (Pfizer). The checkpoint inhibitor may be an antibody against PD- L1.

[0261] The Clec9A binding agent may act synergistically when co-administered with the anti-PD- L1 antibody. The Clec9A binding agent may act synergistically when co-administered with the anti-PD-L1 antibody for use in treating tumor or cancer. For example, co-administration of the Clec9A binding agent and the anti-PD-L1 antibody may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. The combination of the Clec9A binding agent and the anti-PD-L1 antibody may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. The Clec9A binding agent and the anti-PD-L1 antibody may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy.

[0262] Disclosed are combination therapies using the Clec9A binding agent and an immunosuppressive agent. Disclosed is the administration of the Clec9A binding agent to a patient undergoing treatment with an immunosuppressive agent. The immunosuppressive agent may be TNF.

[0263] The Clec9A binding agent may act synergistically when co-administered with TNF. The Clec9A binding agent may act synergistically when co-administered with TNF for use in treating tumor or cancer. For example, co-administration of the Clec9A binding agent and TNF may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. The combination of the Clec9A binding agent and TNF may exhibit improved safety profiles when compared to the agents used alone in the context of monotherapy. The Clec9A binding agent and TNF may be administered at doses that are lower than the doses employed when the agents are used in the context of monotherapy.

[0264] The Clec9A binding agent may act synergistically when used in combination with Chimeric Antigen Receptor (CAR) T-cell therapy. The Clec9A binding agent may act synergistically when used in combination with CAR T-cell therapy in treating tumor or cancer. The Clec9A binding agent may act synergistically when used in combination with CAR T-cell therapy in treating blood-based tumors. The Clec9A binding agent may act synergistically when used in combination with CAR T-cell therapy in treating solid tumors. For example, use of the Clec9A binding agent and CAR T-cells may act synergistically to reduce or eliminate the tumor or cancer, or slow the growth and/or progression and/or metastasis of the tumor or cancer. The Clec9A binding agent of the invention may induce CAR T-cell division. The Clec9A binding agent of the invention may induce CAR T-cell proliferation. The Clec9A binding agent of the invention may prevent anergy of the CAR T cells.

[0265] The CAR T-cell therapy may comprise CAR T cells that target antigens (e.g., tumor antigens) such as, but not limited to, carbonic anhydrase IX (CAIX), 5T4, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CS1, CD138, Lewis-Y, L1-CAM, MUC16, ROR-1, IL13Rα2, gp100, prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), B-cell maturation antigen (BCMA), human papillomavirus type 16 E6 (HPV-16 E6), CD171, folate receptor alpha (FR-a), GD2, human epidermal growth factor receptor 2 (HER2), mesothelin, EGFRvIII, fibroblast activation protein (FAP), carcinoembryonic antigen (CEA), and vascular endothelial growth factor receptor 2 (VEGF-R2), as well as other tumor antigens well known in the art. Additional illustrative tumor antigens include, but are not limited to MART-1/Melan-A, gp100, Dipeptidyl peptidase IV (DPPIV), adenosine deaminase-binding protein (ADAbp), cyclophilin b, Colorectal associated

antigen (CRC)- 0017-1A/GA733, Carcinoembryonic Antigen (CEA) and its immunogenic epitopes CAP-1 and CAP-2, etv6, aml1, Prostate Specific Antigen (PSA) and its immunogenic epitopes PSA-1, PSA-2, and PSA-3, T-cell receptor/CD3- zeta chain, MAGE-family of tumor antigens (e.g., MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-Xp2 (MAGE-B2), MAGE-Xp3 (MAGE-B3), MAGE-Xp4 (MAGE-B4), MAGE-C1, MAGE-C2, MAGE-C3, MAGE-C4, MAGE-C5), GAGE-family of tumor antigens (e.g., GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, GAGE-9), BAGE, RAGE, LAGE-1, NAG, GnT-V, MUM-1, CDK4, tyrosinase, p53, MUC family, HER2/neu, p21 ras, RCAS1, a-fetoprotein, E-cadherin, a-catenin, β-catenin and γ-catenin, p120ctn, gp100 PrneH 17, PRAME, NY-ESO-1, cdc27, adenomatous polyposis coli protein (APC), fodrin, Connexin 37, Ig- idiotype, p15, gp75, GM2 and GD2 gangliosides, viral products such as human papilloma virus proteins, Smad family of tumor antigens, Imp-1, NA, EBV-encoded nuclear antigen (EBNA)-1, brain glycogen phosphorylase, SSX-1, SSX-2 (HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1 CT-7, c-erbB-2, CD19, CD37, CD56, CD70, CD74, CD138, AGS16, MUC1, GPNMB, Ep-CAM, PD-L1, and PD-L2.

[0266] Exemplary CAR T-cell therapy include, but are not limited to, JCAR014 (Juno Therapeutics), JCAR015 (Juno Therapeutics), JCAR017 (Juno Therapeutics), JCAR018 (Juno Therapeutics), JCAR020 (Juno Therapeutics), JCAR023 (Juno Therapeutics), JCAR024 (Juno Therapeutics), CTL019 (Novartis), KTE-C19 (Kite Pharma), BPX-401 (Bellicum Pharmaceuticals), BPX-501 (Bellicum Pharmaceuticals), BPX-601 (Bellicum Pharmaceuticals), bb2121 (Bluebird Bio), CD-19 Sleeping Beauty cells (Ziopharm Oncology), U CART 19 (Collectis), UCART123 (Collectis), UCART38 (Collectis), UCARTCS1 (Collectis), OXB-302 (Oxford BioMedica), MB-101 (Mustang Bio) and CAR T-cells developed by Innovative Cellular Therapeutics.

[0267] The Clec9A binding agent may be used in a method of treating multiple sclerosis (MS) in combination with one or more MS therapeutics including, but not limited to, 3-interferons, glatiramer acetate, T- interferon, IFN-U-2 (U. S. Patent Publication No. 2002/0025304), spirogermaniums (e.g., N-(3-dimethylaminopropyl)-2-aza-8,8-dimethyl-8-germanspiro[4:5]decane, N-(3-dimethylaminopropyl)-2-aza-8,8- diethyl-8- germaspiro [4:5] decane, N-(3-dimethylaminopropyl)-2-aza-8,8-dipropyl-8-germaspiro [4:5] decane, and N-(3-dimethylaminopropyl)-2-aza-8, 8-dibutyl-8-germaspiro[4:5]decane), vitamin D analogs (e.g., 1,25 (OH) 2D3, (see, e.g., U.S. Patent No. 5,716,946)), prostaglandins (e.g., latanoprost, brimonidine, PGE1, PGE2 and PGE3, see, e.g., U. S. Patent Publication No. 2002/0004525), tetracycline and derivatives (e.g., minocycline and doxycycline, see, e.g., U.S. Patent Publication No. 20020022608), a VLA-4 binding antibody (see, e.g., U.S. Patent Publication No. 2009/0202527), adrenocorticotrophic hormone, corticosteroid, prednisone, methylprednisone, 2-chlorodeoxyadenosine, mitoxantrone, sulphasalazine, methotrexate, azathioprine, cyclophosphamide, cyclosporin, fumarate, anti-CD20 antibody (e.g., rituximab), and tizanidine hydrochloride.

[0268] The Clec9A binding agent may be used in combination with one or more therapeutic agents that treat one or more symptoms or side effects of MS. Such agents include, but are not limited to, amantadine, baclofen, papaverine, meclizine, hydroxyzine, sulfamethoxazole, ciprofloxacin, docusate, pemoline, dantrolene, desmopressin, dexamethasone, tolterodine, phenyloin, oxybutynin, bisacodyl, venlafaxine, amitriptyline, methenamine, clonazepam, isoniazid, vardenafil, nitrofurantoin, psyllium hydrophilic mucilloid, alprostadil, gabapentin, nortriptyline, paroxetine, propantheline bromide, modafinil, fluoxetine, phenazopyridine, methylprednisolone, carbamazepine, imipramine, diazepam, sildenafil, bupropion, and sertraline.

[0269] The Clec9A binding agent may be used in a method of treating multiple sclerosis in combination with one or more of the disease modifying therapies (DMTs) described herein (e.g. the agents of Table A). In some embodiments, the present invention provides an improved therapeutic effect as compared to use of one or more of the DMTs described herein (e.g. the agents listed in the Table below) without the one or more disclosed binding agent. In an embodiment, the combination of the Clec9A binding agent and the one or more DMTs produces synergistic therapeutic effects.

Illustrative Disease Modifying Therapies

[0270]		
Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
teriflunomide	AUBAGIO (GENZYME)	Every day; pill taken orally; 7 mg or 14 mg.
interferon beta-1a	AVONEX (BIODEN IDEC)	Once a week; intramuscular (into the muscle) injection; 30 mcg
interferon beta-1b	BETASERON (BAYER HEAL THCARE PHARMACEUTICALS, INC.)	Every other day; subcutaneous (under the skin) injection; 250 mcg.
glatiramer acetate	COPAXONE (TEVA NEUROSCIENCE)	Every day; subcutaneous (under the skin) injection; 20 mg (20,000 mcg) OR Three times a week; subcutaneous (under the skin) injection; 40 mg (40,000 mcg)
interferon beta1-b	EXTAVIA (NOVARTIS PHARMACEUTICALS CORP.)	Every other day; subcutaneous (under the skin) injection; 250 mcg.
fingolimod	GILENYA (NOVARTIS PHARMACEUTICALS CORP.)	Every day; capsule taken orally; 0.5 mg.
Alemtuzumab (anti-CD52 monoclonal antibody)	LEMTRADA (GENZYME)	Intravenous infusion on five consecutive days, followed by intravenous infusion on three consecutive days one year later (12 mg)
mitoxantrone	NOVANTRONE (EMD SERONO)	Four times a year by IV infusion in a medical facility. Lifetime cumulative dose limit of approximately 8-12 doses over 2-3 years (140 mg/m2).
pegylated interferon beta-1a	PLEGRIDY (BIOGEN IDEC)	Every 14 days; subcutaneous (under the skin) injection; 125 mcg
interferon beta-1a	REBIF (EMD SERONO, INC.)	Three times a week; subcutaneous (under the skin) injection; 44 mcg
dimethyl fumarate (BG-12)	TECFIDERA (BIODEN IDEC)	Twice a day; capsule taken orally; 120 mg for one week and 240 mg thereafter

Generic Name	Branded Name/Company	Frequency/Route of Delivery/Usual Dose
Natalizumab (humanized monoclonal antibody VLA-4 antagonist)	TYSABRI (BIOGEN IDEC)	Every four weeks by IV infusion in a registered infusion facility; 300 mg
DMTs in Development		
Amiloride (targets Acid-sensing ion channel-1 Epithelial sodium channel Na ⁺ /H ⁺ exchanger)	PAR PHARMACEUTICAL, PERRIGO COMPANY, SIGMAPHARM LABORATORIES	Oral
ATX-MS-1467 (targets Major histocompatibility complex class II T cell responses to myelin basic protein)	APITOPE / MERCK SERONO	Intradermal Subcutaneous
BAF312 (targets Sphingosine 1-phosphate (S1P) receptor subtypes S1P1 and S1P5 B cell distribution T cell distribution)	NOVARTIS PHARMA	Oral
BGC20-0134 (targets Proinflammatory and anti-inflammatory cytokines)	BTG PLC	Oral
BLIB033 (targets LINGO-1 ("leucine rich repeat and immunoglobulin-like domain-containing, Nogo receptor-interacting protein"))	BIOGEN	Intravenous infusion used in Phase I and Phase II trials Subcutaneous injection used in Phase I trial
Cladribine (targets CD4+T cell DNA synthesis and repair E-selectin Intracellular adhesion molecule-1 Pro-inflammatory cytokines interleukin 2 and interleukin 2R Pro-inflammatory cytokines interleukin 8 and RANTES Cytokine secretion Monocyte and lymphocyte migration)	MERCK SERONO	Oral
Cyclophosphamide (targets T cells, particularly CD4+ helper T cells B cells)	BAXTER HEALTHCARE CORPORATION	Oral, monthly intravenous pulses
Daclizumab (humanized monoclonal antibody targeting CD25 Immune modulator of T cells)	BIOGEN IDEC/ABBVIE BIOTHERAPEUTICS	Projected to be IM injection once monthly
Dalfampridine (targets Voltage-gated potassium channels Degenerin/epithelial sodium channels L-type calcium channels that contain subunit Cavbeta3)	ACORDA THERAPEUTICS / BIOGEN IDEC	One tablet every 12 hours (extended release), 10 mg twice a day
Dronabinol (targets Cannabinoid receptor CB1 Cannabinoid receptor CB2)	ABBVIE INC.	Oral
Fingolimod (targets Alpha4beta1 integrin)	GLAXOSMITHKLINE	Oral
GNbAC1 MSRV-Env (targets envelope protein of the MS-associated retrovirus)	GENEURO SA/ SERVIER	Intravenous infusion
Idebenone (targets Reactive oxygen species)	SANTHERA PHARMACEUTICALS	Oral Dose in clinical trial for PPMS is 2250 mg per day (750 mg dose, 3 times per day)
Imilecleucel-T (targets Myelin-specific, autoreactive T cells)	OPEXA THERAPEUTICS / MERCK SERONO	Subcutaneous Given 5 times per year, according to information from the manufacturer
Laquinimod	TEVA	Projected to be 0.6 mg or 1.2 mg oral tablet taken daily
Masitinib (targets KIT (a stem cell factor, also called c-KIT) receptor as well as select other tyrosine kinases Mast cells)	AB SCIENCE	Oral
MEDI-551 (targets CD19, a B cell-specific antigen that is part of the B cell receptor complex and that functions in determining the threshold for B cell activation B cells Plasmablasts, B cells that express CD19 (but not CD20) and that secrete large quantities of antibodies; depletion of plasmablasts may be useful in autoimmune diseases involving pathogenic autoantibodies)	MEDIMMUNE	Intravenous Subcutaneous
Minocycline (targets T cells Microglia Leukocyte migration Matrix metalloproteases)	VARIOUS	Oral Available as pellet-filled capsules and an oral suspension
MIS416 (targets Innate immune system Pathogen-associated molecular pattern recognition receptors of the innate immune system Myeloid cells of the innate immune system, which might be able to remodel the deregulated immune system activity that occurs in SPMS)	INNATE IMMUNOTHERAPEUTICS	Intravenous
Mycophenolate mofetil (targets Purine synthesis)	MANUFACTURED BY GENENTECH	Oral
Naltrexone (targets Opioid receptors Toll-like receptor 4)	VARIOUS	Given at low dose (3 to 4.5 mg per day) in oral form as "Low-dose naltrexone" (or "LDN")
Ocrelizumab and Ofatumumab (humanized monoclonal antibodies targeting CD20 B cell suppression)	ROCHE/GSK	Projected to be IV infusion
ONO-4641 (targets Sphingosine 1-phosphate receptor)	ONO PHARMACEUTICAL CO.	Oral
Phenytoin (targets Sodium channels)	PFIZER	Intravenous Intramuscular (less favored option) Oral
Ponesimod	ACTELION	To be determined
Raltegravir (targets Retroviral integrase Herpesvirus DNA packaging terminase)	MERCK	Oral 400 mg tablet twice daily, according to information from the manufacturer
RHB-104	REDHILL BIOPHARMA LIMITED	95 mg clarithromycin, 45 mg rifabutin, and 10 mg clofazimine
Riluzole (targets Glutamatergic neurotransmission Glutamate		

DMTs in Develop pment		
uptake and release Voltage-gated sodium channels Protein kinase C)	COVIS PHARMA / SANOFI	Oral

[0271] MS disease progression may be most intensive, and most damaging, at the earliest stages of disease progression. Accordingly, counter to many reimbursement policies and physician practice in light of, for example, costs and side effect mitigation, it may be most beneficial for a patient's long term disease status to begin treatment with the most intensive DMTs, for instance so-called second-line therapies. In some embodiments, a patient is treated with a regimen of the Clec9A binding agent in combination with a second-line therapy. Such a combination is used to reduce the side effect profile of one or more second-line therapies. In some embodiments, the combination is used to reduce dose of frequency of administration of one or more second-line therapies. For example, the doses of agents listed in the Table provided above may be reduced by about 50%, or about 40%, or about 30%, or about 25% in the context of the combination and the/or the frequency of dosing may be decreased to be half as often, or a third as often or may be reduced from, for example, daily to every other day or weekly, every other day to weekly or bi-weekly, weekly to bi-weekly or monthly, etc. Accordingly, in some embodiments, the Clec9A binding agent increase patient adherence by allowing for more convenient treatment regimens. Further, some DMTs have a suggested lifetime dose limitation e.g. for mitoxantrone, the lifetime cumulative dose should be strictly limited to 140 mg/m², or 2 to 3 years of therapy. In some embodiments, supplementation with the Clec9A binding agent preserves patient's access to mitoxantrone by allowing for lower or less frequent dosing with this DMT.

[0272] The patient may be a naive patient, who has not received treatment with one or more DMTs, and the Clec9A binding agent is used to buffer the side effects of a second-line therapy. Accordingly, the naive patient is able to benefit from the long-term benefits of a second-line therapy at disease outset. In some embodiments, the Clec9A binding agent is used as an entry therapy that precedes the use of a second-line therapy. For example, the Clec9A binding agent may be administered for an initial treatment period of about 3 months to stabilize disease and then the patient may be transitioned to a maintenance therapy of a second line agent.

[0273] It is generally believed that naive patients are more likely to respond to therapy as compared to patients that have received, and perhaps failed one or more DMT. In some embodiments, the Clec9a binding agent finds use in patients that have received, and perhaps failed one or more DMT. For example, the Clec9A binding agent may increase the therapeutic effect in patients that have received, and perhaps failed one or more DMT and may allow these patients to respond like naive patients.

[0274] The patient may have received or may be receiving treatment with one or more DMTs and may not be responding well. For example, the patient may be refractory or poorly responsive to one or more DMTs. In some embodiments, the patient is refractory, or poorly responsive to one or more of teriflunomide (AUBAGIO (GENZYME)); interferon beta-1a (AVONEX (BIOGEN IDEC); interferon beta-1 b (BETASERON (BAYER HEALTHCARE PHARMACEUTICALS, INC.); glatiramer acetate (COPAXONE (TEVA NEUROSCIENCE); interferon beta-1b (EXTAVIA (NOVARTIS PHARMACEUTICALS CORP.); fingolimod (GILENYA (NOVARTIS PHARMACEUTICALS CORP.); alemtuzumab (LEMTRADA (GENZYME); mitoxantrone (NOVANTRONE (EMD SERONO); pegylated interferon beta-1a (PLEGRIDY (BIOGEN IDEC); interferon beta-1a (REBIF (EMD SERONO, INC.); dimethyl fumarate (BG-12) (TECFIDERA (BIOGEN IDEC); and natalizumab (TYSABRI (BIOGEN IDEC). The one or more disclosed binding agent may result in a therapeutic benefit of one or more DMTs in the patient and therefore reduces or eliminates the non-responsiveness to the DMT. For instance, this may spare the patient therapy with one or more DMTs at a higher dosing or frequency.

[0275] In patients with more aggressive disease, one approach is an induction treatment model, where a therapy with strong efficacy but strong safety concerns would be given first, followed by a maintenance therapy. An example of such a model might include initial treatment with alemtuzumab, followed by IFN-β, GA, or BG-12. The one or more disclosed binding agent may be used to prevent the need to switch therapies for maintenance. The one or more disclosed binding agent may be used to as maintenance therapy to one or more DMTs, including second line therapies. The one or more disclosed binding agent may be used to as first therapy in an induction, followed by another DMT as a maintenance therapy- such as, for example, a first line therapy.

[0276] The one or more disclosed binding agent may be administered for an initial treatment period of about 3 months to stabilize disease and then the patient may be transitioned to a maintenance therapy of a first line agent.

[0277] The one or more disclosed binding agent may be used to reduce one or more side effects of a DMT, including without limitation any agent disclosed herein. For example, the one or more disclosed binding agent may be used in a regimen that allows dose sparing for one or more DMTs and therefore results in fewer side effects. For example, the one or more disclosed binding agent may may reduce one or more side effects of AUBAGIO or related agents, which may include hair thinning, diarrhea, flu, nausea, abnormal liver tests and unusual numbness or tingling in the hands or feet (paresthesias), levels of white blood cells, which can increase the risk of infections; increase in blood pressure; and severe liver damage. The one or more disclosed binding agent may reduce one or more side effects of AVONEX or related agents which include flu-like symptoms following injection, depression, mild anemia, liver abnormalities, allergic reactions, and heart problems. The one or more disclosed binding agent may reduce one or more side effects of BETASERON or related agents which include flu-like symptoms following injection, injection site reactions, allergic reactions, depression, liver abnormalities, and low white blood cell counts. The one or more disclosed binding agent may reduce one or more side effects of COPAXONE or related agents which include injection site reactions, vasodilation (dilation of blood vessels); chest pain; a reaction immediately after injection, which includes anxiety, chest pain, palpitations, shortness of breath, and flushing. The one or more disclosed binding agent may reduce one or more side effects of EXTAVIA or related agents which include flu-like symptoms following injection, injection site reactions, allergic reactions, depression, liver abnormalities, and low white blood cell counts. The one or more disclosed binding agent may reduce one or more side effects of GILENYA or related agents which include headache, flu, diarrhea, back pain, liver enzyme elevations, cough, slowed heart rate following first dose, infections, and swelling in the eye. The one or more disclosed binding agent may reduce one or more side effects of LEMTRADA or related agents which include rash, headache, fever, nasal congestion, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, hives, itching, thyroid gland disorders, fungal Infection, pain in joints, extremities and back, diarrhea, vomiting, flushing, and infusion reactions (including nausea, hives, itching, insomnia, chills, flushing, fatigue, shortness of breath, changes in the sense of taste, indigestion, dizziness, pain). The one or more disclosed binding agent may reduce one or more side effects of NOVANTRONE or related agents which include blue-green urine 24 hours after administration; infections, bone marrow suppression (fatigue, bruising, low blood cell counts), nausea, hair thinning, bladder infections, mouth sores, and serious liver and heart damage. The one or more disclosed binding agent may reduce one or more side effects of PLEGIDY or related agents which include flu-like symptoms following injection, injection site reactions, depression, mild anemia, liver abnormalities, allergic reactions, and heart problems. The one or more disclosed binding agent may reduce one or more side effects of REBIF or related agents which include flu-like symptoms following injection, injection site reactions, liver abnormalities, depression, allergic reactions, and low red or white blood cell counts. In some embodiments, one or more disclosed binding agent may reduce one or more side effects of TECFIDERA or related agents which include flushing (sensation of heat or itching and a blush on the skin), gastrointestinal issues (nausea, diarrhea, abdominal pain), rash, protein in the urine, elevated liver enzymes; and reduction in blood lymphocyte (white blood cell) counts. The one or more disclosed binding agent may reduce one or more side effects of TYSABRI or related agents which include headache, fatigue, urinary tract infections, depression, respiratory tract infections, joint pain, upset stomach, abdominal discomfort, diarrhea, vaginitis, pain in the arms or legs, rash, allergic or hypersensitivity reactions within two hours of infusion (dizziness, fever, rash, itching, nausea, flushing, low blood pressure, difficulty breathing, chest pain).

[0278] Disclosed is a combination therapy with one or more chimeric agents described in WO 2013/10779, WO 2015/007536, WO 2015/007520, WO 2015/007542, and WO 2015/007903.

[0279] Disclosed are anti-infectives as additional therapeutic agents. The anti-infective may be an antiviral agent including, but not limited to, Abacavir, Acyclovir, Adefovir, Amprenavir, Atazanavir, Cidofovir, Darunavir, Delavirdine, Didanosine, Docosanol, Efavirenz, Elvitegravir, Emtricitabine, Enfuvirtide, Etravirine, Famciclovir, and Foscarnet. The anti-infective may be an anti-bacterial agent including, but not limited to, cephalosporin antibiotics (cephalexin, cefuroxime, cefadroxil, cefazolin, cephalothin, cefaclor, cefamandole, cefoxitin, cefprozil, and ceftobiprole); fluoroquinolone antibiotics (cipro, Levaquin, floxin, tequin, avelox, and norflox); tetracycline antibiotics (tetracycline, minocycline, oxytetracycline, and doxycycline); penicillin antibiotics (amoxicillin, ampicillin, penicillin V, dicloxacillin, carbenicillin, vancomycin, and methicillin); monobactam antibiotics (aztreonam); and carbapenem antibiotics (ertapenem, doripenem, imipenem/cilastatin, and meropenem). The anti-infectives may include anti-malarial agents (e.g., chloroquine, quinine, mefloquine, primaquine, doxycycline, artemether/lumefantrine, atovaquone/proguanil and sulfadoxine/pyrimethamine), metronidazole, tinidazole, ivermectin, pyrantel pamoate, and albendazole.

[0280] The additional therapeutic agent may be an immunosuppressive agent. The immunosuppressive agent may be an antiinflammatory agent such as a steroidal anti-inflammatory agent or a non-steroidal anti-inflammatory agent (NSAID). Steroids, particularly the adrenal corticosteroids and their synthetic analogues, are well known in the art. Examples of useful corticosteroids include, without limitation, hydroxyltriamcinolone, alpha-methyl dexamethasone, beta-methyl betamethasone, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, clobetasol valerate, desonide, desoxymethasone, dexamethasone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, flucolorolone acetonide, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, clocortelone, clescinalone, dichlorisone, difluprednate, flucoloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate. (NSAIDS) that may be used include but are not limited to, salicylic acid, acetyl salicylic acid, methyl salicylate, glycol salicylate, salicylides, benzyl-2,5-diacetoxybenzoic acid, ibuprofen, fulindac, naproxen, ketoprofen, etofenamate, phenylbutazone, and indomethacin. The immunosuppressive agent may be cytostatics such as alkylating agents, antimetabolites (e.g., azathioprine, methotrexate), cytotoxic antibiotics, antibodies (e.g., basiliximab, daclizumab, and muromonab), anti-immunophilins (e.g., cyclosporine, tacrolimus, sirolimus), inteferons, opioids, TNF binding proteins, mycophenolates, and small biological agents (e.g., fingolimod, myriocin). Additional anti-inflammatory agents are described, for example, in U.S. Patent No. 4,537,776.

[0281] The Clec9A binding agent described herein may include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the composition such that covalent attachment does not prevent the activity of the composition. For example, but not by way of limitation, derivatives include composition that have been modified by, inter alia, glycosylation, lipidation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications can be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. In still other embodiments, the Clec9A binding agent described herein further comprise a cytotoxic agent, comprising, in illustrative embodiments, a toxin, a chemotherapeutic agent, a radioisotope, and an agent that causes apoptosis or cell death. Such agents may be conjugated to a composition described herein.

[0282] The Clec9A binding agent described herein may thus be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0283] Illustrative cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimetotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicin, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotane (0,P¹-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0284] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine, bleomycin, VEGF antagonists, EGFR antagonists, platins, taxols, irinotecan, 5-fluorouracil, gemcytabine, leucovorine, steroids, cyclophosphamide, melphalan, vinca alkaloids (e.g., vinblastine, vincristine, vindesine and vinorelbine), mustines, tyrosine kinase inhibitors, radiotherapy, sex hormone antagonists, selective androgen receptor modulators, selective estrogen receptor modulators, PDGF antagonists, TNF antagonists, IL-1 antagonists, interleukins (e.g. IL-12 or IL-2), IL-12R antagonists, Toxin conjugated monoclonal antibodies, tumor antigen specific monoclonal antibodies, Erbitux, Avastin, Pertuzumab, anti-CD20 antibodies, Rituxan, ocrelizumab, ofatumumab, DXL625, HERCEPTIN®, or any combination thereof. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and Pseudomonas toxin may be conjugated to the therapeutic agents (e.g. antibodies) to generate cell-type-specific-killing reagents (Youle, et al., Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, et al., Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

[0285] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the Clec9A binding agent, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32, Scandium-47, Copper-67, Gallium-67, Yttrium-88, Yttrium-90, Iodine-125, Iodine-131, Samarium-153, Lutetium-177, Rhenium-186 or Rhenium-188, and alpha-emitters such as Astatine-211, Lead-212, Bismuth-212, Bismuth-213 or Actinium-225.

[0286] Illustrative detectable moieties further include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further illustrative fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further illustrative chemiluminescent moieties include, but are not limited to, luminol. Further illustrative bioluminescent materials include, but are not limited to, luciferin and aequorin. Further illustrative radioactive materials include, but are not limited to, Iodine-125, Carbon-14, Sulfur-35, Tritium and Phosphorus-32.

Methods of Treatment

[0287] Methods and compositions described herein have application to treating various diseases and disorders, including, but not limited to cancer, infections, immune disorders, and inflammatory diseases or conditions.

[0288] Further, any of the present agents may be for use in the treating, or the manufacture of a medicament for treating, various diseases and disorders, including, but not limited to cancer, infections, immune disorders, inflammatory diseases or conditions, and autoimmune diseases.

[0289] Disclosed is the treatment of, or a patient having cancer. As used herein, cancer refers to any uncontrolled growth of cells that may interfere with the normal functioning of the bodily organs and systems, and includes both primary and metastatic tumors. Primary tumors or cancers that migrate from their original location and seed vital organs can eventually lead to the death of the subject through the functional deterioration of the affected organs. A metastasis is a cancer cell or group of cancer cells, distinct from the primary tumor location, resulting from the dissemination of cancer cells from the primary tumor to other parts of the body. Metastases may eventually result in death of a subject. For example, cancers can include benign and malignant cancers, polyps, hyperplasia, as well as dormant tumors or micrometastases.

[0290] Illustrative cancers that may be treated include, but are not limited to, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (*e.g.* that associated with brain tumors), and Meigs' syndrome.

[0291] In various embodiments, the present invention provides Clec9A binding agents which are part of a chimera that further comprises modified signaling agents for use in the treatment of cancer. In some embodiments, the Clec9A binding agents of the invention significantly reduce and/or eliminate tumors. In some embodiments, the present Clec9A binding agents significantly reduce and/or eliminate tumors when administered to a subject in combination with other anti-cancer agents such as chemotherapeutic agents, checkpoint inhibitors, and immunosuppressive agents. In various embodiments, the combination of Clec9A binding agents and other anti-cancer agents synergistically reduced tumor size and/or eliminated tumor cells.

[0292] Disclosed are cancer combination therapies with a Clec9A binding agent that is part of a chimera comprising one or more targeting moieties and one or more modified signaling agents. Accordingly, chimeric or fusion proteins are provided that include, for example, a targeting moiety against Clec9A and one or more signaling agents and uses thereof in combination with anticancer agents.

[0293] For instance, disclosed are combination therapies for cancer involving chimeras of a Clec9A binding agent described herein and a modified signaling agent, including, without limitation a mutated human interferon, such as IFN alpha, including human interferon alpha 2.

[0294] The present Clec9A binding agent may be part of a chimera that comprises multiple targeting moieties and therefore be present in bispecific or trispecific formats. For instance, disclosed are combination therapies for cancer involving chimeras of a Clec9A binding agent and a checkpoint inhibitor binding agent (*e.g.* anti-PD-L1, anti-PD-1, anti-PD-L2, or anti-CTLA) described herein and a modified signaling agent, including, without limitation a mutated human interferon, such as IFN alpha, including human interferon alpha 2.

[0295] The signaling agent may be modified to have reduced affinity or activity for one or more of its receptors, which allows for attenuation of activity (inclusive of agonism or antagonism) and/or prevents nonspecific signaling or undesirable sequestration of the chimeric protein. The reduced affinity or activity at the receptor may be restorable by attachment with one or more of the targeting moieties described herein. Disclosed is the treatment of, or a patient having a microbial infection and/or chronic infection. Illustrative infections include, but are not limited to, HIV/AIDS, tuberculosis, osteomyelitis, hepatitis B, hepatitis C, Epstein-Barr virus or parvovirus, T cell leukemia virus, bacterial overgrowth syndrome, fungal or parasitic infections.

[0296] The present compositions may be used to treat or prevent one or more inflammatory diseases or conditions, such as inflammation, acute inflammation, chronic inflammation, respiratory disease, atherosclerosis, restenosis, asthma, allergic rhinitis, atopic dermatitis, septic shock, rheumatoid arthritis, inflammatory bowel disease, inflammatory pelvic disease, pain, ocular inflammatory disease, celiac disease, Leigh Syndrome, Glycerol Kinase Deficiency, Familial eosinophilia (FE), autosomal recessive spastic ataxia, laryngeal inflammatory disease; Tuberculosis, Chronic cholecystitis, Bronchiectasis, Silicosis and other pneumoconioses.

[0297] Disclosed is the treatment of autoimmune and/or neurodegenerative diseases.

[0298] The present compositions may be used to treat or prevent one or more conditions characterized by undesirable CTL activity, and/or a conditions characterized by high levels of cell death. For instance, the present compositions may be used to treat or prevent one or more conditions associated with uncontrolled or overactive immune response.

[0299] The present compositions may be used to treat or prevent one or more autoimmune and/or neurodegenerative diseases or conditions, such as MS, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia, Menier's syndrome; transplantation rejection (*e.g.*, prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, Grave's disease, and other autoimmune diseases.

[0300] Disclosed is the treatment or prevention of various autoimmune and/or neurodegenerative diseases. The autoimmune and/or neurodegenerative diseases may be selected from MS (including without limitation the subtypes described herein), Alzheimer's disease (including, without limitation, Early-onset Alzheimer's, Late-onset Alzheimer's, and Familial Alzheimer's disease (FAD), Parkinson's disease and parkinsonism (including, without limitation, Idiopathic Parkinson's disease, Vascular parkinsonism, Drug-induced parkinsonism, Dementia with Lewy bodies, Inherited Parkinson's, Juvenile Parkinson's), Huntington's disease, Amyotrophic lateral sclerosis (ALS, including, without limitation, Sporadic ALS, Familial ALS, Western Pacific ALS, Juvenile ALS, Hiramaya Disease).

[0301] Disclosed is the treatment or prevention of MS. The Clec9a binding agents as described herein may be used to eliminate and reduce multiple MS symptoms. Illustrative symptoms associated with multiple sclerosis, which can be prevented or treated with the compositions and methods described herein, include: optic neuritis, diplopia, nystagmus, ocular dysmetria, internuclear ophthalmoplegia, movement and sound phosphenes, afferent pupillary defect, paresis, monoparesis, paraparesis, hemiparesis, quadraparesis, plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, footdrop, dysfunctional reflexes, paraesthesia, anaesthesia, neuralgia, neuropathic and neurogenic pain, l'hermitte's sign, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor-sphincter dyssynergia, erectile dysfunction, anorgasmy, frigidity, constipation, fecal urgency, fecal incontinence, depression, cognitive dysfunction, dementia, mood swings, emotional lability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, fatigue, Uhthoffs symptom, gastroesophageal reflux, and sleeping disorders. Mitigation or amelioration or one more of these symptoms in a subject can be achieved by the one or more agent as described herein.

[0302] The Clec9A binding agents as described herein may be used to treat or prevent clinically isolated syndrome (CIS). A clinically isolated syndrome (CIS) is a single monosymptomatic attack compatible with MS, such as optic neuritis, brain stem symptoms, and partial myelitis. Patients with CIS that experience a second clinical attack are generally considered to have clinically definite multiple sclerosis (CDMS). Over 80 percent of patients with CIS and MRI lesions go on to develop MS, while approximately 20 percent have a self- limited process. Patients who experience a single clinical attack consistent with MS may have at least one lesion consistent with multiple sclerosis prior to the development of clinically definite multiple sclerosis. In various embodiments, the presently described Clec9a binding agents is used to treat CIS so it does not develop into MS, including, for example RRMS.

[0303] The Clec9A binding agents as described herein may be used to treat or prevent radiologically isolated syndrome (RIS). In RIS, incidental imaging findings suggest inflammatory demyelination in the absence of clinical signs or symptoms. The Clec9A binding agent may be used to treat RIS so it does not develop into MS, including, for example RRMS.

[0304] The Clec9A binding agents as described herein may be used to treat one or more of benign multiple sclerosis; relapsing-remitting multiple sclerosis (RRMS); secondary progressive multiple sclerosis (SPMS); progressive relapsing multiple sclerosis (PRMS); and primary progressive multiple sclerosis (PPMS).

[0305] Benign multiple sclerosis is a retrospective diagnosis which is characterized by 1-2 exacerbations with complete recovery, no lasting disability and no disease progression for 10-15 years after the initial onset. Benign multiple sclerosis may, however, progress into other forms of multiple sclerosis. The Clec9a binding agent may be used to treat benign multiple sclerosis so it does not develop into MS.

[0306] Patients suffering from RRMS experience sporadic exacerbations or relapses, as well as periods of remission. Lesions and evidence of axonal loss may or may not be visible on MRI for patients with RRMS. The Clec9a binding agents as described herein may be used to treat RRMS. RRMS may include patients with RRMS; patients with SPMS and superimposed relapses; and patients with CIS who show lesion dissemination on subsequent MRI scans according to McDonald's criteria. A clinical relapse, which may also be used herein as "relapse," "confirmed relapse," or "clinically defined relapse," is the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities. This change in clinical state must last at least 48 hours and be immediately preceded by a relatively stable or improving neurological state of at least 30 days. In some embodiments, an event is counted as a relapse when the subject's symptoms are accompanied by observed objective neurological changes, consistent with an increase of at least 1.00 in the Expanded Disability Status Scale (EDSS) score or one grade in the score of two or more of the seven FS or two grades in the score of one of FS as compared to the previous evaluation.

[0307] SPMS may evolve from RRMS. Patients afflicted with SPMS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RRMS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SPMS. The Clec9a binding agents as described herein may be used to treat RRMS so it does not develop into SPMS.

[0308] PPMS is characterized by a steady progression of increasing neurological deficits without distinct attacks or remissions. Cerebral lesions, diffuse spinal cord damage and evidence of axonal loss are evident on the MRI of patients with PPMS. PPMS has periods of acute exacerbations while proceeding along a course of increasing neurological deficits without remissions. Lesions are evident on MRI of patients suffering from PRMS. The Clec9A binding agent as described herein may be used to treat RRMS and/or SPMS so it does not develop into PPMS.

[0309] The Clec9A binding agents as described herein may be used in a method of treatment of relapsing forms of MS. The Clec9A binding agent may be used in a method of treatment of relapsing forms of MS to slow the accumulation of physical disability and/or reduce the frequency of clinical exacerbations, and, optionally, for patients who have experienced a first clinical episode and have MRI features consistent with MS. The Clec9a binding agents as described herein may be used in a method of treatment of worsening relapsing-remitting MS, progressive-relapsing MS or secondary-progressive MS to reduce neurologic disability and/or the frequency of clinical exacerbations. The Clec9A binding agents may reduce the frequency and/or severity of relapses.

[0310] The Clec9A binding agents may be used in a method of treatment of relapsing forms of MS in patients who have had an inadequate response to (or are refractory to) one, or two, or three, or four, or five, or six, or seven, or eight, or nine, or ten or more disease modifying therapies (DMTs).

[0311] The subject's symptoms may be assessed quantitatively, such as by EDSS, or decrease in the frequency of relapses, or increase in the time to sustained progression, or improvement in the magnetic resonance imaging (MRI) behavior in frequent, serial MRI studies and compare the patient's status measurement before and after treatment. In a successful treatment, the patient status will have improved (e.g., the EDSS measurement number or frequency of relapses will have decreased, or the time to sustained progression will have increased, or the MRI scans will show less pathology).

[0312] The patient can be evaluated, e.g., before, during or after receiving the Clec9a binding agents e.g., for indicia of responsiveness. Various clinical or other indicia of effectiveness of treatment, e.g., EDSS score; MRI scan; relapse number, rate, or severity; multiple sclerosis functional composite (MSFC); multiple sclerosis quality of life inventory (MSQLI); Paced Serial Addition Test (PASAT); symbol digit modalities test (SDMT); 25-foot walk test; 9-hole peg test; low contrast visual acuity; Modified Fatigue Impact Scale; expanded disability status score (EDSS); multiple sclerosis functional composite (MSFC); Beck Depression Inventory; and 7/24 Spatial Recall Test can be used. In various embodiments, the Clec9A binding agents cause an improvement in one or more of these measures. Further, the patient can be monitored at various times during a regimen. The Clec9a binding agents may cause a disease improvement as assessed by MacDonald dissemination in space and time. For example, for dissemination in space, lesion imaging, such as, by way of illustration, Barkhof-Tintore MR imaging criteria, may be used, including at least one gadolinium- enhancing lesion or 9 T2 hyperintense lesions; at least one infratentorial lesion; at least one juxtacortical lesion; at least about three periventricular lesions; and a spinal cord lesion. For dissemination in time, MRI can also be used; for example, if an MRI scan of the brain performed at ≥ 3 months after an initial clinical event demonstrates a new gadolinium-enhancing lesion, this may indicate a new CNS inflammatory event, because the duration of gadolinium enhancement in MS is usually less than 6 weeks. If there are no gadolinium-enhancing lesions but a new T2 lesion (presuming an MRI at the time of the initial event), a repeat MR imaging scan after another 3 months may be needed with demonstration of a new T2 lesion or gadolinium-enhancing

lesion.

[0313] Disease effects may be assessed using any of the measures described in Lavery, et al. Multiple Sclerosis International, Vol 2014 (2014), Article ID 262350.

[0314] The Clec9A binding agent may result in one or more of: (a) prevention of worsening in disability defined as deterioration by 1.0 point on EDSS, (b) increase in time to relapse, (c) reduction or stabilization of number and/or volume of gadolinium enhancing lesions, (d) decreased annualized relapse rate, (e) increased relapse duration and severity by NRS score, (f) decrease in disease activity as measured by MRI (annual rate of new or enlarging lesions), (g) lower average number of relapses at 1 year, or 2 years, (h) sustained disease progression as measured by the EDSS at 3 months, (i) prevention of conversion to CDMS, (j) no or few new or enhancing T2 lesions, (k) minimal change in hyperintense T2 lesion volume, (l) increased time to McDonald defined MS, (m) prevention of progression of disability as measured by sustained worsening of EDSS at 12 weeks, (n) reduction in time to relapse at 96 weeks, and (o) reduction or stabilization of brain atrophy (e.g. percentage change from baseline). The Clec9A binding agents may be administered and is effective to result in a decreased rate of relapse (e.g., at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or greater reduction in rate of relapse) compared to the rate of relapse before administration (e.g., compared to the rate of relapse following administration for 12 months or for less than 12 months, e.g., about 10, or about 8, or about 4, or about 2 or less months) of treatment, or before commencement of treatment, when measured between 3-24 months (e.g., between 6-18 months, e.g., 12 months) after a previous relapse.

[0315] The Clec9A binding agents may be administered and may be effective to result in a prevention of an increase in EDSS score from a pre-treatment state. The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The EDSS replaced the previous Disability Status Scales which used to bunch people with MS in the lower brackets. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and cerebral.

[0316] The Clec9A binding agents may be administered and may be effective to result in a decreased EDSS score (e.g., a decrease of 1, 1.5, 2, 2.5, 3 points or more, e.g., over at least three months, six months, one year, or longer) compared to the EDSS score following administration of the Clec9a binding agents (e.g. for 12 months or for less than 12 months, e.g., less than 10, 8, 4 or less months, or before the commencement of treatment).

[0317] The Clec9A binding agents may be administered and may be effective to result in a decreased number of new lesions overall or of any one type (e.g., at least 10%, 20%, 30%, 40% decrease), compared to the number of new lesions following administration of the Clec9A binding agents for 12 months or for less than 12 months, e.g., less than 10, 8, 4 or less months, or before commencement of treatment;

[0318] The Clec9A binding agents may be administered and may be effective to result in a decreased number of lesions overall or of any one type (e.g., at least 10%, 20%, 30%, 40% decrease), compared to the number of lesions following administration of the Clec9a binding agents for 12 months or for less than 12 months, e.g., less than 10, 8, 4 or less months, or before commencement of treatment;

[0319] The Clec9A binding agents may be administered and may be effective to result in a reduced rate of appearance of new lesions overall or of any one type (e.g., at least 10%, 20%, 30%, 40% reduced rate), compared to the rate of appearance of new lesions following administration for 12 months or for less than 12 months, e.g., less than 10, 8, 4 or less months, or before commencement of treatment;

[0320] The Clec9A binding agents may be administered and may be effective to result in a reduced increase in lesion area overall or of any one type (e.g., at least 10%, 20%, 30%, 40% decreased increase), compared to an increase in lesion area following administration for 12 months or less than 12 months, e.g., less than 10, 8, 4 or less months, or before commencement of treatment.

[0321] The Clec9A binding agents may be administered and may be effective to result in a reduced incidence or symptom of optic neuritis (e.g., improved vision), compared to the incidence or symptom of optic neuritis following administration for 12 months or for less than 12 months, e.g., less than 10, 8, 4 or less months, or before commencement of treatment.

[0322] The present methods may be useful in treatment a human subject. The human may be a pediatric human. The human may be an adult human. The human may be a geriatric human. The human may be referred to as a patient. The human may be a female. The human may be a male.

[0323] The human may have an age in a range of from about 1 to about 18 months old, from about 18 to about 36 months old, from about 1 to about 5 years old, from about 5 to about 10 years old, from about 10 to about 15 years old, from about 15 to about 20 years old, from about 20 to about 25 years old, from about 25 to about 30 years old, from about 30 to about 35 years old, from about 35 to about 40 years old, from about 40 to about 45 years old, from about 45 to about 50 years old, from about 50 to about 55 years old, from about 55 to about 60 years old, from about 60 to about 65 years old, from about 65 to about 70 years old, from about 70 to about 75 years old, from about 75 to about 80 years old, from about 80 to about 85 years old, from about 85 to about 90 years old, from about 90 to about 95 years old or from about 95 to about 100 years old. The human may have an age of more than 30 years old.

Immune Modulation

[0324] The present compositions may be capable of, or find use in methods of, immune modulation. For instance, the disclosed methods of treatment may involve the immune modulation described herein. The immune modulation may involve IFN signaling, including modified IFN signaling, in the context of a dendritic cell (DC).

[0325] A multi-specific Clec9a binding agent is provided. Such multi- specific Clec9a binding agent of the invention recognizes and binds to Clec9A and one or more antigens found on one or more immune cells, which can include, without limitation, megakaryocytes, thrombocytes, erythrocytes, mast cells, basophils, neutrophils, eosinophils, monocytes, macrophages, natural killer cells, T lymphocytes (e.g., cytotoxic T lymphocytes, T helper cells, natural killer T cells), B lymphocytes, plasma cells, dendritic cells, or subsets thereof. In some embodiments, the Clec9A binding agent specifically binds to an antigen of interest and effectively directly or indirectly recruits one of more immune cells.

[0326] The Clec9a binding agent may specifically bind to an antigen of interest and effectively directly or indirectly recruits one of more immune cells to cause an immunosuppressive effect, e.g. the Clec9a binding agent directly or indirectly recruits an immunosuppressive immune cell. The immunosuppressive immune cell may be a regulatory T cell (or "Tregs" which, as used herein, refers to a subpopulation of T cells which modulate the immune system, abrogate autoimmune disease, maintain tolerance to self-antigens and thwart anti-tumor immune responses). Other immunosuppressive immune cells include myeloid suppressor cells (or "MSC," which, as used herein, refers to a heterogeneous population of cells, defined by their myeloid origin, immature state, and ability to potently suppress T cell responses); tumor associated neutrophils (or "TANs" which, as used herein, refers to a subset of neutrophils that are capable of suppressing immune

responses); tumor associated macrophages (or "TAMs" which, as used herein, refers to a subset of macrophages that may reduce an immune response), M2 macrophages, and/or tumor-inducing mast cells (which as used herein, refers to a subset of bone marrow-derived, long-lived, heterogeneous cellular population). Also, immunosuppressive immune cells include Th2 cells and Th17 cells. Additionally, immunosuppressive immune cells include immune cells, e.g., CD4+ and/or CD8+ T cells, expressing one or more checkpoint inhibitory receptors (e.g. receptors, including CTLA-4, B7-H3, B7-H4, TIM-3, expressed on immune cells that prevent or inhibit uncontrolled immune responses). See Stagg, J. ef. a/., Immunotherapeutic approach in triple-negative breast cancer. Ther Adv Med Oncol. (2013) 5(3):169-181).

[0327] The Clec9a binding agent may stimulate regulatory T cell (Treg) proliferation. Treg cells are characterized by the expression of the Foxp3 (Forkhead box p3) transcription factor. Most Treg cells are CD4+ and CD25+, and can be regarded as a subset of helper T cells, although a small population may be CD8+. Thus the immune response which is to be modulated may comprise inducing proliferation of Treg cells, optionally in response to an antigen. Thus the method may comprise administering to the subject a composition comprising the antigen, wherein the antigen is associated with a binding agent having affinity for Clec9A. The antigen may be administered with an adjuvant which promotes proliferation of Treg cells.

[0328] Insofar as this method involves stimulating proliferation and differentiation of Treg cells in response to a specific antigen, it can be considered to be a method of stimulating an immune response. However, given that Treg cells may be capable of modulating the response of other cells of the immune system against an antigen in other ways, e.g. inhibiting or suppressing their activity, the effect on the immune system as a whole may be to modulate (e.g. suppress or inhibit) the response against that antigen. Thus the methods can equally be referred to as methods of modulating (e.g. inhibiting or suppressing) an immune response against an antigen.

[0329] The methods may therapeutically or prophylactically inhibit or suppress an undesirable immune response against a particular antigen, even in a subject with pre-existing immunity or an on-going immune response to that antigen. This may be particularly useful, for example, in the treatment of autoimmune disease.

[0330] Under certain conditions, it may also be possible to tolerize a subject against a particular antigen by targeting the antigen to an antigen presenting cell expressing Clec9A. Disclosed is thus a method for inducing tolerance in a subject towards an antigen, comprising administering to the subject a composition comprising the antigen, wherein the antigen is associated with a binding agent having affinity for Clec9A and wherein the antigen is administered in the absence of an adjuvant. Tolerance in this context typically involves depletion of immune cells which would otherwise be capable of responding to that antigen, or inducing a lasting reduction in responsiveness to an antigen in such immune cells.

[0331] It may be particularly desirable to raise a Treg response against an antigen to which the subject exhibits, or is at risk of developing, an undesirable immune response. For example, it may be a self-antigen against which an immune response occurs in an autoimmune disease. Examples of autoimmune diseases in which specific antigens have been identified as potentially pathogenically significant include multiple sclerosis (myelin basic protein), insulin-dependent diabetes mellitus (glutamic acid decarboxylase), insulin-resistant diabetes mellitus (insulin receptor), celiac disease (gliadin), bullous pemphigoid (collagen type XVII), auto-immune haemolytic anaemia (Rh protein), auto-immune thrombocytopenia (Gpllb/IIla), myaesthesia gravis (acetylcholine receptor), Graves' disease (thyroid-stimulating hormone receptor), glomerulonephritis, such as Goodpasture's disease (alpha3(IV)NC1 collagen), and pernicious anaemia (intrinsic factor). Alternatively the target antigen may be an exogenous antigen which stimulates a response which also causes damage to host tissues. For example, acute rheumatic fever is caused by an antibody response to a Streptococcal antigen which cross-reacts with a cardiac muscle cell antigen. Thus these antigens, or particular fragments or epitopes thereof, may be suitable antigens.

[0332] The present agents, or methods using these agents, may disrupt Clec9A signaling (e.g. via neutralization of Clec9A), e.g. by reducing or inhibiting Clec9A binding to its ligand. Some autoimmune diseases are characterized by unusually high levels of cell death and it is believed that immune responses against self antigens associated with these cells may contribute to the pathogenesis of these conditions. Clec9A antagonists may therefore be used to prevent Clec9A from binding to the ligand exposed in dead and dying cells (e.g. those undergoing immunogenic cell death) and may thus inhibit or prevent stimulation of immune responses against these antigens.

[0333] The present agents, or methods using these agents, may reduce or suppress autoreactive T cells. The multi-specific Clec9a binding agent, optionally through an interferon signaling in the context of a chimera, may cause this immunosuppression. The multi-specific Clec9a binding agent may stimulate PD-L1 or PD-L2 signaling and/or expression which may suppress autoreactive T cells. The Clec9A binding agent, optionally through an interferon signaling in the context of a chimera, may cause this immunosuppression. The Clec9A binding agent may stimulate PD-L1 or PD-L2 signaling and/or expression which may suppress autoreactive T cells.

[0334] The present methods may comprise modulating the ratio of regulatory T cells to effector T cells in favor of immunosuppression, for instance, to treat autoimmune diseases. For instance, the present methods, may reduce and/or suppress one or more of cytotoxic T cells; effector memory T cells; central memory T cells; CD8⁺ stem cell memory effector cells; TH1 effector T-cells; TH2 effector T cells; TH9 effector T cells; TH17 effector T cells. For instance, the present methods, may increase and/or stimulate one or more of CD4⁺ CD25⁺ FOXP3⁺ regulatory T cells, CD4⁺ CD25⁺ regulatory T cells, CD4⁺ CD25⁻ regulatory T cells, CD4⁺ CD25^{high} regulatory T cells, TIM-3⁺ PD-1⁺ regulatory T cells, lymphocyte activation gene-3 (LAG-3)⁺ regulatory T cells, CTLA-4/CD152⁺ regulatory T cells, neuropilin-1 (Nrp-1)⁺ regulatory T cells, CCR4⁺ CCR8⁺ regulatory T cells, CD62L (L-selectin)⁺ regulatory T cells, CD45RBlow regulatory T cells, CD127IOW regulatory T cells, LRRC32/GARP⁺ regulatory T cells, CD39⁺ regulatory T cells, GITR⁺ regulatory T cells, LAP⁺ regulatory T cells, 1B11⁺ regulatory T cells, BTLA⁺ regulatory T cells, type 1 regulatory T cells (Tr1 cells), T helper type 3 (Th3) cells, regulatory cell of natural killer T cell phenotype (NKTregs), CD8⁺ regulatory T cells, CD8⁺ CD28⁻ regulatory T cells and/or regulatory T-cells secreting IL-10, IL-35, TGF-β, TNF-α, Galectin-1, IFN-γ and/or MCP1.

[0335] The present methods may favor immune inhibitory signals over immune stimulatory signals. The present methods may allow for reversing or suppressing immune activating or co-stimulatory signals. The present methods may allow for providing immune inhibitory signals. For instance, the present agents and methods may reduce the effects of an immune stimulatory signal, which, without limitation, is one or more of 4-1 BB, OX-40, HVEM, GITR, CD27, CD28, CD30, CD40, ICOS ligand; OX-40 ligand, LIGHT (CD258), GITR ligand, CD70, B7-1, B7-2, CD30 ligand, CD40 ligand, ICOS, ICOS ligand, CD137 ligand and TL1A. Further, the present agents and methods may increase the effects of an immune inhibitory signal, which, without limitation, is one or more of CTLA-4, PD-L1, PD-L2, PD-1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), and various B-7 family ligands (including, but are not limited to, B7-1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7).

Kits

[0336] Disclosed are also kits for the administration of any Clec9A binding agent described herein (e.g. with or without additional therapeutic agents). The kit is an

assemblage of materials or components, including at least one of the inventive pharmaceutical compositions described herein. Thus, the kit may contains at least one of the pharmaceutical compositions described herein.

[0337] The exact nature of the components configured in the kit depends on its intended purpose. The kit may be configured for the purpose of treating human subjects.

[0338] Instructions for use may be included in the kit. Instructions for use typically include a tangible expression describing the technique to be employed in using the components of the kit to effect a desired therapeutic outcome, such as to treat cancer. Optionally, the kit also contains other useful components, such as, diluents, buffers, pharmaceutically acceptable carriers, syringes, catheters, applicators, pipetting or measuring tools, bandaging materials or other useful paraphernalia as will be readily recognized by those of skill in the art.

[0339] The materials and components assembled in the kit can be provided to the practitioner stored in any convenience and suitable ways that preserve their operability and utility. For example, the components can be provided at room, refrigerated or frozen temperatures. The components are typically contained in suitable packaging materials. In various embodiments, the packaging material is constructed by well-known methods, preferably to provide a sterile, contaminant-free environment. The packaging material may have an external label which indicates the contents and/or purpose of the kit and/or its components.

Definitions

[0340] As used herein, "a," "an," or "the" can mean one or more than one. Further, the term "about" when used in connection with a referenced numeric indication means the referenced numeric indication plus or minus up to 10% of that referenced numeric indication. For example, the language "about 50" covers the range of 45 to 55.

[0341] An "effective amount," when used in connection with medical uses is an amount that is effective for providing a measurable treatment, prevention, or reduction in the rate of pathogenesis of a disease of interest.

[0342] As used herein, something is "decreased" if a read-out of activity and/or effect is reduced by a significant amount, such as by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or more, up to and including at least about 100%, in the presence of an agent or stimulus relative to the absence of such modulation. As will be understood by one of ordinary skill in the art, in some embodiments, activity is decreased and some downstream read-outs will decrease but others can increase.

[0343] Conversely, activity is "increased" if a read-out of activity and/or effect is increased by a significant amount, for example by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or more, up to and including at least about 100% or more, at least about 2-fold, at least about 3-fold, at least about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least about 8-fold, at least about 9-fold, at least about 10-fold, at least about 50-fold, at least about 100-fold, in the presence of an agent or stimulus, relative to the absence of such agent or stimulus.

[0344] As referred to herein, all compositional percentages are by weight of the total composition, unless otherwise specified. As used herein, the word "include," and its variants, is intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that may also be useful in the compositions and methods of this technology. Similarly, the terms "can" and "may" and their variants are intended to be non-limiting, such that recitation that an embodiment can or may comprise certain elements or features does not exclude other embodiments of the present technology that do not contain those elements or features.

[0345] Although the open-ended term "comprising," as a synonym of terms such as including, containing, or having, is used herein to describe and claim the invention, the present invention, or embodiments thereof, may alternatively be described using alternative terms such as "consisting of or "consisting essentially of."

[0346] As used herein, the words "preferred" and "preferably" refer to embodiments of the technology that afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the technology. The amount of compositions described herein needed for achieving a therapeutic effect may be determined empirically in accordance with conventional procedures for the particular purpose. Generally, for administering therapeutic agents for therapeutic purposes, the therapeutic agents are given at a pharmacologically effective dose. A "pharmacologically effective amount," "pharmacologically effective dose," "therapeutically effective amount," or "effective amount" refers to an amount sufficient to produce the desired physiological effect or amount capable of achieving the desired result, particularly for treating the disorder or disease. An effective amount as used herein would include an amount sufficient to, for example, delay the development of a symptom of the disorder or disease, alter the course of a symptom of the disorder or disease (e.g., slow the progression of a symptom of the disease), reduce or eliminate one or more symptoms or manifestations of the disorder or disease, and reverse a symptom of a disorder or disease. Therapeutic benefit also includes halting or slowing the progression of the underlying disease or disorder, regardless of whether improvement is realized.

[0347] Effective amounts, toxicity, and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to about 50% of the population) and the ED50 (the dose therapeutically effective in about 50% of the population). The dosage can vary depending upon the dosage form employed and the route of administration utilized. The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD50/ED50. In some embodiments, compositions and methods that exhibit large therapeutic indices are preferred. A therapeutically effective dose can be estimated initially from in vitro assays, including, for example, cell culture assays. Also, a dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 as determined in cell culture, or in an appropriate animal model. Levels of the described compositions in plasma can be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay. The dosage can be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

[0348] In certain embodiments, the effect will result in a quantifiable change of at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 70%, or at least about 90%. In some embodiments, the effect will result in a quantifiable change of about 10%, about 20%, about 30%, about 50%, about 70%, or even about 90% or more. Therapeutic benefit also includes halting or slowing the progression of the underlying disease or disorder, regardless of whether improvement is realized.

[0349] As used herein, "methods of treatment" are equally applicable to use of a composition for treating the diseases or disorders described herein and/or

compositions for use and/or uses in the manufacture of a medicaments for treating the diseases or disorders described herein.

EXAMPLES

[0350] The term "AcTaferon" is occasionally used herein to reference an interferon-based chimera.

[0351] In the following examples, unless noted, mutations to IFN are relative to human IFN-α2: SEQ ID NO: 86. The Q124R mutant is representative of an attenuated human IFN alpha 2 mutant that can be assayed in vivo in a murine model. Specifically, Q124R is a human IFN mutation that is suitable for use in the mouse (i.e. it is a human mutant IFN that functions in mouse). See Nat. Comm. 2014;5:3016. doi: 10.1038/ncomms4016.

[0352] The R33A/E120R mutant is representative of human IFN alpha 2 mutant that is non-functional (and is used as a control)

[0353] Anti-human PD-L1 VHH used in these Examples is SEQ ID NO: 256.

[0354] Anti-BcM O VHH is used in these Examples as a control (targeting an irrelevant antigen, i.e. "untargeted").

Example 1. Construction and Evaluation of VHHs Specific for Mouse Clec9A

Isolation of antigen-specific VHHs

[0355] A VHH library was subject to 3 consecutive rounds of panning (in solution), performed on stably transfected CHO-K1 cells expressing mouse Clec9A. The enrichment for antigen-specific phages was assessed after each round of panning by comparing the number of phagemid particles eluted from transfected cells after panning (output) with the number of phagemid particles used for panning (input). The phage output increased about 50- and 30-fold in 2nd and 3rd rounds, respectively, as compared to the output from 1st round. The input phage was always about 10¹¹ and the output from first round was about 10⁹ phage particles suggesting that there was already enrichment for target-specific phages in the first round. A total of 285 colonies (95 and 190 from 1st & 2nd rounds, respectively) were randomly selected and their crude periplasmic extracts (including soluble VHHs) were analyzed by cell ELISA for specific binding to transfected CHO-K1, as compared to parental CHO-K1 cells. None of these colonies scored positive in cell ELISA suggesting that either the ELISA is not sensitive enough in this case or the antigen is affected by cell fixation in ELISA. We therefore switched to FACS for the identification of antigen specific VHHs. Here, we sequenced 190 randomly selected colonies from 1st and 2nd panning rounds (95 from each round) and then grouped VHHs based on CDR3 sequences. These experiments resulted in the identification of 28 different VHHs belonging to 7 different groups. Table 1 below provides a description of 28 clones representing the 28 different anti-mouse Clec9A VHH genes. E. coli TG1 harboring recombinant phagemid pHEN4 containing anti-mouse Clec9A VHH sequences was generated and stored at -80°C. The vector pHEN4 codes for ampicillin resistance.

Table 1.

<i>E. coli</i> strain + Vector	VHH (Nb)	NSF Reference No. (Glycerol stock)
TG1, pHEN4	R1MCL 3	1727
TG1, pHEN4	R1MCL 7	1728
TG1, pHEN4	R1MCL 9	1729
TG1, pHEN4	R1MCL 12	1730
TG1, pHEN4	R1MCL 13	1731
TG1, pHEN4	R1MCL 33	1732
TG1, pHEN4	R1MCL 41	1733
TG1, pHEN4	R1MCL 71	1734
TG1, pHEN4	R1MCL 85	1735
TG1, pHEN4	R1MCL 95	1736
TG1, pHEN4	R1MCL 5	1737
TG1, pHEN4	R1MCL 15	1738
TG1, pHEN4	R1MCL 17	1739
TG1, pHEN4	R1MCL 18	1740
TG1, pHEN4	R1MCL 20	1741
TG1, pHEN4	R1MCL 28	1742
TG1, pHEN4	R1MCL 36	1743
TG1, pHEN4	R1MCL 41	1744
TG1, pHEN4	R1MCL 43	1745
TG1, pHEN4	R1MCL 47	1746
TG1, pHEN4	R1MCL 49	1747
TG1, pHEN4	R1MCL 57	1748
TG1, pHEN4	R1MCL 65	1749
TG1, pHEN4	R1MCL 66	1750
TG1, pHEN4	R1MCL 74	1751
TG1, pHEN4	R1MCL 85	1752
TG1, pHEN4	R1MCL 86	1753
TG1, pHEN4	R1MCL 93	1754

[0356] Using crude periplasmic extracts including VHHs, representative(s) of each group was (were) analyzed by FACS for specificity to mouse Clec9A using CHO-K1 cells transfected with mouse Clec9A. The parental non-transfected CHO-K1 cells served as negative control cell. The representative VHHs tested for their specificity towards mouse Clec9A were as follows: R1 MCL3, R1 MCL7, R1 MCL9, R1 MCL12, R1 MCL13, R1 MCL33, R1 MCL71, R1 MCL95, R2MCL15, R2MCL18, R2MCL20, R2MCL28, R2MCL36, R2MCL41, R2MCL43, R2MCL47, R2MCL57, R2MCL74, R2MCL86, R2MCL93. All representatives tested were positive for CHO-K1 cells transfected with mouse Clec9A showing that all 28 VHHs bound mouse Clec9A specifically. Next, a representative of each group was analyzed by FACS for specificity to mouse and human Clec9A using CHO-K1 cells transfected with either mouse Clec9A or human Clec9A. Here also, the parental non-transfected CHO-K1 cells served as negative control cell. The representative VHHs tested for cross-species reactivity were as follows: R1 MCL3, R1 MCL7, R1 MCL9, R1 MCL12, R1 MCL33, R2MCL18, R2MCL43. None of these VHHs showed any specific binding to human Clec9A suggesting that these VHHs recognize epitopes unique to mouse Clec9A.

Expression and purification of VHHs

[0357] The VHH genes were recloned from pHEN4 to pHEN6c vectors. Specifically, the VHH gene was amplified by PCR using recombinant pHEN4 harboring the VHH gene as template and primers A6E and 38. Primers A6E and 38 were framework 1 and framework 4 primers, respectively. The primer sequences were as follows:

- Primer A6E (5' GAT GTG CAG CTG CAG GAG TCT GGR*GGA GG 3') (SEQ ID NO:291).
 - Primer 38 (5' GGA CTA GTG CGG CCG CTG GAG ACG GTG ACC TGG GT 3') (SEQ ID NO:292).
 - Universal reverse primer (5' TCA CAC AGG AAA CAG CTA TGA C 3') (SEQ ID NO:293).
 - Universal forward primer (5' CGC CAG GGT TTT CCC AGT CAC GAC 3') (SEQ ID NO:294).
- *R stands for A or G.

[0358] The amplification protocol included about 30 cycles of PCR, each cycle included 30 seconds at 94°C, 30 seconds at 55°C and 45 seconds at 72°C, followed by 10 minutes extension at 72°C at the end of PCR. A fragment of about 400 bp was amplified. All resulting VHHs produced using the protocol described herein start with the following sequence: QVQLQESGGG (SEQ ID NO:295).

[0359] The PCR product was purified (e.g. by Qiaquick PCR purification kit from Qiagen) and digested overnight with PstI. The purified PCR product was digested with BstEII overnight (or with Eco91 I from Fermentas). The temperature used for digestion varied. For example, digestion with BstEII was done at 50°C or 60°C depending on the supplier of the enzyme.

[0360] For ligation, the PCR product was purified. The pHEN6c vector was digested with PstI for 3 hours, purified as described above, and then digested with BstEII for 2 to 3 hours. Alternatively, digestion was carried out using Eco91 I from Fermentas. The digested vector was ran on 1% agarose gel, with the vector band excised out of the gel and purified (e.g. by Qiaquick gel extraction kit from Qiagen). The PCR fragment was subsequently ligated to the vector.

[0361] Electrocompetent WK6 cells were transformed with the ligation reaction, and transformants were selected using LB/agar/ampicillin (100 µg/ml)/glucose (1%) plates. Positive clones were screened by PCR using universal reverse and universal forward primers. A fragment of about 550 bp was amplified, if the insert was present. To verify the identity of the clones, at least 2 clones per each VHH were sequenced using universal reverse primers. Antigen binding capacity was retested by ELISA or any other appropriate assay.

[0362] Following the above protocol, the VHH gene cloned in pHEN6c vector was generated which contained PelB signal sequence at the N-terminus and His₆-tail at the C-terminus. The PelB leader sequence directed the VHH to the periplasmic space of the E.coli, and the His-tag was used for the purification and detection of VHH (e.g. in ELISA, Western Blot, etc.).

[0363] Expression and purification of the VHHs were carried out. Specifically, on day 1, 10-20 ml of LB + ampicillin (100 g/ml) + glucose (1%) were inoculated with a freshly transformed WK6 colony. This pre-culture was incubated at 37°C overnight with shaking at 200-250 rpm. On day 2, a TB medium was used for expressing the VHHs. The TB medium included, per liter: 2.3 g KH₂P0₄, 16.4 g K₂HP0₄.3H₂O, 12 g Tryptone (Duchefa Biochemie), 24 g Yeast (Duchefa Biochemie), and 4 ml 100% glycerol (Duchefa Biochemie).

[0364] A baffled shaker flask of 1 liter was filled with 330 ml TB and autoclaved. KH₂P0₄ and K₂HP0₄.3H₂O were not autoclaved. Instead, KH₂P0₄ and K₂HP0₄.3H₂O were prepared, filter sterilized, and then added to the rest of the medium that was already autoclaved. About 1 ml of the pre-culture was added to 330 ml of TB supplemented with 100 g/ml Ampicillin, 2 mM MgCl₂ and 0.1% glucose and subsequently grew at 37°C with shaking (200-250 rpm) until an OD₆₀₀ of 0.6-0.9 was reached. IPTG (final concentration of 1 mM) was added to induce VHH expression. The culture was incubated at 28°C with shaking overnight (about 16-18 hours). The OD₆₀₀ after overnight induction was usually between 25 and 30. At least 1 liter of culture (3 bottles) per clone was prepared with an average yield of between 1 and 15 mg/l.

[0365] Extraction of the VHHs from the periplasm of E. coli was carried out on day 3. The solutions used included: TES: 0.2 M Tris pH 8.0, 0.5 mM EDTA, 0.5 M sucrose, and TES/4: TES diluted 4 times in water.

[0366] The overnight induced cultures were centrifuged for 8 minutes at 8000 rpm. The cell pellets from 1 liter culture were resuspended in 12 ml TES by pipetting up and down and shaken for 1 hour on ice. Per each 12 ml TES used, about 18 ml TES/4 were added and incubated on ice for an additional hour with shaking followed by centrifugation for 30 minutes at 8000 rpm at 4°C. The supernatant which contained proteins extracted from the periplasmic space was transferred to fresh falcon tubes.

[0367] The VHHs were subsequently purified by IMAC which utilized the following solution: HIS-select (SIGMA), PBS, and 50 mM NaAcetate pH 4.6.

[0368] His-select was equilibrated with PBS. Specifically, per periplasmic extract derived from 1 liter culture, 1 ml of Resin (about 2 ml His-select solution) was added to a 50 ml falcon tube. PBS was also added to final volume of 50 ml and mixed. Centrifugation was carried out at 2000 rpm for 2 minutes, and the supernatant was discarded. The resin was washed with PBS twice as described above. The periplasmic extract was added to the resin, incubated for 30 minutes to 1 hour at room temperature with gentle shaking. The samples were loaded on PD-10 columns with a filter at the bottom (GE healthcare, cat. No. 17-0435-01) and washed with 50 to 100 ml PBS (50-100 ml PBS per 1 ml resin used). Elution was carried out for 3 times, each time with 1 ml PBS/0.5 M imidazole per 1 ml resin used (for efficient elution, resuspend the beads and leave overnight at 4°C with the bottom of the column closed). Dialysis was performed overnight at 4°C against PBS (cutoff 3500 Daltons) to remove imidazole. For efficient dialysis, the dialysis buffer (PBS) was changed 2-3 times. Alternatively, instead of elution with

imidazole, the bound VHHs could be eluted with 10 ml 50 mM Na-acetate pH 4.6. If 50 mM Na-acetate pH 4.6 was used to elute VHHs, the eluted VHHs was immediately neutralized with 1 M Tris pH 8.0, and no dialysis was required.

[0369] The amount of protein was estimated by OD280 measurement of eluted sample. Extinction coefficient of each clone was determined by protParam tool under primary structure analysis at the Expasy proteomics server. Further purification of VHHs could be achieved by different methods. For example, the samples could be concentrated (Vivaspin 5000 MW cutoff, Vivascience) by centrifuging at 2000 rpm at 4°C until an appropriate volume for loading on a Superdex 75 16/60 was obtained (max. 4 ml). The concentrated sample was loaded on a Superdex 75 16/60 column equilibrated with PBS. Peak fractions were pooled, and OD280 measurements were performed for quantification. In general, VHHs eluted after 85-95 minutes when run at 1 ml/min. Aliquots of concentrated VHH samples were stored at -20°C at a concentration of about 1 mg/ml.

Functional analysis of VHHs

[0370] The VHHs were tested for binding to Clec9A. **Figure 1** shows binding of the various VHHs to CHO cells stably expressing Clec9A. In all experiments, the VHHs were labeled as follows:

mClec9A VHH MBU-I-number	single cells/single cells Geometric Mean (FL1-H)	group
20140226 CHO mClec9A.control	3.74	
20140226 CHO mClec9A.10487	6.44	1
20140226 CHO mClec9A.10488	5.97	3
20140226 CHO mClec9A.10489	7.36	2
20140226 CHO mClec9A.10490	6.01	7
20140226 CHO mClec9A.10491	5.8	3
20140226 CHO mClec9A.10492	6.09	4
20140226 CHO mClec9A.10493	5.45	1
20140226 CHO mClec9A.10494	6.26	4
20140226 CHO mClec9A.10495	8.49	6
20140226 CHO mClec9A.10496	6.04	4
20140226 CHO mClec9A.10497	12.7	1
20140226 CHO mClec9A.10498	6.07	1
20140226 CHO mClec9A.10499	7.74	1
20140226 CHO mClec9A.10501	7.31	6
20140226 CHO mClec9A.10502	6.03	3
20140226 CHO mClec9A.10503	7.14	6
20140226 CHO mClec9A.10504	8.36	1
20140226 CHO mClec9A.10505	6.46	5
20140226 CHO mClec9A.10507	5.32	1
20140226 CHO mClec9A.10508	8.99	2
20140226 CHO mClec9A.10509	6.08	1
20140226 CHO mClec9A.10510	5.9	3
20140226 CHO mClec9A.10511	10.5	1
20140226 CHO mClec9A.10512	5.61	3
20140226 CHO mClec9A.10513	6.01	3
20140226 CHO mClec9A.10514	7.59	6

[0371] Experiments were carried out to characterize the activity of the VHHs in treating tumors. In the experiments of **Figure 2**, female C57BL/6J mice were injected s.c. with 6x10⁵ B16Bl6-mCD20 cells in 50 µl PBS. Seven days later, perilesional (= s.c. at the edge of the tumor) treatments were started. WT mIFN was injected in a dose of 8x10⁶ IU, while 5500 IU of the chimeric protein were injected. Treatments were given at days 8, 9, 10, 11, 12, 14, 16 and 17 after tumor cell inoculation. Control mice were injected with 100 µl PBS. Tumor growth was monitored using a digital caliper. Plotted are means ± SEM (n=5) of tumor sizes (**Figure 2** panel A) and body weight changes (**Figure 2** panel B). One day after the last treatment (day 18), EDTA-blood was collected from the tail vein for analysis of hematological parameters (**Figure 2** panel C) using a Hemavet 950FS Analyzer (Drew Scientific).

[0372] As shown in **Figure 2**, panel A, administration of VHHs against Clec9A effectively reduced tumor size. **Figure 2**, panels B and C, demonstrate that treatment with the VHHs did not result in weight loss or hematological toxicity, respectively. Importantly, panels B and C show improved safety parameters (body weight, blood count parameters) of the chimeras relative to wild type interferon.

Example 2. Construction and Evaluation of VHHs Specific for Human Clec9A

Isolation of antigen-specific VHHs

[0373] A VHH library was subject to 2 consecutive rounds of panning (in solution), performed on stably transfected CHO-K1 cells expressing human Clec9A. The enrichment for antigen-specific phages was assessed after each round of panning by comparing the number of phagemid particles eluted from transfected cells after panning (output) with the number of phagemid particles used for panning (input). The phage output increased about 1 CP- fold in the 2nd round, as compared to the output from 1st round. The input phage was about 10¹¹ and the output from first round was about 2 x 10⁸ phage particles. 95 colonies from round were randomly selected and their crude periplasmic extracts (including soluble VHHs) were analyzed by cell ELISA for specific binding to transfected CHO-K1, as

compared to parental CHO-K1 cells. None of these colonies scored positive in cell ELISA suggesting that either the ELISA was not sensitive enough in this case or the antigen was affected by cell fixation in ELISA. FACS analysis was therefore used for the identification of antigen-specific VHs. Here, 190 randomly selected colonies from 1st and 2nd panning rounds (95 from each round) were sequenced and then the VHs were grouped based on CDR3 sequences. These experiments resulted in the identification of 27 different VHs belonging to 11 different groups (**Figure 5**). The nucleotide and amino acid sequences of the 27 anti- human Clec9A VHs are shown in **Figures 3** and **4**, respectively. Table 2 below provides a description of 27 clones representing the 27 different anti-human Clec9A VH genes. E. coli TG1 harboring recombinant phagemid pHEN4 containing anti-human Clec9A VH sequences was generated and stored at -80°C. The vector pHEN4 codes for ampicillin resistance.

Table 2.

<i>E. coli</i> strain + Vector	VH (Nb)	NSF Reference No. (Glycerol stock)
TG1, pHEN4	R1MCL 16	1755
TG1, pHEN4	R1MCL 21	1756
TG1, pHEN4	R1MCL 23	1757
TG1, pHEN4	R1MCL 27	1758
TG1, pHEN4	R1MCL 34	1759
TG1, pHEN4	R1MCL 50	1760
TG1, pHEN4	R1MCL 56	1761
TG1, pHEN4	R1MCL 82	1762
TG1, pHEN4	R1MCL 3	1763
TG1, pHEN4	R1MCL 8	1764
TG1, pHEN4	R1MCL 10	1765
TG1, pHEN4	R1MCL 13	1766
TG1, pHEN4	R1MCL 14	1767
TG1, pHEN4	R1MCL 18	1768
TG1, pHEN4	R1MCL 22	1769
TG1, pHEN4	R1MCL 24	1770
TG1, pHEN4	R1MCL 25	1771
TG1, pHEN4	R1MCL 27	1772
TG1, pHEN4	R1MCL 32	1773
TG1, pHEN4	R1MCL 38	1774
TG1, pHEN4	R1MCL 41	1775
TG1, pHEN4	R1MCL 42	1776
TG1, pHEN4	R1MCL 49	1777
TG1, pHEN4	R1MCL 53	1778
TG1, pHEN4	R1MCL 69	1779
TG1, pHEN4	R1MCL 87	1780
TG1, pHEN4	R1MCL 94	1781

[0374] Using crude periplasmic extracts including VHs, representative(s) of each group was (were) analyzed by FACS for specificity to human and mouse Clec9A using CHO-K1 cells transfected with either mouse Clec9A or human Clec9A. The parental non-transfected CHO-K1 cells served as negative control cell. The representative VHs tested were as follows: R1 CHCL16, R1 CHCL27, R1 CHCL34, R1 CHCL50, R2CHCL3, R2CHCL10, R2CHCL13, R2CHCL24, R2CHCL25, R2CHCL27, R2CHCL32, R2CHCL38, R2CHCL49, R2CHCL69 and R2CHCL87. All representatives tested were positive for CHO-K1 cells transfected with human Clec9A showing that all 27 VHs bound human Clec9A specifically. Moreover, VH R2CHCL10 from group 5 also reacted strongly with mouse Clec9A in FACS. VH R1 CHCL34, also from group 5, reacted with mouse Clec9A but very weakly. VH R1 CHCL82 from group 5 was not tested in FACS. Additionally, VH R2CHCL32 from group 7 weakly reacted with mouse Clec9A in FACS. The other 2 members of the group 7 (VHs R1 CHCL56 and R2CHCL69) were not tested in FACS.

Expression and purification of VHs

[0375] The VH genes were recloned from pHEN4 to pHEN6c vectors. Specifically, the VH gene was amplified by PCR using recombinant pHEN4 harboring the VH gene as template and primers A6E and 38. Primers A6E and 38 were framework1 and framework4 primers, respectively. The primer sequences were as follows:

- Primer A6E (5' GAT GTG CAG CTG CAG GAG TCT GGR* GGA GG 3') (SEQ ID NO:291).
- Primer 38 (5' GGA CTA GTG CGG CCG CTG GAG ACG GTG ACC TGG GT 3') (SEQ ID NO:292).
- Universal reverse primer (5' TCA CAC AGG AAA CAG CTA TGA C 3') (SEQ ID NO:293).
- Universal forward primer (5' CGC CAG GGT TTT CCC AGT CAC GAC 3') (SEQ ID NO:294).

*R stands for A or G.

[0376] The amplification protocol included about 30 cycles of PCR, each cycle included 30 seconds at 94°C, 30 seconds at 55°C and 45 seconds at 72°C, followed by 10 minutes extension at 72°C at the end of PCR. A fragment of about 400 bp was amplified.

[0377] The PCR product was purified (e.g. by Qiaquick PCR purification kit from Qiagen) and digested overnight with PstI. The purified PCR product was digested with BstEII overnight (or with Eco91 I from Fermentas). The temperature used for digestion varied. For example, digestion with BstEII was done at 50°C or 60°C depending on the supplier of the enzyme.

[0378] For ligation, the PCR product was purified. The pHEN6c vector was digested with PstI for 3 hours, purified as described above, and then digested with BstEII for 2 to 3 hours. Alternatively, digestion was carried out using Eco91 I from Fermentas. The digested vector was ran on 1% agarose gel, with the vector band excised out of the gel and purified (e.g. by Qiaquick gel extraction kit from Qiagen). The PCR fragment was subsequently ligated to the vector.

[0379] Electrocompetent WK6 cells were transformed with the ligation reaction, and transformants were selected using LB/agar/ampicillin (100 µg/ml)/glucose (1%) plates. Positive clones were screened by PCR using universal reverse and universal forward primers. A fragment of about 550 bp was amplified, if the insert was present. To verify the identity of the clones, at least 2 clones per each VHH were sequenced using universal reverse primers. Antigen binding capacity was retested by ELISA or any other appropriate assay.

[0380] Following the above protocol, the VHH gene cloned in pHEN6c vector was generated which contained PelB signal sequence at the N-terminus and His₆-tail at the C-terminus. The PelB leader sequence directed the VHH to the periplasmic space of the E.coli, and the His-tag was used for the purification and detection of VHH (e.g. in ELISA, Western Blot, etc.).

[0381] Expression and purification of the VHHs were carried out. Specifically, on day 1, 10-20 ml of LB + ampicillin (100 g/ml) + glucose (1%) were inoculated with a freshly transformed WK6 colony. This pre-culture was incubated at 37°C overnight with shaking at 200-250 rpm. On day 2, a TB medium was used for expressing the VHHs. The TB medium included, per liter: 2.3 g KH2P04,16.4 g K2HP04.3H2O, 12 g Tryptone (Duchefa Biochemie), 24 g Yeast (Duchefa Biochemie), and 4 ml 100% glycerol (Duchefa Biochemie)

[0382] A baffled shaker flask of 1 liter was filled with 330 ml TB and autoclaved. KH2P04and K2HP04.3H2O were not autoclaved. Instead, KH2P04and K2HP04.3H2O were prepared, filter sterilized, and then added to the rest of the medium that was already autoclaved. About 1 ml of the pre-culture was added to 330 ml of TB supplemented with 100 g/ml Ampicillin, 2 mM MgCl2 and 0.1% glucose and subsequently grew at 37°C with shaking (200-250 rpm) until an ODwo of 0.6-0.9 was reached. IPTG (final concentration of 1 mM) was added to induce VHH expression. The culture was incubated at 28°C with shaking overnight (about 16-18 hours). The ODwo after overnight induction was usually between 25 and 30. At least 1 liter of culture (3 bottles) per clone was prepared with an average yield of between 1 and 15 mg/l.

[0383] Extraction of the VHHs from the periplasm of E. coli was carried out on day 3. The solutions used included: TES: 0.2 M Tris pH 8.0, 0.5 mM EDTA, 0.5 M sucrose, and TES/4: TES diluted 4 times in water.

[0384] The overnight induced cultures were centrifuged for 8 minutes at 8000 rpm. The cell pellets from 1 liter culture were resuspended in 12 ml TES by pipetting up and down and shaken for 1 hour on ice. Per each 12 ml TES used, about 18 ml TES/4 were added and incubated on ice for an additional hour with shaking followed by centrifugation for 30 minutes at 8000 rpm at 4°C. The supernatant which contained proteins extracted from the periplasmic space was transferred to fresh falcon tubes.

[0385] The VHHs were subsequently purified by IMAC which utilized the following solution: HIS-select (SIGMA), PBS, and 50 mM NaAcetate pH 4.6.

[0386] His-select was equilibrated with PBS. Specifically, per periplasmic extract derived from 1 liter culture, 1 ml of Resin (about 2 ml His-select solution) was added to a 50 ml falcon tube. PBS was also added to final volume of 50 ml and mixed. Centrifugation was carried out at 2000 rpm for 2 minutes, and the supernatant was discarded. The resin was washed with PBS twice as described above. The periplasmic extract was added to the resin, incubated for 30 minutes to 1 hour at room temperature with gentle shaking. The samples were loaded on PD-10 columns with a filter at the bottom (GE healthcare, cat. No. 17-0435-01) and washed with 50 to 100 ml PBS (50-100 ml PBS per 1 ml resin used). Elution was carried out for 3 times, each time with 1 ml PBS/0.5 M imidazole per 1 ml resin used (for efficient elution, resuspend the beads and leave overnight at 4°C with the bottom of the column closed). Dialysis was performed overnight at 4°C against PBS (cutoff 3500 daltons) to remove imidazole. For efficient dialysis, the dialysis buffer (PBS) was changed 2-3 times. Alternatively, instead of elution with imidazole, the bound VHHs could be eluted with 10 ml of 50 mM Na-acetate pH 4.6. If 50 mM Na-acetate pH 4.6 was used to elute VHHs, the eluted VHHs was immediately neutralized with 1 M Tris pH 8.0, and no dialysis was required.

[0387] The amount of protein was estimated by OD280 measurement of eluted samples. Extinction coefficient of each clone was determined by protParam tool under primary structure analysis at the Expasy proteomics server. Further purification of VHHs could be achieved by different methods. For example, the samples could be concentrated (Vivaspin 5000 MW cutoff, Vivascience) by centrifuging at 2000 rpm at 4°C until an appropriate volume for loading on a Superdex 75 16/60 was obtained (max. 4 ml). The concentrated sample was loaded on a Superdex 75 16/60 column equilibrated with PBS. Peak fractions were pooled, and OD280 measurements were performed for quantification. In general, VHHs eluted after 85-95 minutes when run at 1 ml/min. Aliquots of concentrated VHH samples were stored at -20°C at a concentration of about 1 mg/ml.

[0388] The sequences of **Figure 3** and **Figure 4** are assigned sequence identifiers as shown in the table below. Further, binding characteristics of the anti-human Clec9A VHHs, after purification, was assayed by binding to HEK-293T cells transfected with Clec9A is shown in the table below. Briefly, Hek293T cells were transfected a human Clec9A expression-plasmid using a standard calcium phosphate procedure. Two days after transfection, cells were resuspended in FACS buffer (PBS supplemented with 2% FBS and 0,5 mM EDTA) and incubated with a serial dilution VHH (1000 ng/ml; 1 over 3) for two hours at 4°C. Unbound VHHs were washed away with FACS buffer. Samples were further stained with a FITC-coupled anti-His Ab for 45 minutes at 4°C and analysed with a FACSCalibur (BD Biosciences) and the CellQuest Pro Version 4.0.2 software (BD Biosciences).

Clone	Sequence Identifier	Binding
R1CHCL23	SEQ ID NO:78	ND
R2CHCL18	SEQ ID NO:77	ND
R2CHCL22	SEQ ID NO:75	++
R2CHCL49	SEQ ID NO:73	ND
R2CHCL53	SEQ ID NO:74	ND
R2CHCL25	SEQ ID NO:76	+
R1CHCL27	SEQ ID NO:79	-
R1CHCL82	SEQ ID NO:68	++
R2CHCL10	SEQ ID NO:66	+++
R1CHCL34	SEQ ID NO:67	+
R2CHCL3	SEQ ID NO:69	+
R1CHCL50	SEQ ID NO:60	+++
R2CHCL8	SEQ ID NO:59	+++

Clone	Sequence Identifier	Binding
R1CHCL21	SEQ ID NO:61	-
R2CHCL87	SEQ ID NO:62	+++
R2CHCL24	SEQ ID NO:63	+++
R2CHCL38	SEQ ID NO:64	-
R1CHCL 16	SEQ ID NO:65	++
R1CHCL56	SEQ ID NO:71	ND
R2CHCL69	SEQ ID NO:70	-
R2CHCL32	SEQ ID NO:72	-
R2CHCL14	SEQ ID NO:81	ND
R2CHCL42	SEQ ID NO:82	ND
R2CHCL13	SEQ ID NO:80	ND
R2CHCL41	SEQ ID NO:83	-
R2CHCL94	SEQ ID NO:84	++
R2CHCL27	SEQ ID NO:85	ND

Example 3. Combination Therapy Using Clec9A Chimeras and Tumor Necrosis Factor

[0389] The anti-tumor effects of a combination therapy using VHHs specific for mouse Clec9A and Tumor Necrosis Factor (TNF) were tested. Mice were inoculated subcutaneously with B16 (a mouse melanoma cell line) to induce tumors. The mice were subsequently given perilesional (= s.c. at the edge of the tumor) treatments with a chimeric Clec9A VHH specific for mouse Clec9A fused with a modified human interferon alpha 2 (Q124R mutant, "AcTa Clec9A") with or without TNF. Control mice were treated with PBS or either the chimeric Clec9A VHH alone or TNF alone. Tumor growth was monitored using a digital caliper. EDTA-blood was also collected from the tail vein for analysis of hematological parameters using a Hemavet 950FS Analyzer (Drew Scientific).

[0390] As shown in **Figure 6**, panel A, combined treatment using the chimeric Clec9A VHH and TNF elicited potent antitumor effects with no tumor recurrence by day 38 compared to treatment with either agent alone. **Figure 6**, panel B, shows that the combination treatment was well tolerated and induced no hematological toxicity compared to treatment with wildtype IFN alone or wildtype IFN with TNF. Altogether these data suggests a synergistic effect for combination therapy using chimeric Clec9A VHHs and TNF. The Q124R mutant is representative of an attenuated human IFN alpha 2 mutant that can be assayed in vivo in a murine model. Specifically, Q124R is a human IFN mutation that is suitable for use in the mouse (i.e. it is a human mutant IFN that functions in mouse). See Nat. Comm. 2014;5:3016. doi: 10.1038/ncomms4016.

Example 4. Combination Therapy Using Clec9A Chimeras and anti-PD-L1 Antibodies

[0391] **Figure 7** shows the combined effect of a chimera of a VHH specific for mouse Clec9A fused to a modified human IFN alpha 2 (Q124R mutant) and an anti-PD-L1 antibody ("Clec9A-AcTaferon + anti-PD-L1") in comparison to PBS (negative control), chimera of a VHH specific for mouse Clec9A fused to a modified human IFN (Q124R mutant, "Clec9A-AcTaferon") alone, and anti-PD-L1 antibody ("anti-PD-L1") alone.

[0392] As demonstrated by the in vivo experiment of **Figure 7**, the combination of a chimera of Clec9A fused to a modified human IFN and an anti-PD-L1 antibody provides synergy with regard to tumor progression. Specifically, the combined treatment provided not only stasis but also tumor shrinkage. This is particularly notable in comparison to, for example, anti-PD-L1 antibody alone, as the mice treated with such were displaying growing tumors at the end of the experiment.

[0393] The Q124R mutant is representative of an attenuated human IFN alpha 2 mutant that can be assayed in vivo in a murine model. Specifically, Q124R is a human IFN mutation that is suitable for use in the mouse (i.e. it is a human mutant IFN that functions in mouse). See Nat. Comm. 2014;5:3016. doi: 10.1038/ncomms4016.

Example 5. Combination Therapy Using Clec9A Chimeras and Chemotherapy

[0394] **Figure 8** shows the combined effect of a chimera of a VHH specific for mouse Clec9A fused to a modified human IFN (Q124R) and fused to an anti-PD-L1 VHH, and doxorubicin ("Clec9A-Q124R-PD-L1 + doxo"), compared to a chimera of a VHH specific for mouse Clec9A fused to a modified human IFN ("Q124R") and fused to an anti-PD-L1 VHH ("Clec9A-Q124R-PD-L1"), doxorubicin ("doxo"), and PBS (negative control).

[0395] As demonstrated by the in vivo experiment of **Figure 8**, the combination of a chimera of a VHH specific for mouse Clec9A fused to a modified human interferon (Q124R) and fused to an anti-PD-L1 VHH and doxorubicin provides synergy with regard to tumor progression. Importantly, 5 out of 6 mice in the combination therapy group showed a complete tumor regression.

[0396] The Q124R mutant is representative of an attenuated human IFN alpha 2 mutant that can be assayed in vivo in a murine model. Specifically, Q124R is a human IFN mutation that is suitable for use in the mouse (i.e. it is a human mutant IFN that functions in mouse). See Nat. Comm. 2014;5:3016. doi: 10.1038/ncomms4016.

Example 6. Stimulation of T Cell Proliferation by Mouse Clec9A Chimeras

[0397] Chimeric Antigen Receptor (CAR) T-cell therapy is often compromised by the extremely inhospitable solid tumor microenvironment which imposes an immunosuppressive effect on the CAR T cells. For examples, various immunosuppressive cytokines, regulatory modulators, and co-inhibitory receptors are present in the tumor microenvironment which can induce anergy of the CAR T cells. One mechanism for enhancing the efficacy of CAR T-cell therapy entails an

induction of the T cells to divide and proliferate within the tumor microenvironment.

[0398] Experiments were conducted to evaluate whether a VHH specific for mouse Clec9A fused to a modified human IFN (Q124R) could induce proliferation of CAR T cells in vivo. Specifically, carboxyfluorescein succinimidyl ester (CFSE)-labeled T cell receptor transgenic CD8+ T cells (pmel-1) which recognize the melanocyte differentiation antigen gp100 present on tumor cells were adoptively transferred to mice bearing B16 melanoma tumors. The mice were subsequently treated with either PBS (control) or a VHH specific for mouse Clec9A fused to a modified human IFN (Q124R). T cell proliferation was assessed by evaluating the extent of CFSE-labeled T cells present in the tumor draining lymph nodes using FACS analysis.

[0399] As shown in **Figure 9**, treating the mice with the VHH substantially induced T cell division and proliferation as compared to treatment with PBS. Without wishing to be bound by theory, it is believed that T cell division and proliferation was mediated via dendritic cell activation. Altogether these results suggest that the use of VHHs specific for Clec9A fused to IFN synergistically enhances CAR T-cell therapy.

Example 7. VHHs Specific for Human Clec9A are Effective in an Experimental Autoimmune Encephalomyelitis (EAE) Model

[0400] This Example shows the therapeutic effects of VHHs specific for mouse Clec9A in an EAE mouse model which mimics human multiple sclerosis (MS). In short, 4 in 5 mice treated with a fusion of Clec9A-IFNQ124R never developed MS symptoms. A single treated mouse got sick, but recovered quickly. Three out of 5 animals treated with a high dose of wild type IFN, that suppressed disease development, died. Mice treated with low-dose wt IFN showed loss of weight. This is in stark contrast with Clec9A-IFNQ124R AcTaferon (*i.e.* fusion protein) treated animals which actually gained weight.

[0401] For **Figures 10-12:** various AcTaferons were used. In this context, these refer to attenuated interferon, *i.e.* hIFN Q124R ("Q") which was linked to various targeting domains that included VHHs against Bell 10, mCD20, CD8, or Clec9A at 5000 IU. For comparison, wild type interferon was used ("WT mIFN" at either 5000 IU or 1,000,000 IU as noted. PBS buffer is a mock control (*i.e.* negative).

[0402] The treatment schedule for this study was as follows:

- d0 = sc injection MOG + CFA/mtb, + ip PT
- d2 = ip PT
- d7 = start daily treatments ip, and

clinical scoring was as follows:

0-1	varying degrees of less horizontal tail if mouse held by the neck
1.5	limp tail (totally vertical) but with still a tiny bit tension in it 2 totally limp tail
2.5	+ hind paws closed (toes no longer spread open)
3	+ waddled walk (but still using both hind paws)
3.5	one hind paw no longer used when walking
4	both hind paws...
4.5	+ no longer able to turn if put on the back
5	moribund
6	dead.

[0403] In Figure 10, Panel A, male C57Bl/6J mice (8 wks old) were immunized s.c. with 2x100 µl of an emulsion of myelin-specific peptide (Mouse Oligodendrocyte Glycoprotein amino acids 35-55 MEVGWYRSPFSRWHLRNGK, (SEQ ID NO:296), 1 mg/ml) and Complete Freund's Adjuvant (5mg/ml) at day 0, followed by an i.p. injection of 50 ng pertussis toxin. At day 2, a second pertussis toxin dose was inoculated i. p. Starting at day 7, mice were treated daily (i.p.) with 5000 IU of AcTaferon linked to a VHH binding to either Bell 10 (*i.e.* an irrelevant target, thus the untargeted control), mCD8, mCD20 or mClec9A (n=5, except for mCD8-targeted AcTaferon, where n=4). As positive controls, untargeted wild type mIFN (linked to the BclM O VHH) was injected either at 5,000 IU or 1,000,000 IU. Control mice received PBS treatments. Mice were scored daily for progressive paresis and paralysis. Scores between 0 and 2 were given for varying degrees of decreased tail tone, score 2 for a completely paralyzed tail; score 3 for hind limb weakness and starting paraplegia; score 4 for full paraplegia; score 5 for quadriplegia (at which stage the mice should be euthanized) and score 6 if the mouse died. Of note, if mice suddenly died with a score of less than 1, their death was attributed to toxicity of the treatment. These mice were not included for calculation of the mean clinical score (this was only the case for mice treated with high-dose wild type IFN). **Figure 10**, Panel B, shows body weight change. Body weights were also measured daily. Mean weight was calculated including that of mice that died.

[0404] **Figure 11** shows the mean (± S.E.M.) cumulative clinical scores of days 10 to 28 after treatment. First signs of paralysis were visible from day 13 on (n=5, n=4 for mCD8-targeted AcTaferon). **Figure 12** shows an evaluation of the toxic side effects of daily treatments with the various AcTaferons. Shown are mortality during the course of the experiment (panel A) and leukocyte counts at day 25. Specifically, EDTA-treated blood was collected from the tail vein of mice 3 hours after the last treatment, and lymphocytes (panel B), monocytes (panel C), neutrophils (panel D), platelets (panel E) and red blood cells (panel F) were counted using a HEMAVET950FS hematological analyzer (Drew Scientific). Plotted are means ± S.E.M. (n=5, n=4 for mCD8-targeted AcTaferon, n=2 for wild type mIFN 1.000.000 IU).

Example 8. Dendritic Cell Signaling Induced by Anti-human Clec9A VHH Chimeras

[0405] A dendritic cell pSTAT signaling assay was undertaken. Chimeras studied were anti-human Clec9A VHH/ /human IFN R149A and anti-human Clec9A

VHH/human IFN R33A/E120R. Two doses of the agents were studied: 100 ng/ml and 500 ng/ml.

[0406] The anti-human Clec9A VHH used in this Example was R2CHCL24 (SEQ ID NO:63).

[0407] Briefly, human PBMCs were isolated from blood obtained from healthy donors. Approximately 120 ml of blood was collected from each donor using heparin coated tubes (12 tubes). The blood was kept at room temperature and processed immediately Briefly, blood was diluted 1 :1 with DPBS and 25 ml was gently layered onto 15 ml of Lympholyte H. After centrifugation, the mononuclear cell rings were collected and cells were washed three times with DPBS (PBS Dulbecco's Phosphate Buffered Saline, Wisent, catalog #311-425-LL) and counted. Dendritic cells were enriched from the PBMC population using "DC- enrichment kit" containing a combination of lineage specific monoclonal antibodies in PBS and a suspension of magnetic particles (STEMCELL Technologies Catalogue number 19251), according to manufacturer's instructions.

[0408] Dendritic cells (DC) were stimulated for 15 minutes in the presence or absence of test items and controls (PBS) and the level of phosphorylated-STAT1 (pSTAT1 , specifically pY701-STAT1) was determined in isolated DC cell populations (Lin-(CD14/CD16/CD20/CD56/CD3)/HLA-DR+) by flow cytometry. Post stimulation, cells were fixed (BD Cytofix fixation buffer, BD Bioscience, catalog #554655), then permeabilized with Perm buffer II (BD PhosFlow Perm Buffer, BD Bioscience, catalog #558052). Cells were then stained for phosphoSTAT1 and for DC surface markers (Lin-/HLA-DR+) (see table below). Both intra-cellular and surface staining were performed at the same time. Flow cytometry and data acquisition was performed after cell washing with DPBS.

Table showing list of antibodies for flow cytometry staining

Marker/Product Name	Fluorochrome	Clone	Purpose	Supplier-Catalog Number
pSTAT1	AlexaFluor657	4a	phospho-STAT1	BD-562070
Anti-human CD3	PE	UCHT1	T cells marker Lineage depletion	BD-561809
Anti-human CD14	PE	M5E2	Monocytes markers Lineage depletion	BD-555398
anti-human CD16	PE	B73.1	NK, Neutrophils, Monocytes markers Lineage depletion	BD-561313
anti-human CD19	PE	HIB19	B cells markers Lineage depletion	BD-555413
anti-human CD56	PE	B159	NK cells markers Lineage depletion	BD-555516
Anti-human HLA-DR	FITC	TU36	MHC II markers Lineage depletion	BD-555560
Anti-human CD11c	BV421	B-Ly6	DC discrimination	BD-562561
LIVE/DEAD Fixable Aqua Dead Cell Stain	Aqua	N/Ap	Viability dye	ThermoFisher-L34957
Normal mouse IgG	N/Ap	N/Ap	Fc receptor blocker Blocking agent	ThermoFisher-L10400C

[0409] **Figure 13** shows the data, expressed as a fold change of the percentage of pSTAT+ dendritic cells. This study clearly shows that a human CLEC9A antigen-targeting construct comprising an IFN signaling agent whose activity is recoverable upon cell targeting (IFN R149A) promotes IFN signaling in human dendritic cells (as determined by pSTAT1 induction). In contrast, no IFN signaling activation is observed with a CLEC9A-targeting construct that incorporates an IFN signaling agent whose activity is not recoverable (IFN R33A/E120R). Thus, as observed for comparable IFN fusion constructs targeting mouse CLEC9A, targeting IFN to human dendritic cells using a targeting moiety directed at human CLEC9A antigen results in triggering of a pronounced IFN signal transduction.

Example 9. Modeled Human Anti-Tumor Effects

[0410] The anti-human Clec9A VHH used in this Example was R2CHCL24 (SEQ ID NO:63).

Selection of human cord blood

[0411] Stem cells were HLA-type matched with the expression of HLA-A2 by the tumor cells used during the experiments. To that end, only HLA-A2 positive cord bloods were selected to proceed with CD34 stem cell purification. Cells were stained with HLA-A2-FITC (BD Pharmingen) or HLA-ABC-PE (BD Pharmingen), the latter as a positive control. Samples were acquired on an Attune Nxt Acoustic Focusing Cytometer (Life Technologies).

Purification of CD34⁺ stem cells from human cord blood

[0412] Viable mononuclear cells from human cord bloods were isolated using Fycoll (Lymphoprep, Stemcell technologies) gradient separation prior to CD34+ MACS isolation using a direct CD34+ progenitor cell isolation kit (Miltenyi). Flow cytometric staining using human CD3-PE (BD Phamringen)/human-CD34-APC (BD Pharmingen) was used to evaluate purity of the isolated stem cells. Samples were acquired on an Attune Nxt Acoustic Focusing Cytometer (Life Technologies). Purity of injected cells reached 95-98%.

Generation of humanized mice

[0413] Newborn NSG mice (1-2 days of age) were sublethally irradiated with 100 cGy prior to intrahepatic delivery of 10⁵ CD34+ human stem cells. At 6 weeks after cell transfer, peripheral blood was analyzed for the presence of both human and mouse CD45 (both BD) cells to analyze the effect of engraftment. Samples where acquired on a LSR flow cytometer (BD) and analyzed by FACS Diva software (BD).

[0414] The antitumor potential of chimeras was assessed in tumor-bearing humanized mice models. Newborn NSG mice (1-2 days of age) were sublethally irradiated with 100 cGy prior to intrahepatic delivery of 10⁵ CD34+ human stem cells (from HLA-A2 positive cord bloods). At week 13 after stem cell transfer mice were s.c. inoculated with 2.5 x 10⁶ human RL follicular lymphoma cells. Mice were treated i.p. daily starting at day 6 after tumor inoculation with 30 µl of Flt3L protein. Daily perilesional chimera delivery (30 g) was started at day 10 after tumor inoculation, when a palpable tumor was reached. Treatment with the anti-human Clec9a VHH/anti-human PD-L1 VHH/human IFN-R149A bi-specific chimera resulted in stabilization of the tumor growth, which was even more pronounced when combined with Flt3L injections in contrast to injection of PBS. The graph shows tumor growth as mean ± SEM. Accordingly, the anti-human Clec9a VHH/anti-

human PD-L1 VHH/human IFN-R149A bi-specific chimera showed clear antitumor effects on a human tumor (RL) grown in humanized mice (mice with a reconstituted human immune system). See **Figure 14**.

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SEQUENCE LISTING

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<110> Orionis Biosciences Inc.

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Asn Pro Thr Ser Gly Cys Ser Trp Leu Phe Gln Pro Arg Gly Ala Ala
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Ala Ser Pro Thr Phe Leu Leu Tyr Leu Ser Gln Asn Lys Pro Lys Ala
65 70 75 80

Ala Glu Glv Leu Asp Thr Gln Arg Phe Ser Glv Lys Arg Leu Glv Asp

----- 85 90 95 -----

Thr Phe Val Leu Thr Leu Ser Asp Phe Arg Arg Glu Asn Glu Gly Tyr
100 105 110

Tyr Phe Cys Ser Ala Leu Ser Asn Ser Ile Met Tyr Phe Ser His Phe
115 120 125

Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro Arg
130 135 140

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
145 150 155 160

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
165 170 175

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
180 185 190

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His
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Gly

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Gly

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Gly

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Gly

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Gly

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Gly

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Val	Gly	Leu	Lys	Ala	Glu	Tyr
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Arg Lys Val Gly Gly Pro Asp Tyr
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Asn Thr Phe Gly Asn Val Tyr
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Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Trp Leu Lys
50 55 60

Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
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Leu Val Ala Leu Ser Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
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Val Ser Ser
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20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Thr
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
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Val Ser Ser
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35 40 45

Ala Arg Ile Thr Asn Ile Gly Leu Pro Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Asn Ala Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
85 90 95

Leu Val Ala Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
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Val Ser Ser
115

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile Asn
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
35 40 45

Ala Arg Ile Thr Asn Leu Gly Leu Pro Asn Tyr Ala Asp Ser Val Glu
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Lys Asp Glu Asn Thr Val Tyr Leu
65 70 75 80

Glu Met Asn Thr Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Tyr
85 90 95

Leu Val Gly Leu Lys Ala Glu Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
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Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val

35

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Ala Ala Ile Thr Ser Gly Gly Arg Val Val Tyr Ser Asp Ser Val Lys
505560

Gly Arg Gly Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65707580

Gln Ile Ala Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
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202530

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354045

Ala Ala Ile Thr Ser Gly Gly Arg Thr Ala Tyr Ala Asp Ser Val Lys
505560

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr Leu
65707580

Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Asp Val Tyr Tyr Cys Lys
859095

Ala Tyr Ile Arg Gly Glu Asp Tyr Trp Gly Lys Gly Thr Gln Val Thr
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Val Ser Ser
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Leu Asn
202530

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Leu Val
354045

Ala His Ile Thr Ser Asp Gly Arg Ile Val Tyr Ala Asp Pro Val Lys
505560

Gly Arg Phe Thr Ile Ser Arg Val Asp Gly Lys Asn Met Val Thr Leu
65707580

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
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Val Ser Ser
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile Ser Asn Tyr
20 25 30
Asp Met Ala Trp Ser Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45
Ala Arg Ile Ser Gly Ser Gly Asp Arg Thr Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
Gln Ile Gln Asp Phe Gly Ser Pro Ser Phe Ser Gly Gln Gly Thr Gln
100 105 110
Val Thr Val Ser Ser
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Ile Ser Asn Tyr
20 25 30
Asp Met Ala Trp Ser Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45
Ala Arg Ile Ser Gly Ser Gly Asp Arg Thr Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95
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100 105 110
Val Thr Val Ser Ser
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20 25 30
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35 40 45
Ala Arg Ile Ser Gly Ser Gly Asp Arg Thr Asp Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Asn Cys
85 90 95
Gln Thr Gln Ile Phe Gly Ser Pro Asn Phe Ser Gly Gln Gly Thr Gln
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Val Thr Val Ser Ser
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20 25 30
Leu Met Gln Trp His Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45
Ala Ser Ile Thr Trp Ser Thr Gly Asn Thr His Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Thr Cys
85 90 95
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100 105 110
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20 25 30
Asp Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Tyr Val
35 40 45
Ala Val Ile Ser Ser Ser Gly Asp Ser Thr His Tyr Ser Asp Phe Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Ser
65 70 75 80
Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
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100 105 110
Thr Val Ser Ser
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20 25 30
Asp Met Ala Trp Tyr Arg Gln Ala Pro Gly Lys Glu Arg Glu Tyr Val
35 40 45
Ala Val Ile Ser Ser Ser Gly Asp Ser Thr His Tyr Ser Asp Phe Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Ser
65 70 75 80
Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95
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100 105 110

Thr Val Ser Ser
115

<210> 72
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 72
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Glu Arg Asn Leu Arg Ser Tyr
20 25 30

Asp Met Ala Trp Trp Arg Gln Ala Pro Gly Lys Glu Arg Glu Tyr Val
35 40 45

Ala Val Ile Thr Ser Ser Gly Asp Ser Thr His Tyr Ser Asp Phe Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Ser
65 70 75 80

Leu Gln Met Asp Ser Leu Lys Pro Glu Asp Thr Ala Ser Tyr Tyr Cys
85 90 95

Asn Val Asn Ala Ile Arg Gln Trp Pro Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 73
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 73
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ile Ser Gly Leu Thr Phe Ser Asn Tyr
20 25 30

His Met Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Thr Trp Ser Asp Ala Ser Ile Tyr Tyr Ala Gly Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ile Val Tyr
65 70 75 80

Leu Gln Ile Asp Asn Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 74
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 74
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Thr Leu Ser Cys Ala Ile Ser Gly Leu Thr Phe Ser Ser Tyr
20 25 30

His Met Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Thr Trp Ser Asp Thr Ser Ile Tyr Tyr Ala Gly Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ile Val Tyr
65 70 75 80

Leu Gln Ile Asp Asn Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 75
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 75
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ile Ser Gly Leu Thr Phe Ser Arg Tyr
20 25 30

His Met Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Thr Trp Ser Asp Gly Thr Thr Tyr Tyr Pro Gly Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr
65 70 75 80

Leu Gln Ile Asp Asn Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 76
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 76
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr Leu Ser Ser Tyr
20 25 30

Tyr Ile Ala Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Arg Trp Ser Asp Asp Ser Thr Tyr Tyr Pro Gly Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr
65 70 75 80

Leu Arg Met Asp Asn Leu Lys Pro Glu Asp Thr Ala Arg Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 77
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 77
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr Phe Ser Ser Tyr
20 25 30

Tyr Thr Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Ser Trp Ser Asp Asp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Lys Pro Gly Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 78
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 78
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Leu Thr Leu Ser Ser Tyr
20 25 30

His Met Gly Trp Tyr Arg Gln Ala Pro Gly Arg Glu Arg Glu Phe Val
35 40 45

Ala Gln Ile Ser Trp Ser Asp Asp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Asp Ala Arg Lys Val Gly Gly Pro Asp Tyr Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
115

<210> 79
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 79
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Val Thr Gly Trp Tyr Arg Gln Thr Pro Gly Lys Glu Arg Glu Pro Val
35 40 45

Ala Thr Val Ser Trp Gly Gly Val Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ala Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Asn
85 90 95

Val Asn Thr Phe Gly Asn Val Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 80
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 80
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

20 25 30

Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala His Ile Gly Ser Gly Gly Gly Tyr Pro Ser Tyr Thr Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Glu Met Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 84
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 84
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30

Val Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala His Ile Gly Ser Gly Gly Gly His Ala Thr Tyr Thr Asp Ser Val
50 55 60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Glu Phe Leu Gly Arg Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 85
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 85
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Gly Ser Gly Gly Gly Ile Thr Ser Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Lys His Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Glu Thr Val Ile Lys Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 86
<211> 165
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 86
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 87
<211> 165
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 87
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 88
<211> 157
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 88
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val
1 5 10 15

Val Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg
20 25 30

Ala Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu
35 40 45

Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe
50 55 60

Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
65 70 75 80

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

85	90	95		
Ile Lys Ser Pro Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys	100	105	110	
Pro Trp Tyr Glu Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys	115	120	125	
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe	130	135	140	
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu	145	150	155	
<210> 89				
<211> 171				
<212> PRT				
<213> Artificial Sequence				
<220>				
<223> Synthetic Sequence				
<400> 89				
Leu Pro Gly Val Gly Leu Thr Pro Ser Ala Ala Gln Thr Ala Arg Gln	1	5	10	15
His Pro Lys Met His Leu Ala His Ser Asn Leu Lys Pro Ala Ala His	20	25	30	
Leu Ile Gly Asp Pro Ser Lys Gln Asn Ser Leu Leu Trp Arg Ala Asn	35	40	45	
Thr Asp Arg Ala Phe Leu Gln Asp Gly Phe Ser Leu Ser Asn Asn Ser	50	55	60	
Leu Leu Val Pro Thr Ser Gly Ile Tyr Phe Val Tyr Ser Gln Val Val	65	70	75	80
Phe Ser Gly Lys Ala Tyr Ser Pro Lys Ala Thr Ser Ser Pro Leu Tyr	85	90	95	
Leu Ala His Glu Val Gln Leu Phe Ser Ser Gln Tyr Pro Phe His Val	100	105	110	
Pro Leu Leu Ser Ser Gln Lys Met Val Tyr Pro Gly Leu Gln Glu Pro	115	120	125	
Trp Leu His Ser Met Tyr His Gly Ala Ala Phe Gln Leu Thr Gln Gly	130	135	140	
Asp Gln Leu Ser Thr His Thr Asp Gly Ile Pro His Leu Val Leu Ser	145	150	155	160
Pro Ser Thr Val Phe Phe Gly Ala Phe Ala Leu	165	170		
<210> 90				
<211> 281				
<212> PRT				
<213> Artificial Sequence				
<220>				
<223> Synthetic Sequence				
<400> 90				
Met Ala Met Met Glu Val Gln Gly Gly Pro Ser Leu Gly Gln Thr Cys	1	5	10	15
Val Leu Ile Val Ile Phe Thr Val Leu Leu Gln Ser Leu Cys Val Ala	20	25	30	
Val Thr Tyr Val Tyr Phe Thr Asn Glu Leu Lys Gln Met Gln Asp Lys	35	40	45	
Tyr Ser Lys Ser Gly Ile Ala Cys Phe Leu Lys Glu Asp Asp Ser Tyr	50	55	60	
Trp Asp Pro Asn Asp Glu Glu Ser Met Asn Ser Pro Cys Trp Gln Val	65	70	75	80
Lys Trp Gln Leu Arg Gln Leu Val Arg Lys Met Ile Leu Arg Thr Ser	85	90	95	
Glu Glu Thr Ile Ser Thr Val Gln Glu Lys Gln Gln Asn Ile Ser Pro	100	105	110	
Leu Val Arg Glu Arg Gly Pro Gln Arg Val Ala Ala His Ile Thr Gly	115	120	125	
Thr Arg Gly Arg Ser Asn Thr Leu Ser Ser Pro Asn Ser Lys Asn Glu	130	135	140	

Lys Ala Leu Gly Arg Lys Ile Asn Ser Trp Glu Ser Ser Arg Ser Gly
145 150 155 160

His Ser Phe Leu Ser Asn Leu His Leu Arg Asn Gly Glu Leu Val Ile
165 170 175

His Glu Lys Gly Phe Tyr Tyr Ile Tyr Ser Gln Thr Tyr Phe Arg Phe
180 185 190

Gln Glu Glu Ile Lys Glu Asn Thr Lys Asn Asp Lys Gln Met Val Gln
195 200 205

Tyr Ile Tyr Lys Tyr Thr Ser Tyr Pro Asp Pro Ile Leu Leu Met Lys
210 215 220

Ser Ala Arg Asn Ser Cys Trp Ser Lys Asp Ala Glu Tyr Gly Leu Tyr
225 230 235 240

Ser Ile Tyr Gln Gly Gly Ile Phe Glu Leu Lys Glu Asn Asp Arg Ile
245 250 255

Phe Val Ser Val Thr Asn Glu His Leu Ile Asp Met Asp His Glu Ala
260 265 270

Ser Phe Phe Gly Ala Phe Leu Val Gly
275 280

<210> 91
<211> 153
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 91
Ala Pro Val Arg Ser Leu Asn Cys Thr Leu Arg Asp Ser Gln Gln Lys
1 5 10 15

Ser Leu Val Met Ser Gly Pro Tyr Glu Leu Lys Ala Leu His Leu Gln
20 25 30

Gly Gln Asp Met Glu Gln Gln Val Val Phe Ser Met Ser Phe Val Gln
35 40 45

Gly Glu Glu Ser Asn Asp Lys Ile Pro Val Ala Leu Gly Leu Lys Glu
50 55 60

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

Gln Leu Glu Ser Val Asp Pro Lys Asn Tyr Pro Lys Lys Lys Met Glu
85 90 95

Lys Arg Phe Val Phe Asn Lys Ile Glu Ile Asn Asn Lys Leu Glu Phe
100 105 110

Glu Ser Ala Gln Phe Pro Asn Trp Tyr Ile Ser Thr Ser Gln Ala Glu
115 120 125

Asn Met Pro Val Phe Leu Gly Gly Thr Lys Gly Gly Gln Asp Ile Thr
130 135 140

Asp Phe Thr Met Gln Phe Val Ser Ser
145 150

<210> 92
<211> 133
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 92
Ala Pro Thr Ser Ser Ser Thr Lys Lys Thr Gln Leu Gln Leu Glu His
1 5 10 15

Leu Leu Leu Asp Leu Gln Met Ile Leu Asn Gly Ile Asn Asn Tyr Lys
20 25 30

Asn Pro Lys Leu Thr Arg Met Leu Thr Phe Lys Phe Tyr Met Pro Lys
35 40 45

Lys Ala Thr Glu Leu Lys His Leu Gln Cys Leu Glu Glu Leu Lys
50 55 60

Pro Leu Glu Glu Val Leu Asn Leu Ala Gln Ser Lys Asn Phe His Leu
65 70 75 80

Arg Pro Arg Asp Leu Ile Ser Asn Ile Asn Val Ile Val Leu Glu Leu
85 90 95

Lys Gly Ser Glu Thr Thr Phe Met Cys Glu Tyr Ala Asp Glu Thr Ala
100 105 110

Thr Ile Val Glu Phe Leu Asn Arg Trp Ile Thr Phe Cys Gln Ser Ile
115 120 125

Ile Ser Thr Leu Thr
130

<210> 93
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 93
His Lys Cys Asp Ile Thr Leu Gln Glu Ile Ile Lys Thr Leu Asn Ser
1 5 10 15

Leu Thr Glu Gln Lys Thr Leu Cys Thr Glu Leu Thr Val Thr Asp Ile
20 25 30

Phe Ala Ala Ser Lys Asn Thr Thr Glu Lys Glu Thr Phe Cys Arg Ala
35 40 45

Ala Thr Val Leu Arg Gln Phe Tyr Ser His His Glu Lys Asp Thr Arg
50 55 60

Cys Leu Gly Ala Thr Ala Gln Gln Phe His Arg His Lys Gln Leu Ile
65 70 75 80

Arg Phe Leu Lys Arg Leu Asp Arg Asn Leu Trp Gly Leu Ala Gly Leu
85 90 95

Asn Ser Cys Pro Val Lys Glu Ala Asn Gln Ser Thr Leu Glu Asn Phe
100 105 110

Leu Glu Arg Leu Lys Thr Ile Met Arg Glu Lys Tyr Ser Lys Cys Ser
115 120 125

Ser

<210> 94
<211> 185
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 94
Ala Pro Val Pro Pro Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His
1 5 10 15

Arg Gln Pro Leu Thr Ser Ser Glu Arg Ile Asp Lys Gln Ile Arg Tyr
20 25 30

Ile Leu Asp Gly Ile Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser
35 40 45

Asn Met Cys Glu Ser Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn
50 55 60

Leu Pro Lys Met Ala Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn
65 70 75 80

Glu Glu Thr Cys Leu Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu
85 90 95

Val Tyr Leu Glu Tyr Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln
100 105 110

Ala Arg Ala Val Gln Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln
115 120 125

Lys Lys Ala Lys Asn Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr
130 135 140

Asn Ala Ser Leu Thr Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln
145 150 155 160

Asp Met Thr Thr His Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln
165 170 175

Ser Ser Leu Arg Ala Leu Arg Gln Met
180 185

<210> 95
<211> 114
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 95

Ser Pro Gly Pro Val Pro Pro Ser Thr Ala Leu Arg Glu Leu Ile Glu
1 5 10 15

Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn Gly
20 25 30

Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala Ala
35 40 45

Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys Thr
50 55 60

Gln Arg Met Leu Ser Gly Phe Cys Pro His Lys Val Ser Ala Gly Gln
65 70 75 80

Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln Phe
85 90 95

Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe Arg Glu Gly Arg
100 105 110

Phe Asn

<210> 96

<211> 194

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 96

Met Ala Ala Glu Pro Val Glu Asp Asn Cys Ile Asn Phe Val Ala Met
1 5 10 15

Lys Phe Ile Asp Asn Thr Leu Tyr Phe Ile Ala Glu Asp Asp Glu Asn
20 25 30

Leu Glu Ser Asp Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile
35 40 45

Arg Asn Leu Asn Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro
50 55 60

Leu Phe Glu Asp Met Thr Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg
65 70 75 80

Thr Ile Phe Ile Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met
85 90 95

Ala Val Thr Ile Ser Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys
100 105 110

Glu Asn Lys Ile Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile
115 120 125

Lys Asp Thr Lys Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly
130 135 140

His Asp Asn Lys Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe
145 150 155 160

Leu Ala Cys Glu Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys
165 170 175

Glu Asp Glu Leu Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu
180 185 190

Asp Leu

<210> 97

<211> 270

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 97

Met Lys Pro Lys Met Lys Tyr Ser Thr Asn Lys Ile Ser Thr Ala Lys
1 5 10 15

Trp Lys Asn Thr Ala Ser Lys Ala Leu Cys Phe Lys Leu Gly Lys Ser
20 25 30

Gln Gln Lys Ala Lys Glu Val Cys Pro Met Tyr Phe Met Lys Leu Arg
35 40 45

Ser	Gly	Leu	Met	Ile	Lys	Lys	Glu	Ala	Cys	Tyr	Phe	Arg	Arg	Glu	Thr
50					55						60				
Thr	Lys	Arg	Pro	Ser	Leu	Lys	Thr	Gly	Arg	Lys	His	Lys	Arg	His	Leu
65					70					75					80
Val	Leu	Ala	Ala	Cys	Gln	Gln	Gln	Ser	Thr	Val	Glu	Cys	Phe	Ala	Phe
				85					90					95	
Gly	Ile	Ser	Gly	Val	Gln	Lys	Tyr	Thr	Arg	Ala	Leu	His	Asp	Ser	Ser
				100					105					110	
Ile	Thr	Gly	Ile	Ser	Pro	Ile	Thr	Glu	Tyr	Leu	Ala	Ser	Leu	Ser	Thr
		115					120					125			
Tyr	Asn	Asp	Gln	Ser	Ile	Thr	Phe	Ala	Leu	Glu	Asp	Glu	Ser	Tyr	Glu
	130					135					140				
Ile	Tyr	Val	Glu	Asp	Leu	Lys	Lys	Asp	Glu	Lys	Lys	Asp	Lys	Val	Leu
145					150					155					160
Leu	Ser	Tyr	Tyr	Glu	Ser	Gln	His	Pro	Ser	Asn	Glu	Ser	Gly	Asp	Gly
				165					170					175	
Val	Asp	Gly	Lys	Met	Leu	Met	Val	Thr	Leu	Ser	Pro	Thr	Lys	Asp	Phe
			180						185				190		
Trp	Leu	His	Ala	Asn	Asn	Lys	Glu	His	Ser	Val	Glu	Leu	His	Lys	Cys
	195						200					205			
Glu	Lys	Pro	Leu	Pro	Asp	Gln	Ala	Phe	Phe	Val	Leu	His	Asn	Met	His
	210					215					220				
Ser	Asn	Cys	Val	Ser	Phe	Glu	Cys	Lys	Thr	Asp	Pro	Gly	Val	Phe	Ile
225					230					235					240
Gly	Val	Lys	Asp	Asn	His	Leu	Ala	Leu	Ile	Lys	Val	Asp	Ser	Ser	Glu
				245					250					255	
Asn	Leu	Cys	Thr	Glu	Asn	Ile	Leu	Phe	Lys	Leu	Ser	Glu	Thr		
			260					265					270		
<210> 98															
<211> 447															
<212> PRT															
<213> Artificial Sequence															
<220>															
<223> Synthetic Sequence															
<400> 98															
Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Val	Glu	Val	Lys	Lys	Pro	Gly	Ala
1			5						10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
			20					25					30		
Tyr	Met	Tyr	Trp	Val	Arg	Gln	Ala</								

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 99

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 99

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 100
<211> 440
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 100
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
115 120 125

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
180 185 190

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
210 215 220

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225 230 235 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245 250 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
260 265 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
275 280 285

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
290 295 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
305 310 315 320

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
325 330 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
340 345 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
355 360 365

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
370 375 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385 390 395 400

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
405 410 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
420 425 430

Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> 101

<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 101
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 102
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 102
Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 103
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 103
Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 104
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 104
Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 105
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 105
Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 106
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 106
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 107
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 107
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 108
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 108
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 109
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 109

Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 110
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 110
Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Asn Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 111
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 111
Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
1 5 10 15

Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
20 25 30

Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
35 40 45

Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
50 55 60

Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
65 70 75 80

Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
85 90 95

Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
100 105 110

Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
115 120 125

Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
130 135 140

Thr Ser His Ser Arg Thr Pro Glu Glv Leu Trp Gln Val Thr Ser Val

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145          150          155          160

Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
      165          170          175

Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
      180          185          190

Gln Met Glu Pro Arg Thr His Pro Thr Trp Leu Leu His Ile Phe Ile
      195          200          205

Pro Phe Cys Ile Ile Ala Phe Ile Phe Ile Ala Thr Val Ile Ala Leu
      210          215          220

Arg Lys Gln Leu Cys Gln Lys Leu Tyr Ser Ser Lys Asp Thr Thr Lys
225          230          235          240

Arg Pro Val Thr Thr Thr Lys Arg Glu Val Asn Ser Ala Ile
      245          250

<210> 112
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 112
Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
1      5      10      15

Ile Ala Ala Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile
      20      25      30

Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser
      35      40      45

His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn
      50      55      60

Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu
65          70          75          80

Pro Leu Gly Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp
      85      90      95

Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr
      100     105     110

Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr
      115     120     125

His Ile Leu Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln
      130     135     140

Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val
145     150     155     160

Pro Ala Asn Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val
      165     170     175

Thr Ser Val Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys
      180     185     190

Val Phe Trp Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp
      195     200     205

Leu Gln Ser Gln Met Glu Pro Arg Thr His Pro Thr Trp Glu Pro Lys
      210     215     220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225     230     235     240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
      245     250     255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
      260     265     270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
      275     280     285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
      290     295     300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305     310     315     320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
      325     330     335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
      340     345     350
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340 345 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
355 360 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
370 375 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385 390 395 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly Lys
450

<210> 113
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<220>
<221> BRANCHED
<222> (9)..(15)
<223> SNTSESFK(SNTSESF)FRVTQLAPKAQIKE

<400> 113
Ser Asn Thr Ser Glu Ser Phe Lys Ser Asn Thr Ser Glu Ser Phe Phe
1 5 10 15

Arg Val Thr Gln Leu Ala Pro Lys Ala Gln Ile Lys Glu
20 25

<210> 114
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 114
Glu Val Gln Leu Gln Gln Ser Gly Pro Val Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asn Ile Asn Pro Tyr Asn Gly Gly Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

Met Glu Ile Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Ile Tyr Asp Gly Ser Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ala Leu Thr Val Ser Ser
115

<210> 115
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 115
Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Cys Ala Ser Gln Gly
1 5 10 15

Gly Lys Val Thr Val Thr Cys Lys Ala Ser Gln Asp Ile Asn Asn Tyr
20 25 30

Met Ala Thr Thr Gln His Lys Pro Glu Lys Gly Pro Arg Leu Leu Ile

Met Ala Asp Tyr Gln His Lys Phe Gly Lys Gly Phe Arg Leu Leu Ile
35 40 45

His Tyr Thr Ser Thr Leu Leu Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asn Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 116
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 116
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly His Ile Asn Pro Ser Ser Gly Phe Thr Thr Tyr Asn Gln Asn Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Tyr Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Glu Asp Tyr Asp Val Asp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 117
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 117
Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Ser Val Asp Thr Asn
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Phe Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 118
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 118
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Thr Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Gly Ser Phe Tyr Glu Tyr Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 119
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 119
Gln Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Leu Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 120
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 120
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Lys
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Glu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Ala Glu Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 121
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 121
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ala Ser Ile His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Val Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Gly Asp Lys His Gln Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 122
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 122
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Ser Ser Ile His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ala Ile Thr Trp Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Gly Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Ala Gln Ser Ser Trp Tyr Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 123
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 123
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Gly Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asn
20 25 30

Ala Met Ala Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Leu Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Glu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Ala Asp Arg Val Asp Ser Asn Trp Tyr Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 124
<211> 120
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 124

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

<210> 125

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 125

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

<210> 126

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 126

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

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Lys Asp Arg Ala Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Arg Asp Ser Ser Gly Tyr His Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 130
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 130
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Thr Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Glu Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 131
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 131
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 132
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 132
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
35 40 45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala

50					55					60					
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser
65					70					75					80
Ser	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ser	Trp
				85					90					95	
Glu	Ile	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	
			100					105					110		

<210> 133
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

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<400> 133
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1             5             10             15

Gln Arg Leu Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
      20             25             30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
      35             40             45

Lys Leu Leu Ile Lys Phe Gly Ser Asn Leu Glu Ser Gly Ile Pro Ala
 50             55             60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65             70             75             80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Trp
      85             90             95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100             105             110

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<210> 134
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 134

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

<210> 135
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 135

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 136
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 136
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 137
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 137
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 138
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 138
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 139
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 139
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
20 25 30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 140
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 140
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 141
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 141
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 142
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 142
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

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Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 143
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 143
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Ser Thr Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 144
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 144
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 145
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 145
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

[illegible]

<210> 146
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 146

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 147
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

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<400> 147
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1          5          10          15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
          20          25          30
Asp Val His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
          35          40          45
Gly Trp Leu His Ala Asp Thr Gly Ile Thr Lys Phe Ser Gln Lys Phe
          50          55          60
Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
          65          70          75          80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
          85          90          95
Ala Arg Glu Arg Ile Gln Leu Trp Phe Asp Tyr Trp Gly Gln Gly Thr
          100          105          110
Leu Val Thr Val Ser Ser
          115

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<210> 148
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 148

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 149

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 149

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Ile Phe Ser Thr Tyr
20 25 30

Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn His Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gln Gly Ile Ala Ala Ala Leu Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 150

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 150

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 151

<211> 113

<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 151
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Val Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Asn Ser Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 152
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 152
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 153
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 153
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Asp Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Arg Ala His Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Lys Phe His Phe Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 154
<211> 106

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 154
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 155
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 155
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Lys Ala His Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Lys Tyr Asp Tyr Val Ser Gly Ser Pro Phe Gly Met Asp Val
 100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 156
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 156
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
 85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 157

<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 157
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Ser Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Asp Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Ala Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Ser Gly Trp Ser Arg Tyr Tyr Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 158
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 158
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 159
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 159
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Leu Phe Gly Ile Ala His Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Lys Tyr Ser Tyr Val Ser Gly Ser Pro Phe Gly Met Asp Val
100 105 110

Met Glu Gly Gly Thr Thr Val Thr Thr Val Ser Ser
115 120

trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 160
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 160
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Thr
85 90 95
Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 161
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 161
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Thr Phe Asp Asp Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Ser Trp Asn Arg Gly Arg Ile Glu Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Ala Lys Gly Arg Phe Arg Tyr Phe Asp Trp Phe Leu Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 162
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 162
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 163
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 163
Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Val
35 40 45

Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65 70 75 80

Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Tyr Gly Gly Trp Leu Ser Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 164
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 164
Asp Ile Val Met Thr Gln Ser His Lys Leu Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Asp Ser Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys
100 105

<210> 165
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 165
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
20 25 30

Ser Ile Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Met Trp Ala Gly Gly Gly Thr Asn Ser Asn Ser Val Leu Lys
50 55 60

Ser Arg Leu Ile Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala

859095

Arg Tyr Tyr Gly Asn Ser Pro Tyr Tyr Ala Ile Asp Tyr Trp Gly Gln
100105110

Gly Thr Ser Val Thr Val Ser Ser
115120

<210> 166

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 166

Asp Ile Val Thr Thr Gln Ser His Lys Leu Met Ser Thr Ser Val Gly
151015

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
202530

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
354045

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
505560

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65707580

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Asp Ser Ser Tyr Pro Leu
859095

Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys
100105

<210> 167

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 167

Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
151015

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Tyr Ser Ile Ile Ser Asp
202530

Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Leu
354045

Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
505560

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65707580

Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
859095

Arg Arg Gly Gly Trp Leu Leu Pro Phe Asp Tyr Trp Gly Gln Gly Thr
100105110

Thr Leu Thr Val Ser Ser
115

<210> 168

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 168

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
151015

Glu Lys Val Ser Met Gly Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
202530

Ser Asn Gln Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
354045

Ser Pro Lys Leu Leu Ile Asp Trp Ala Ser Thr Arg Glu Ser Gly Val
505560

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Gly Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 169

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 169

Glu Val Lys Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asp Ile Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Phe Pro Arg Asp Asn Asn Thr Lys Tyr Asn Glu Asn Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu His Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Thr Lys Glu Asn Trp Val Gly Asp Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Leu Ser Ser
115

<210> 170

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 170

Asp Ile Val Met Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Ile Arg Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Thr Ser Pro Lys Arg Trp Ile Ser
35 40 45

Asp Thr Ser Lys Leu Thr Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ala Leu Thr Ile Ser Ser Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser Ser Tyr Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 171

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 171

Glu Val Gln Leu Gln Gln Ser Gly Pro Asp Leu Val Thr Pro Gly Ala
1 5 10 15

Ser Val Arg Ile Ser Cys Gln Ala Ser Gly Tyr Thr Phe Pro Asp Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile

35 40 45

Gly Asp Ile Asp Pro Asn Tyr Gly Gly Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Val Asp Arg Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ala Leu Thr Asp Trp Gly Gln Gly Thr Ser Leu Thr Val
100 105 110

Ser Ser

<210> 172
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 172

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

Tyr Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Phe Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Thr Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Asn Asn Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 173
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 173

Glu Val Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 174
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 174

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

202530

Val Met His Trp Val Lys Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
354045

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
505560

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65707580

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 175
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 175

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
151015

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
202530

Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
354045

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
505560

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65707580

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 176
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 176

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
151015

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
202530

Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
354045

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
505560

Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65707580

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 177
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 177
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Tyr Val Asn Pro Phe Asn Asp Gly Thr Lys Tyr Asn Glu Met Phe
50 55 60

Lys Gly Arg Ala Thr Ile Thr Ser Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ala Trp Gly Tyr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 178
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 178
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Ser Leu Glu Glu Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 179
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 179
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Ser Leu Glu Ala Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 180
<211> 111
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 180

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Ser Leu Glu Ala Glu Asp Ala Ala Met Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 181

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 181

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Val Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Val Asp Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Arg Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 182

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 182

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Ser Ser Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Val Thr Ser Met Val Ala Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 183

<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 183
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Ala Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Gln Lys Tyr Val
20 25 30

Phe Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Arg Ser Gly Asn His
85 90 95

Arg Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu
100 105

<210> 184
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 184
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Gly Glu Gln Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Trp Asn Tyr Gly Tyr Tyr Asp Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 185
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 185
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Phe Gly Thr Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Ile
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 186
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 186
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 187
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 187
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Glu Val Glu Ile Lys
100 105

<210> 188
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 188
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Arg Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Tyr Asp Ser Ser Gly Tyr Leu Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 189
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 189
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ile Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 190
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 190
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Gly Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gln Leu Tyr Ser Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 191
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 191
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Ser Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Leu Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Leu Pro Pro
85 90 95

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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105
<210> 192
<211> 121
<212> PRT
<213> Artificial Sequence
<220>
<223> Synthetic Sequence
<400> 192
Glu Val Gln Leu Leu Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Ser Gly Ser Gly Gly Phe Thr Phe Ser Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Ser Ala Val Tyr Ser Cys
85 90 95
Ala Lys Val Leu Val Gly Phe Asn Asn Gly Cys Trp Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser
115 120
<210> 193
<211> 108
<212> PRT
<213> Artificial Sequence
<220>
<223> Synthetic Sequence
<400> 193
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45
Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Asn Asp His
85 90 95
Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105
<210> 194
<211> 120
<212> PRT
<213> Artificial Sequence
<220>
<223> Synthetic Sequence
<400> 194
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Asp Leu Val Thr Ser Met Val Ala Phe Asp Tyr Trp Gly Gln
100105110

Gly Thr Leu Val Thr Val Ser Ser
115120

<210> 195
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 195
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
151015

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Gln Lys Tyr Val
202530

Phe Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Val Leu Val Ile Tyr
354045

Glu Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
505560

Ser Ser Gly Thr Met Ala Thr Leu Thr Ile Ser Gly Ala Gln Val Glu
65707580

Asp Glu Ala Asp Tyr Tyr Cys Tyr Ser Thr Asp Arg Ser Gly Asn His
859095

Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100105

<210> 196
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 196
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
202530

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
354045

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65707580

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly
100105110

Gln Gly Thr Leu Val Thr Val Ser Ser
115120

<210> 197
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 197
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
151015

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser
202530

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
354045

Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
505560

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

65 - - - 70 - 75 - 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 198
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 198
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 199
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 199
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 200
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 200
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

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Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 201
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 201
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val
65 70 75 80

Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 202
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 202
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 203
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 203
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 204
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 204
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val
65 70 75 80

Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 205
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 205
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 206
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 206
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 207
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 207
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 208
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 208
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 209
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 209
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
 20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
 35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
65 70 75 80

Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 210
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 210
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
 20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
 35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 211
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 211
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
 20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
 35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Ile Pro Pro Arg Phe Ser Gly
 50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Ile Glu Ser
65 70 75 80

Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 212
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 212
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 213
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 213
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 214
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 214
Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 215
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 215
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 216
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 216
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Arg Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Asp Cys Ala
85 90 95

Arg Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Glu
115

<210> 217
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 217
Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Lys Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Ile Val Ser Ala
115

<210> 218
<211> 116
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 218

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Thr Tyr
20 25 30

Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Arg Gly Val Thr Thr Asp Tyr Asn Ala Ala Phe Met
50 55 60

Ser Arg Leu Thr Ile Thr Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser
115

<210> 219

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 219

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
20 25 30

Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ser Gly Gly Val Thr Asp Tyr Asn Ala Ala Phe Ile
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser
115

<210> 220

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 220

Glu Val Lys Leu Phe Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Thr Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Asn Pro Asp Ser Thr Thr Ile Asn Tyr Ala Pro Ser Leu
50 55 60

Lys Asp Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Pro Gly Asp Tyr Gly Tyr Asp Phe Asp Cys Trp Gly Gln Gly
100 105 110

100105110

Thr Thr Leu Thr Val Ser Ser
115

<210> 221

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 221

Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
151015

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
202530

Tyr Trp Asn Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
354045

Gly Tyr Ile Ser Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
505560

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65707580

Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
859095

Arg Ser Leu Leu Trp Phe Ser Thr Gly Phe Ala Tyr Trp Gly Gln Gly
100105110

Thr Leu Val Thr Val Ser Ala
115

<210> 222

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 222

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
151015

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
202530

Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
354045

Gly Val Ile Trp Ser Gly Gly Ile Thr Asp Tyr Asn Ala Ala Phe Lys
505560

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65707580

Lys Met Asn Ser Leu Gln Ala Asn Asp Thr Ala Ile Tyr Phe Cys Ala
859095

Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100105110

Thr Val Ser Ser
115

<210> 223

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 223

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
151015

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Tyr
202530

Gly Met Ser Trp Ala Arg Gln Ile Pro Glu Lys Arg Leu Glu Trp Val
354045

Ala Ser Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Leu Gly Ser Val Gln
505560

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Gly Tyr Asp Ala Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Ser Val Ser Glu
115

<210> 224
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 224
Glu Val Gln Leu Gln Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Gly
20 25 30

Tyr Trp Thr Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
35 40 45

Gly Tyr Ile Ser Tyr Thr Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Ile Ser Ile Ser Arg Asp Thr Ser Lys Ser Gln Tyr Tyr Leu
65 70 75 80

Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Gln Arg Asp Trp Leu Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ala
115

<210> 225
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 225
Glu Glu Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Ile Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Ile Leu Tyr Leu
65 70 75 80

Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Gly Tyr Asp Ala Gly Phe Ala Phe Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Ala Ser Ala
115

<210> 226
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 226
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Thr Tyr
20 25 30

Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Arg Gly Val Thr Thr Asp Tyr Asn Ala Ala Phe Met
50 55 60

Ser Arg Leu Thr Ile Thr Lys Asp Asn Ser Lys Asn Gln Val Val Leu
65 70 75 80

Thr Met Asn Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Leu Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 227
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 227
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Arg Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Tyr Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asp Cys Ala
85 90 95

Arg Gly Tyr Asp Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 228
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 228
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Ser Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 229
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 229
Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Ser Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 230
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 230
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ala Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ile Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 231
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 231
Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 232
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 232
Asp Val Leu Met Thr Gln Thr Pro Leu Tyr Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ile Ile Val His Ser
20 25 30

Asn Ala Asn Thr Tyr Leu Glu Trp Phe Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 233
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 233
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Leu Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu Tyr Trp Asn Gln Gln Lys Pro Gly Ser Ser Pro Lys Val Trp
35 40 45

Ile Tyr Asn Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Ser Tyr Phe Cys His Gln Trp Arg Ser Tyr Pro
85 90 95

Pro Thr Leu Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 234
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 234
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Asn Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Gly Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 235
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 235
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

1 3 10 13

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln Asn Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 236
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 236
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Ser Asn Gln Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Asn Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Ser Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Lys Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 237
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 237
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Tyr Ser Tyr Val His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 238
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 238
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ala Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Tyr Thr Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 239
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 239
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Ser Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65 70 75 80

Pro Val Glu Ala Asn Asp Thr Ala Asn Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 240
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 240
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Ser Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 241
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 241
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

20										25					30				
Trp	Met	His	Trp	Ile	Arg	Gln	Ser	Pro	Ser	Arg	Gly	Leu	Glu	Trp	Leu				
		35					40					45							
Gly	Asn	Ile	Tyr	Pro	Gly	Thr	Gly	Gly	Ser	Asn	Phe	Asp	Glu	Lys	Phe				
	50					55					60								
Lys	Asn	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr				
65					70					75					80				
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
				85					90					95					
Thr	Arg	Trp	Thr	Thr	Gly	Thr	Gly	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Thr				
		100						105					110						
Val	Thr	Val	Ser	Ser															
		115																	

<210> 242
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

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<400> 242
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1             5              10              15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr Tyr
          20                25              30
Trp Met His Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu
      35             40              45
Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
    50            55              60
Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65           70              75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
          85              90              95
Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
      100             105              110
Val Thr Val Ser Ser
     115
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<210> 243
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 243

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

<210> 244
<211> 113
<212> PRT
<213> Artificial Sequence
<220>

<223> Synthetic Sequence

<400> 244
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 245
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 245
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Ile
50 55 60

Pro Pro Arg Phe Ser Gly Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Asn Ile Glu Ser Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 246
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 246
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
35 40 45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 247
<211> 113

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 247
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 248
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 248
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
35 40 45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 249
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 249
Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 250
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 250
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 251
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 251
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

Ser Pro Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 252
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 252
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
35 40 45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys
<210> 253
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 253
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
20 25 30

Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 254
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 254
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 255
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 255
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
20 25 30

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Trp Ala
35 40 45

Ser Ser Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Ser Cys
85 90 95

Ala Ala Ser Gln Ala Pro Ile Thr Ile Ala Thr Met Met Lys Pro Phe
100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 256
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 256
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
20 25 30
Ala Lys Cys Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Trp Val
35 40 45
Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95
Ala Ala Arg His Gly Gly Pro Leu Thr Val Glu Tyr Phe Phe Asp Tyr
100 105 110
Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 257
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 257
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Tyr Tyr
20 25 30
Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Ala Arg Glu Gly Val
35 40 45
Ser Cys Ile Ser Gly Gly Asp Asn Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Gly Gly Trp Lys Tyr Cys Ser Gly Tyr Asp Pro Glu Tyr Ile
100 105 110
Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 258
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 258
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Gln Tyr
20 25 30
Asp Val Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

33 40 43

Ala Phe Ser Ser Ser Gly Gly Arg Thr Ile Tyr Pro Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Phe Ser Arg Asp Asn Thr Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Thr Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Lys
85 90 95

Ile Asp Trp Tyr Leu Asn Ser Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 259
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 259
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Asp Ala Ser Asn Ser
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Trp Val
35 40 45

Ala Arg Ile Thr Gly Gly Gly Leu Ile Ala Tyr Thr Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Glu Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Thr Ile Asn Ser Arg Asp Gly Trp Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser

<210> 260
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 260
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Thr Ile Ser Cys Ala Ala Ser Gly Ile Thr Phe Ser Asp Ser
20 25 30

Ile Val Ser Trp Tyr Arg Arg Ala Arg Gly Lys Gln Arg Glu Trp Val
35 40 45

Ala Gly Ile Ser Asn Gly Gly Thr Thr Lys Tyr Ala Glu Ser Val Leu
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Asn Val Tyr Leu
65 70 75 80

Gln Met Asn Gly Leu Asn Pro Glu Asp Thr Ala Val Tyr Leu Cys Lys
85 90 95

Val Arg Gln Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
100 105 110

<210> 261
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 261
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
20 25 30

Ala Lys Cys Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Trp Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Ala Arg His Gly Gly Pro Leu Thr Val Glu Tyr Phe Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 262
<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 262
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Ser Thr Val Leu Ile Asn
20 25 30

Ala Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Ser Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Asn
85 90 95

Ala Asp Val Tyr Pro Gln Asp Tyr Gly Leu Gly Tyr Val Glu Gly Lys
100 105 110

Val Tyr Tyr Gly His Asp Tyr Trp Gly Thr Gly Thr Leu Val Thr Val
115 120 125

Ser Ser
130

<210> 263
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 263
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Thr Phe Ser Asn Tyr
20 25 30

Val Ser Asn Tyr Ala Met Gly Trp Gly Arg Gln Ala Pro Gly Thr Gln
35 40 45

Arg Glu Leu Val Ala Ser Ile Ser Asn Gly Asp Thr Thr Asn Tyr Ala
50 55 60

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
65 70 75 80

Thr Val Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Phe Glu His Gln Val Ala Gly Leu Thr Trp Gly Gln Gly
100 105 110

Thr Gln Val Thr Val Ser Ser
115

<210> 264
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<220>
<221> misc-feature
<222> (27)..(27)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc-feature
<222> (32)..(32)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc-feature
<222> (75)..(75)
<223> Xaa can be any naturally occurring amino acid

<400> 264
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Xaa Ala Leu Lys Ile Xaa
20 25 30

Val Met Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Leu Val
35 40 45

Ala Ala Ile Thr Ser Gly Gly Arg Thr Asn Tyr Ser Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Gly Asp Asn Ala Xaa Asn Thr Val Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Arg
85 90 95

Glu Trp Asn Ser Gly Tyr Pro Pro Val Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Gln Val Thr Val Ser Ser
115

<210> 265
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 265
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Gly
20 25 30

Thr Met Gly Trp Phe Arg Arg Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Ser Ile Pro Trp Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ala Gln Asn Thr Val Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Phe Lys Glu Arg Ser Thr Gly Trp Asp Phe Ala Ser Trp Gly Gln
100 105 110

Gly Ile Gln Val Thr Val Ser Ser
115 120

<210> 266
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 266
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Thr Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Tyr Tyr
20 25 30

Gly Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

Ser Phe Ile Ser Gly Ser Asp Gly Ser Thr Tyr Tyr Ala Glu Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Asp Pro Trp Gly Pro Pro Ser Ile Ala Thr Met Thr Ser Tyr
100 105 110

Glu Tyr Lys His Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 267
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 267
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Thr Met Ile Trp Leu Arg Arg Ala Pro Gly Lys Gly Phe Glu Trp Val
35 40 45

Ser Thr Ile Asp Lys Asp Gly Asn Thr Asn Tyr Val Asp Ser Val Lys
50 55 60

Gly Arg Phe Ala Val Ser Arg Asp Asn Thr Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Met Tyr Tyr Cys Thr
85 90 95

Lys His Gly Ser Ser Ala Arg Gly Gln Gly Thr Arg Val Thr Val Ser
100 105 110

Ser

<210> 268
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 268
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Glu Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Asn Ser Gly Gly Gly Ile Thr Tyr Arg Gly Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Glu
85 90 95

Asn Gly Gly Ser Ser Tyr Arg Arg Gly Gln Gly Thr Gln Val Thr Val
100 105 110

Ser Ser

<210> 269
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Sequence

<400> 269
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Leu Lys Lys Pro Gly Ala

1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 270

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 270

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Thr Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 271

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 271

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 272

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Sequence

<400> 272
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Thr Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ser

<210> 273
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
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Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Arg Ser Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Thr Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Pro Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
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Ser Ser

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Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Thr Val Thr Pro Gly
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Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
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Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
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Lys

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Asp Ile Val Met Thr Gln Ser Pro Ala Ser Leu Ser Val Thr Pro Gly
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Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
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Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
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Lys

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Asp Ile Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
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Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
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Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
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Lys

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Glu Lys Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
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Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
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Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
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Gly Gly Gly Gly Ser
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<223> (GGGGS)n (n=1-4)

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Gly Gly Gly Ser
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Leu Tyr Gly Leu Tyr Gly Leu Tyr
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Leu Tyr

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<223> (EAAAK)_n (n=1-3)

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<400> 286
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Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Ala
35 40 45

<210> 287
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<400> 287
Pro Ala Pro Ala Pro
1 5

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<400> 288
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Leu Asp

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<400> 294
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<211> 21

<212> PRT

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<400> 296
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Tyr Arg Asn Gly Lys
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- **MUYLDERMANS S**Nanobodies: natural single-domain antibodiesAnnual Review of Biochemistry, 2013, vol. 82, 775-797 [\[0415\]](#)
- **LESTERHUIS WJAARNTZEN EHDE VRIES IJSCHUURHUIS DHFIGDOR CGADEMA GJPUNT CJ**Dendritic cell vaccines in melanoma: from promise to proof?Critical Reviews in Oncology/Hematology, 2008, vol. 66, 118-134 [\[0415\]](#)
- **VULINK ARADFORD KJMELIEF CHART DND**Dendritic cells in cancer immunotherapyAdvances in Cancer Research, 2008, vol. 99, 363-407 [\[0415\]](#)
- **LUFT TPANG KCTHOMAS EHERTZOG PHART DNTRAPANI JCEBON J**Type I IFNs enhance the terminal differentiation of dendritic cellsJournal of Immunology, 1998, vol. 161, 1947-1953 [\[0415\]](#)
- **PAQUETTE RLHSU NCKIERTSCHER SMPARK ANTRAN LROTH MDGLASPY JA**Interferon-alpha and granulocyte-macrophage colony-stimulating factor differentiate peripheral blood monocytes into potent antigen-presenting cellsJournal of Leukocyte Biology, 1998, vol. 64, 358-367 [\[0415\]](#)
- **RADVANYI LGBANERJEE AWEIR MMESSNER H**Low levels of interferon-alpha induce CD86 (B7.2) expression and accelerates dendritic cell maturation from human peripheral blood mononuclear cellsScandinavian Journal of Immunology, 1999, vol. 50, 499-509 [\[0415\]](#)

Patentkrav

1. Kimærisk protein, der omfatter:

(a) en targeteringsdel, der omfatter et genkendelsesdomæne, som genkender og bindes til et element A af C-type-lectindomænefamilien 9 (Clec9A), hvori genkendelsesdomænet omfatter et kun-tungkædeantistof (VHH), et humaniseret VHH eller et kameliseret VHH; og

(b) et modificeret signaleringsmiddel, hvor det modificerede signaleringsmiddel er et humant interferon alpha 2 (IFN α 2) omfattende en aminosyresekvens med mindst 98 % identitet med en sekvens valgt fra SEQ ID NO: 86 eller 87 og med én eller flere mutationer på positionerne R149, L153, og M148 med hensyn til SEQ ID NO: 86 eller 87;

hvori det muterede, humane IFN α 2 har reduceret affinitet eller aktivitet sammenlignet med humant vildtype-IFN α 2, og hvor det muterede, humane IFN α 2's reducerede affinitet eller aktivitet kan gendannes ved binding til targeteringsdelen.

2. Kimærisk protein ifølge krav 1, der endvidere omfatter én eller flere supplerende targeteringsdele.

3. Kimærisk protein ifølge et hvilket som helst af de foregående krav, hvori den ene eller flere mutationer er L153A, R149A og M148A med hensyn til SEQ ID NO: 86 eller 87.

4. Kimærisk protein ifølge et hvilket som helst af de foregående krav, hvori genkendelsesdomænet omfatter tre komplementaritetsbestemmende områder (CDR1, CDR2 og CDR3), hvori:

(a) CDR1 omfatter en aminosyresekvens valgt fra en hvilken som helst af SEQ ID NO: 2-21;

(b) CDR2 omfatter en aminosyresekvens valgt fra en hvilken som helst af SEQ ID NO: 22-43; og

(c) CDR3 omfatter en aminosyresekvens valgt fra en hvilken som helst af SEQ ID NO: 44-58, LGR og VIK.

5. Kimærisk protein ifølge et hvilket som helst af de foregående krav til anvendelse i behandling eller forebyggelse af cancer.

6. Kimærisk protein ifølge et hvilket som helst af kravene 1-4 eller til anvendelsen ifølge

krav 5, hvori mutationen er R149A med hensyn til SEQ ID NO: 86 eller 87.

7. Kimærisk protein ifølge et hvilket som helst af kravene 1-4 eller til anvendelsen ifølge krav 5, hvori mutationen er L153A med hensyn til SEQ ID NO: 86 eller 87.

5

8. Kimærisk protein ifølge et hvilket som helst af kravene 1-4 eller til anvendelsen ifølge krav 5, hvori mutationen er M148A med hensyn til SEQ ID NO: 86 eller 87.

9. Farmaceutisk sammensætning, der omfatter det kimæriske protein ifølge et hvilket som
10 helst af de foregående krav, og en egnet excipiens.

DRAWINGS

FIGURE 1

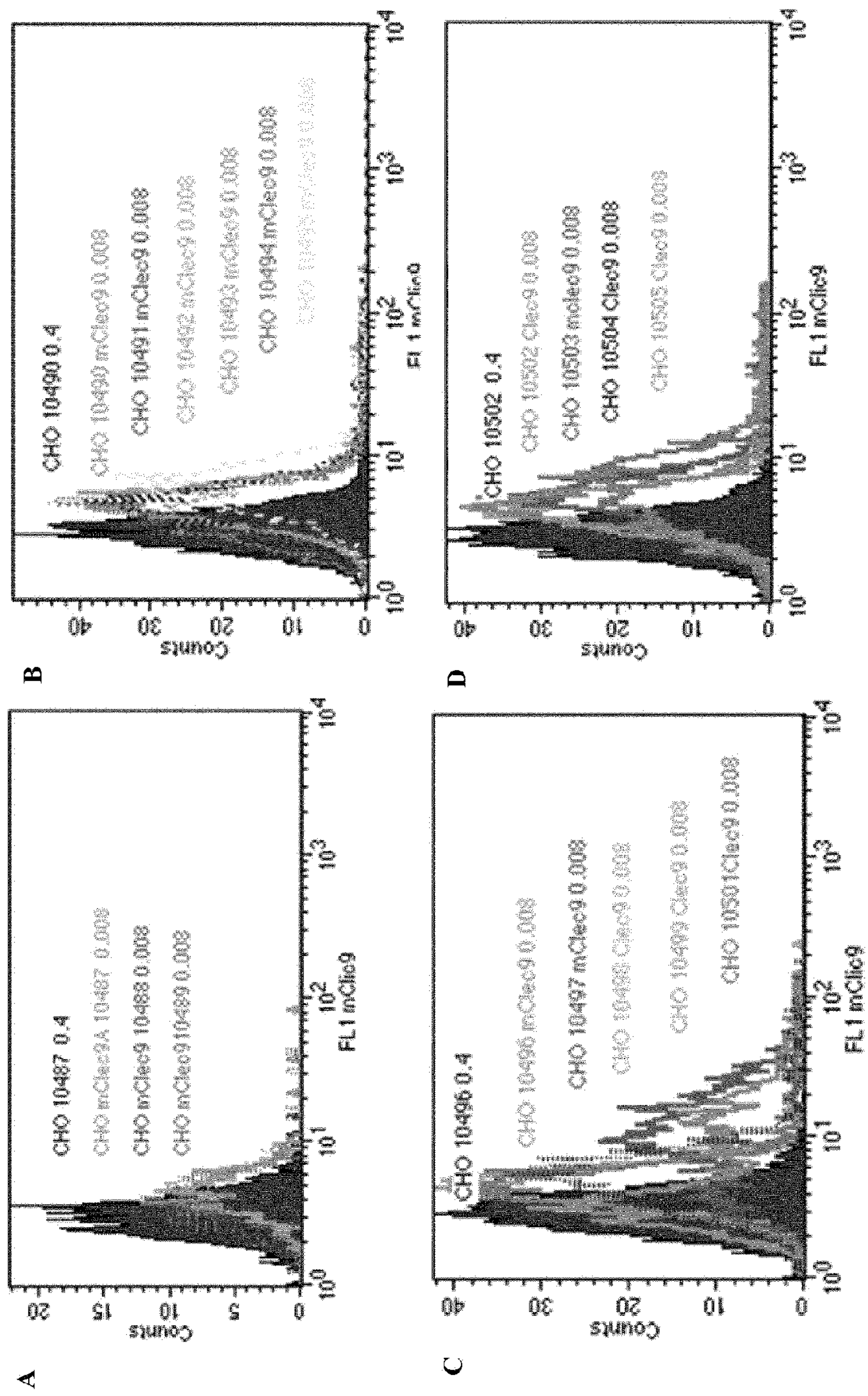
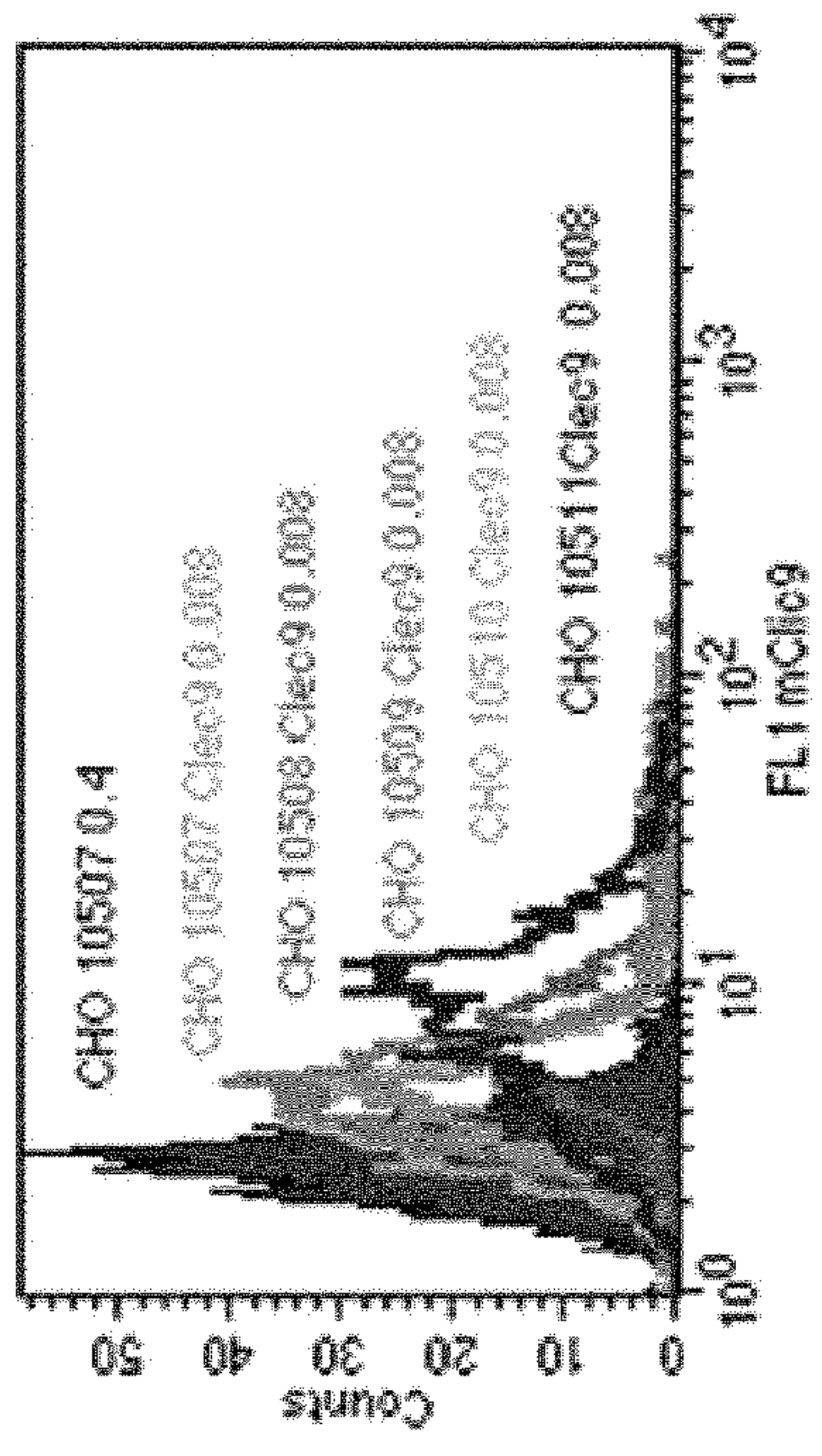


FIGURE 1 (CONTINUED)

E



F

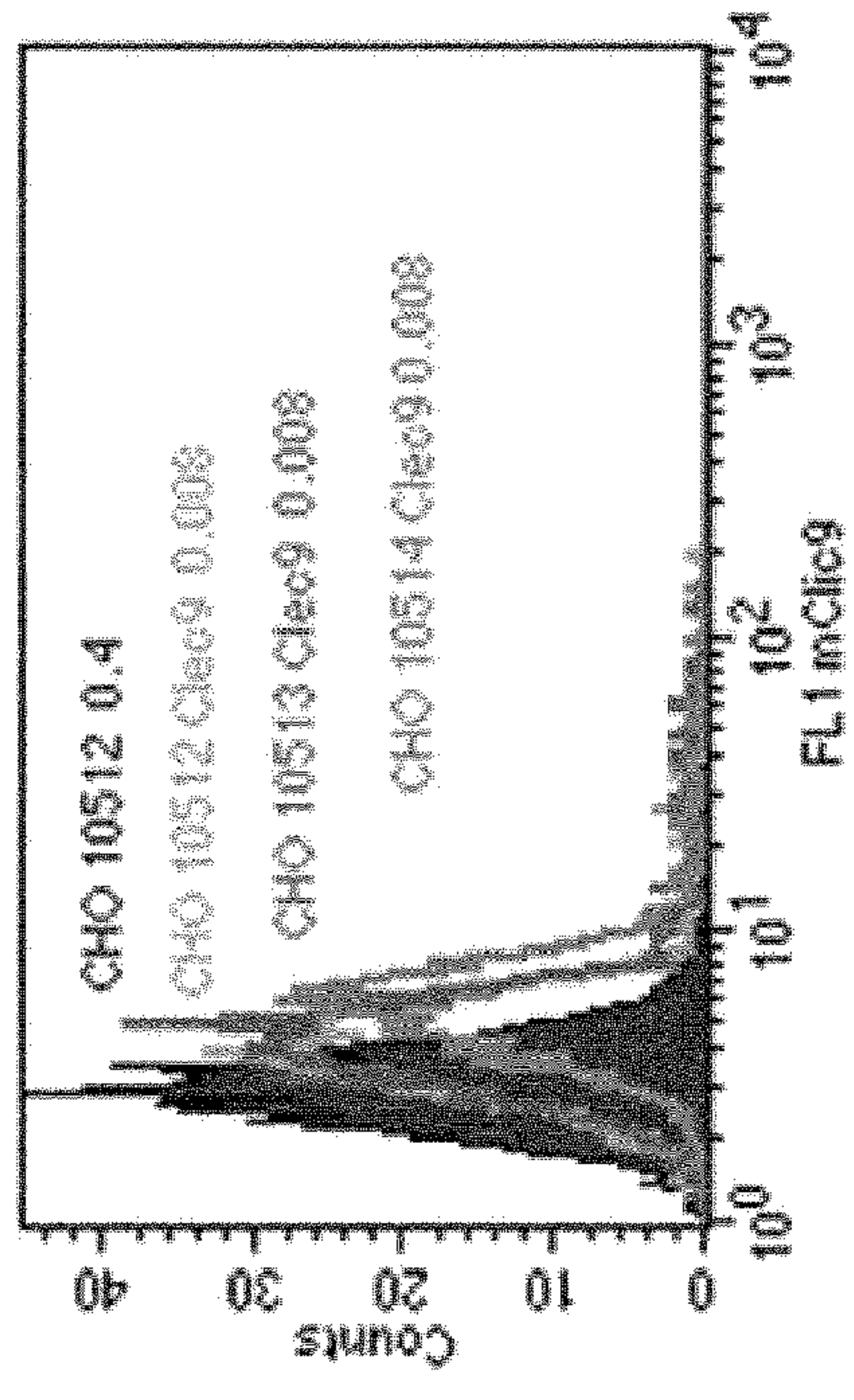


FIGURE 2
A.

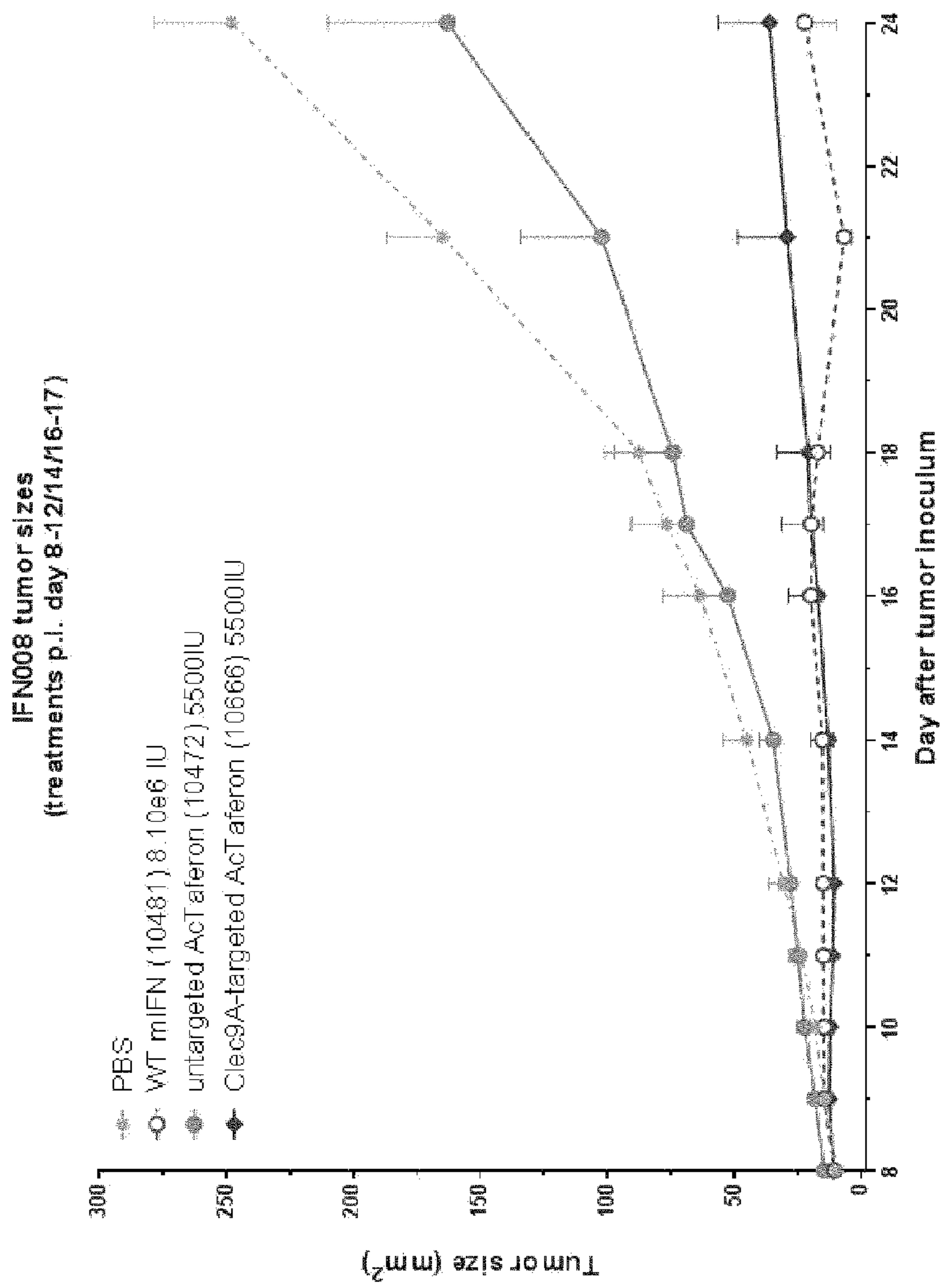


FIGURE 2 (CONTINUED)

B.

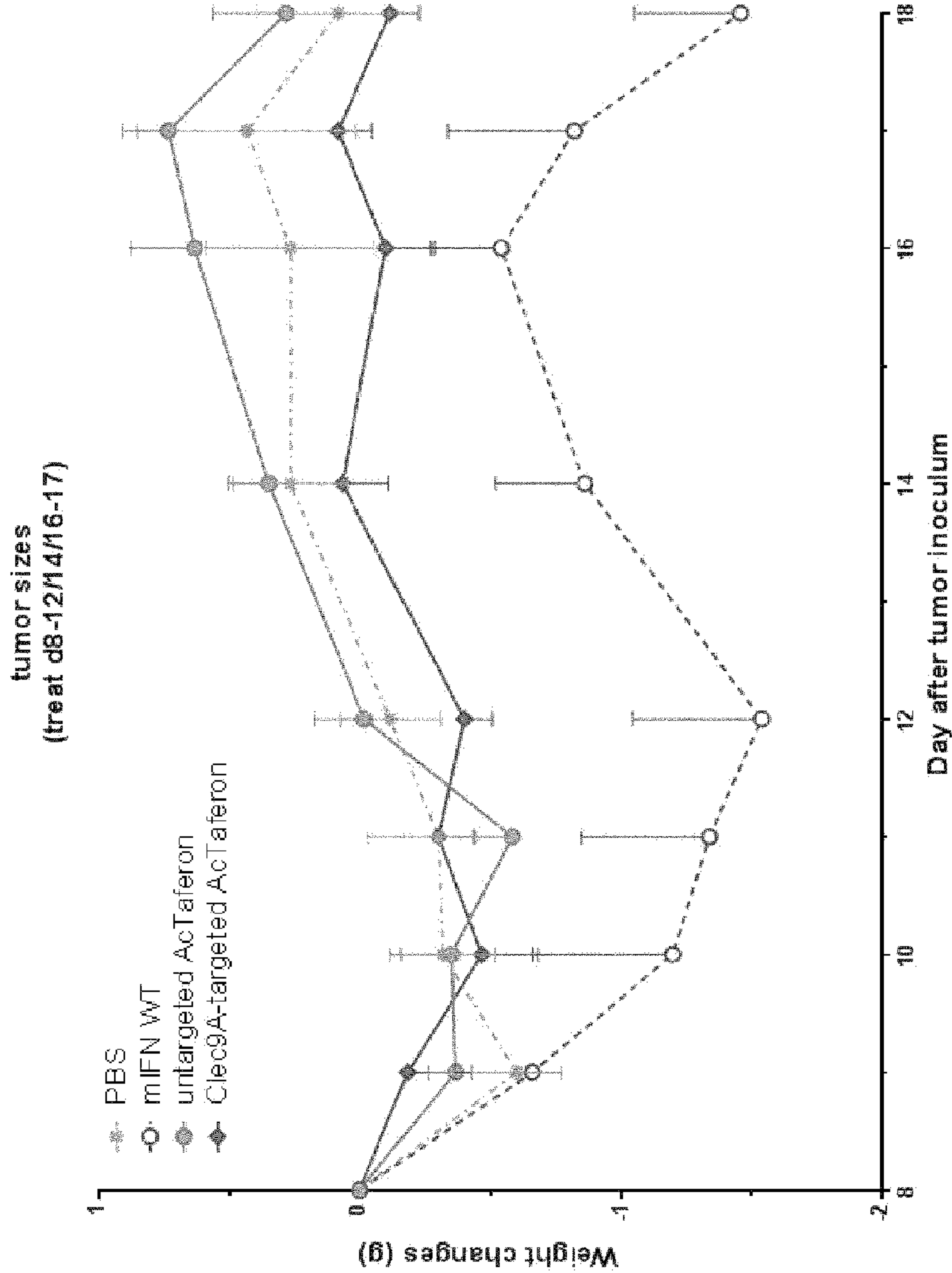


FIGURE 2 (CONTINUED)

C.

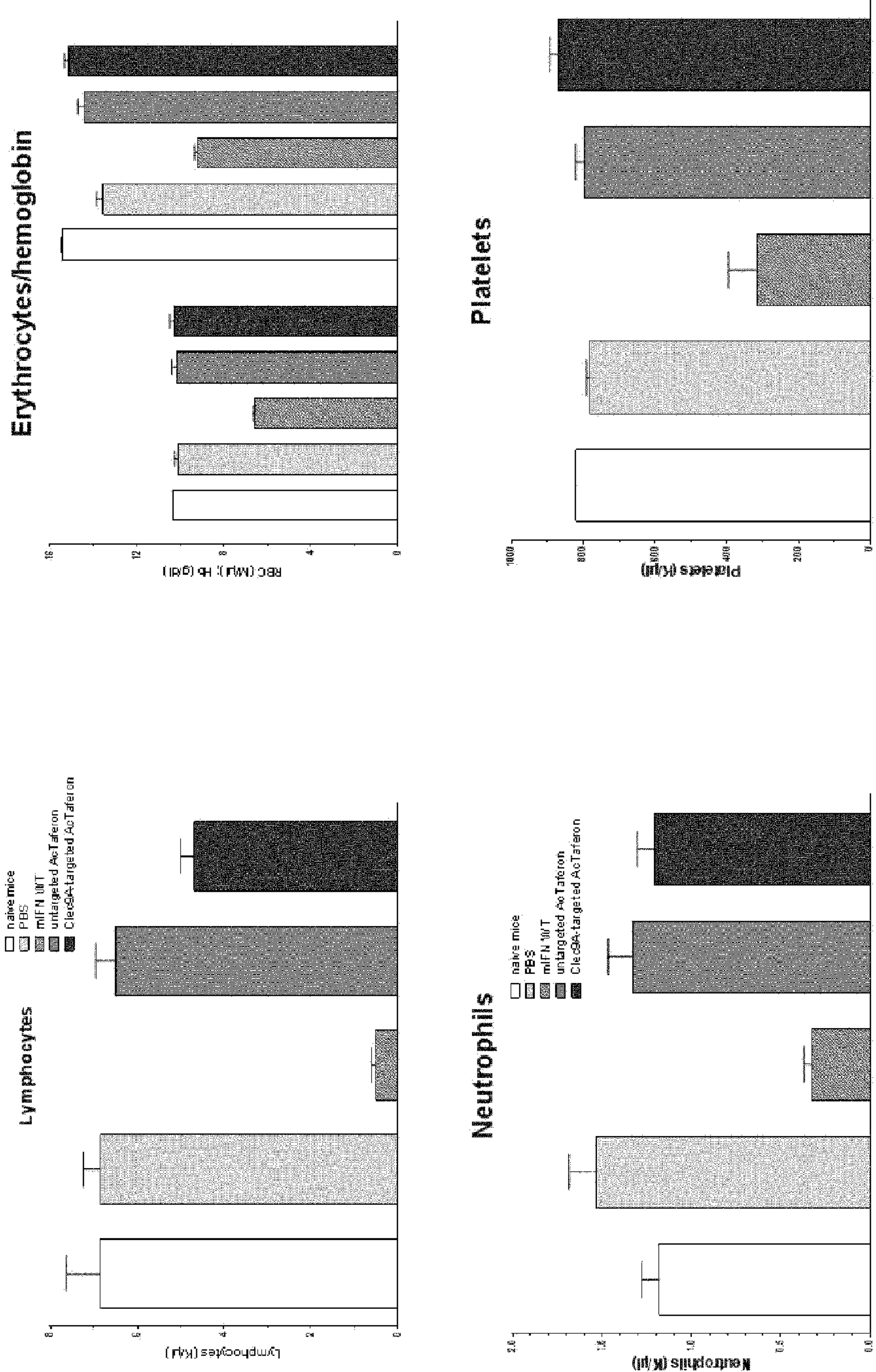


FIGURE 3 (CONTINUED)

R1CHOL16	CTCTCAGGGAGAGAGGCGAGTCTGGTCCACATATTAC---GAGTGA TGATGGATATGTATANGCAGACCCGCTGAGGSGCCGATTCACCA TCTCCAGAGTCCAGGSCCAGAACATG	231
R1CHOL56	CTCTCAGGGAGAGAGGCGAGTATGTCCAGTGA TTAGCTTGAGTGGAGATGACAGCACTATTCA GACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	231
R2CHOL69	CTCTCAGGGAGAGAGGCGAGTATGTCCAGTGA TTAGCTTGAGTGGAGATGACAGCACTATTCA GACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL32	CTCTCAGGGAGAGAGGCGAGTATGTCCAGTGA TTAGCTTGAGTGGAGATGACAGCACTATTCA GACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL44	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL12	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL41	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL13	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL41	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL94	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R2CHOL27	CTCTCAGGGAGAGAGGCGTCCAGTCCGAGTAT TTAGCTAGTGGTGGTATACCAAGCTATA CAGACTTCGTGAGGSCCGGTTCCACATCTCCGAGACA CAGGSCCAGAACACAG	234
R1CHOL23	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL18	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL22	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL49	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL53	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL25	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGCAAGCTA---AAGTAGGTGGTCCGAGACTACTGCGGSCCAGGSGAACCCAG	336
R1CHOL27	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCATCTATTACTGTATGTCAATA---CTTTTGGCAAT---GTCTACTGCGGSCCAGGSGAACCCAG	330
R1CHOL82	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCATCTATTACTGTATGTCAATA---CTTTTGGCAAT---GTCTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL34	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCATCTATTACTGTATGTCAATA---CTTTTGGCAAT---GTCTACTGCGGSCCAGGSGAACCCAG	336
R2CHOL3	GTGTATCTGCCAGTGAACAATCTGAGAAACCTGAGCAGCAAGCGGCATCTATTACTGTGATGTG---CTATTCA TGG---GGACTACTGCGGSCCAGGSGAACCCAG	333
R1CHOL50	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R2CHOL8	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R2CHOL21	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R2CHOL87	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R2CHOL24	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R2CHOL38	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R1CHOL16	GTGTATCTGCCAAATGAACAGCGCTGAAAACCTTGAGGACAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	330
R1CHOL56	GTGTATCTGCCAGTGAACAATCTGAGAAACCTTGAGCAGCAAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	333
R2CHOL69	GTGTATCTGCCAGTGAACAATCTGAGAAACCTTGAGCAGCAAGCGGCCTCTATTACTGTATGTAGTAGCA---CTATAAGGCT---GAATACTGCGGSCCAGGSGAACCCAG	333
R2CHOL14	CTTTTATCTGCCAAATGAACACTTGAAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321
R2CHOL42	CTGTATCTGCCAGTGAACAATCTGAGAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321
R2CHOL13	CTGTATCTGCCAAATGAACACTTGAAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321
R2CHOL41	CTGTATCTGCCAAATGAACACTTGAAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321
R2CHOL94	CTGTATCTGCCAAATGAACACTTGAAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321
R2CHOL27	CTGTATCTGCCAAATGAACACTTGAAAACCTTGAGCAGCGGCCTGTATTACTGCGGAATG---TTGGGAGAGAGGCGGCAGGSGAACCCAG	321

FIGURE 3 (CONTINUED)

R1CHOL23	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:	360	*	380	*	400	*	
R2CHOL18	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL22	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL49	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL53	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL25	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R1CHOL27	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R1CHOL82	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL10	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R1CHOL34	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							399
R2CHOL3	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							396
R1CHOL50	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R2CHOL6	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R1CHOL21	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R2CHOL87	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R2CHOL24	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							411
R2CHOL38	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R1CHOL16	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							393
R1CHOL56	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							396
R2CHOL69	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							396
R2CHOL32	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							396
R2CHOL14	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384
R2CHOL42	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384
R2CHOL13	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384
R2CHOL41	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384
R2CHOL94	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384
R2CHOL27	:	GTGACGCTCTCCAGCGGCCGCTACCGGTACGAGCTTCGGGACTACGGTTCCGCTCGAGGCATAG	:							384

FIGURE 4 (CONTINUED)

	120
R2CHCL8	: VTSS
R1CHCL90	: VTSS
R1CHCL21	: VTSS
R2CHCL87	: VTSS
R2CHCL24	: VTSS
R2CHCL38	: VTSS
R1CHCL16	: VTSS
R2CHCL10	: VTSS
R1CHCL34	: VTSS
R1CHCL82	: VTSS
R2CHCL3	: VTSS
R2CHCL69	: VTSS
R1CHCL56	: VTSS
R2CHCL32	: VTSS
R2CHCL49	: VTSS
R2CHCL53	: VTSS
R2CHCL22	: VTSS
R2CHCL35	: VTSS
R2CHCL18	: VTSS
R1CHCL23	: VTSS
R1CHCL27	: VTSS
R2CHCL13	: VTSS
R2CHCL14	: VTSS
R2CHCL42	: VTSS
R2CHCL41	: VTSS
R2CHCL94	: VTSS
R2CHCL27	: VTSS

FIGURE 5

Group	Member(s)
1	R1CHCL21, R1CHCL50, R2CHCL8, R2CHCL87
2	R2CHCL24
3	R2CHCL38
4	R1CHCL16
5	R1CHCL34, R1CHCL82, R2CHCL10
6	R2CHCL3
7	R1CHCL56, R2CHCL32, R2CHCL69
8	R1CHCL23, R2CHCL18, R2CHCL22, R2CHCL25, R2CHCL49, R2CHCL53
9	R1CHCL27
10	R2CHCL13, R2CHCL14, R2CHCL41, R2CHCL42, R2CHCL94
11	R2CHCL27

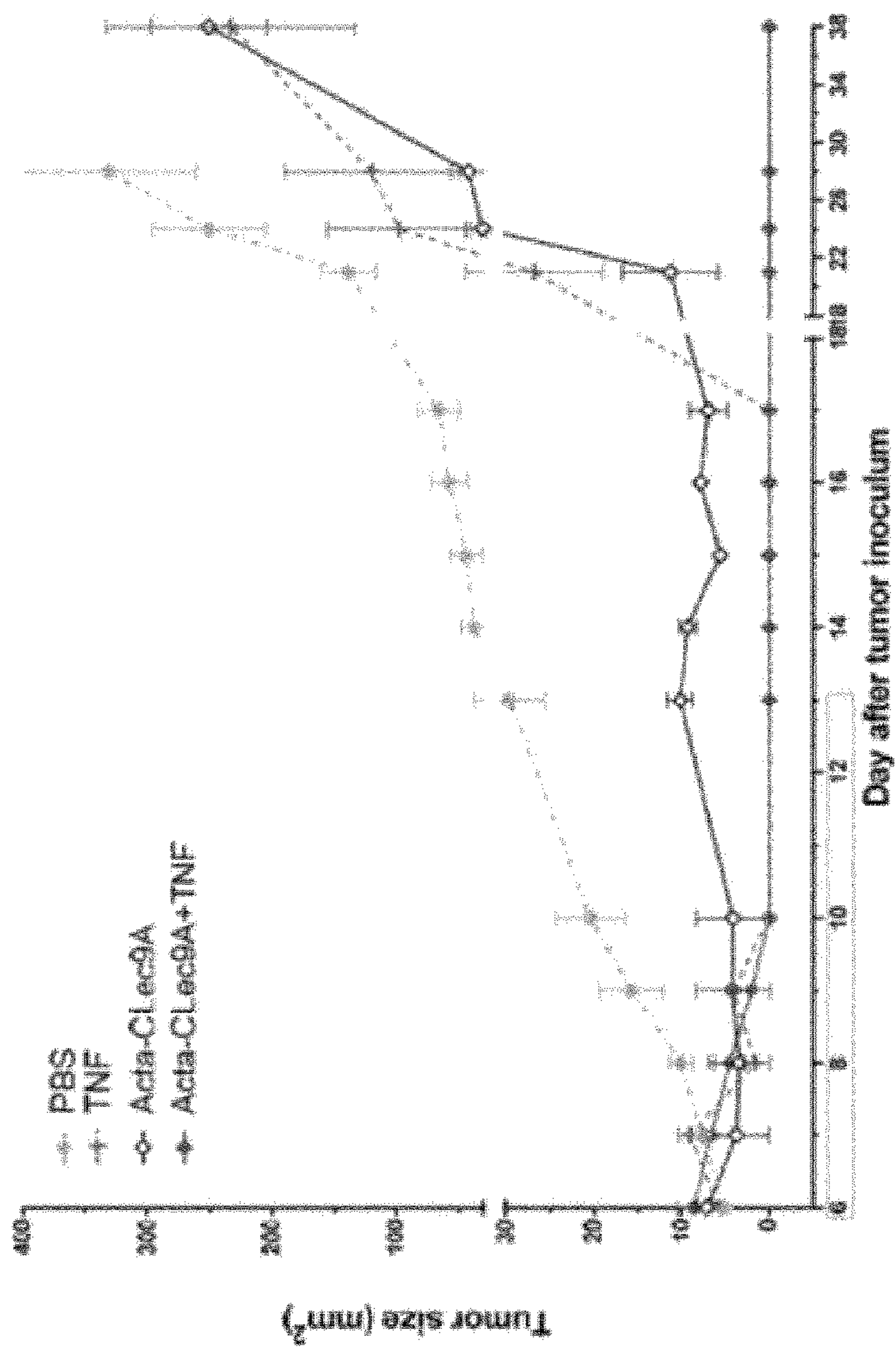


FIGURE 6

A.

FIGURE 6 (Continued)

B.

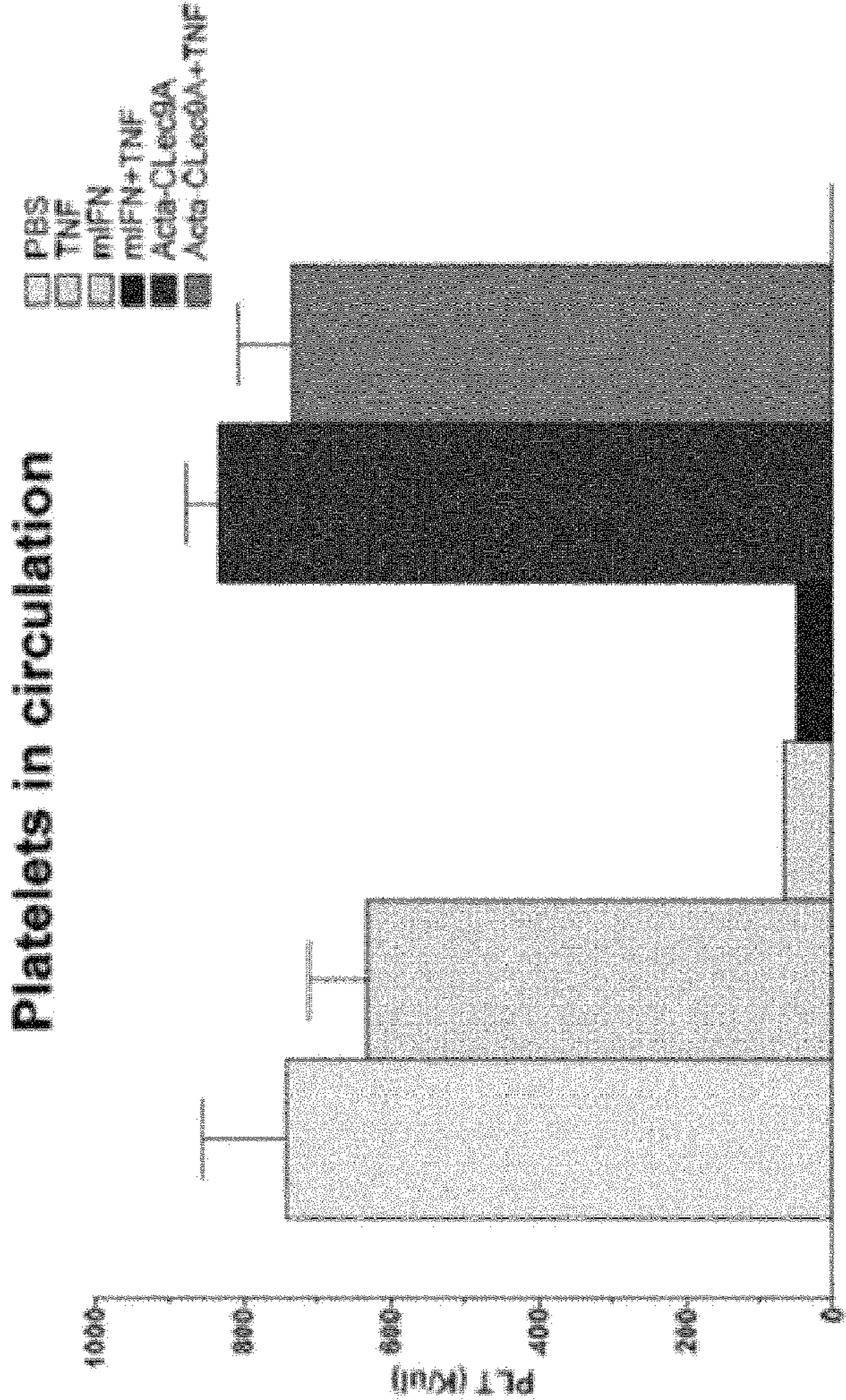


FIGURE 7

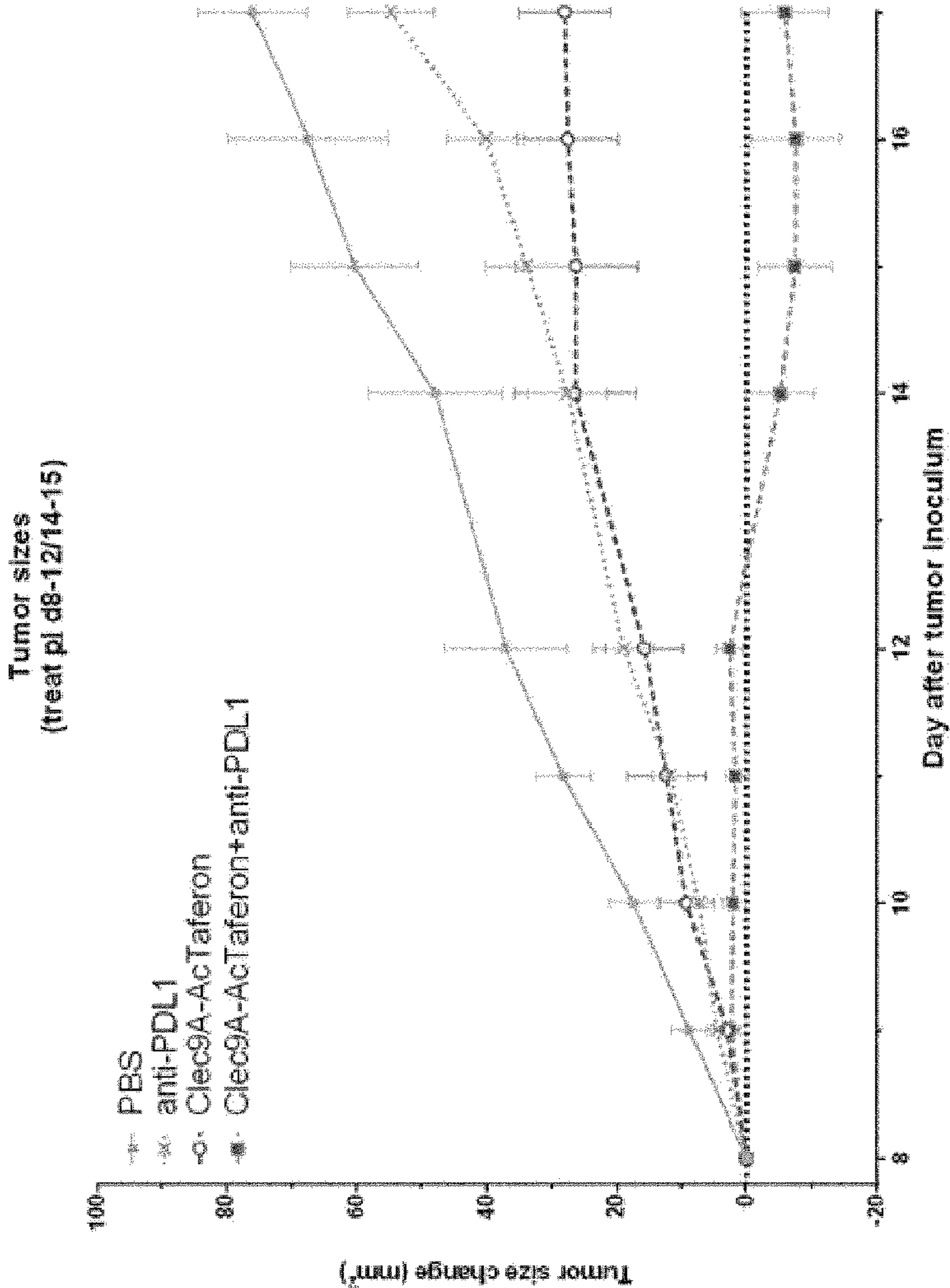


FIGURE 8

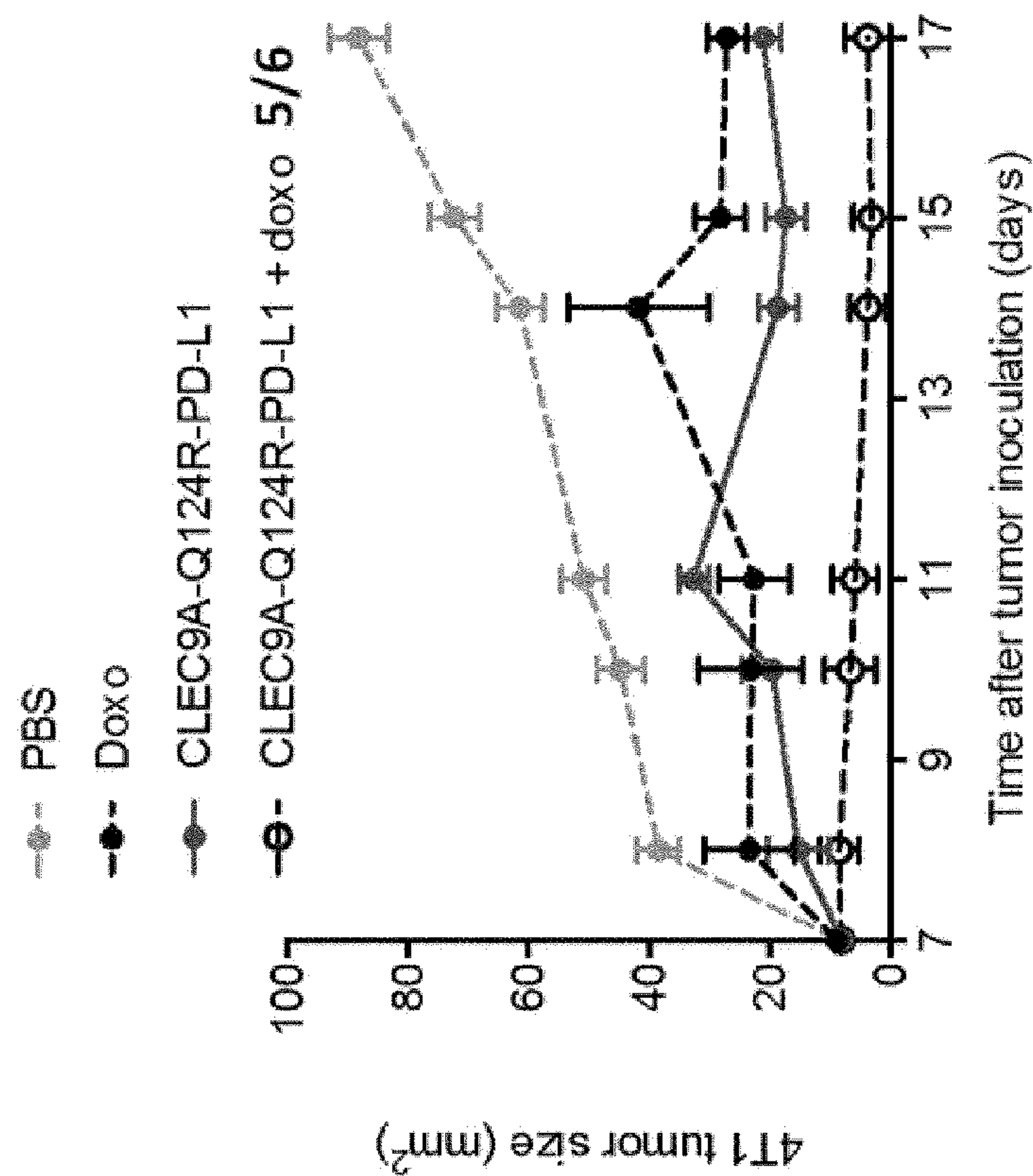


FIGURE 9

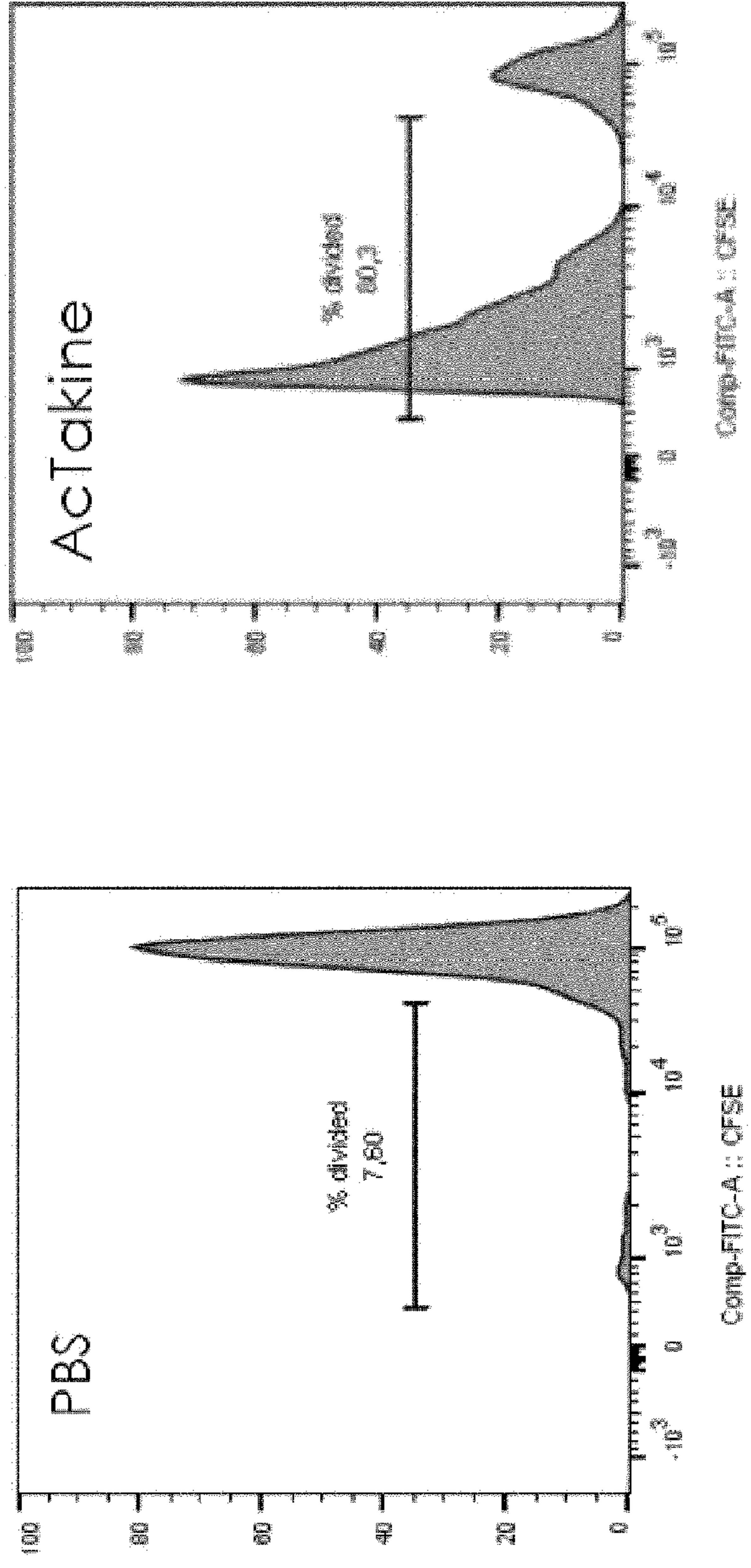


FIGURE 10
A.

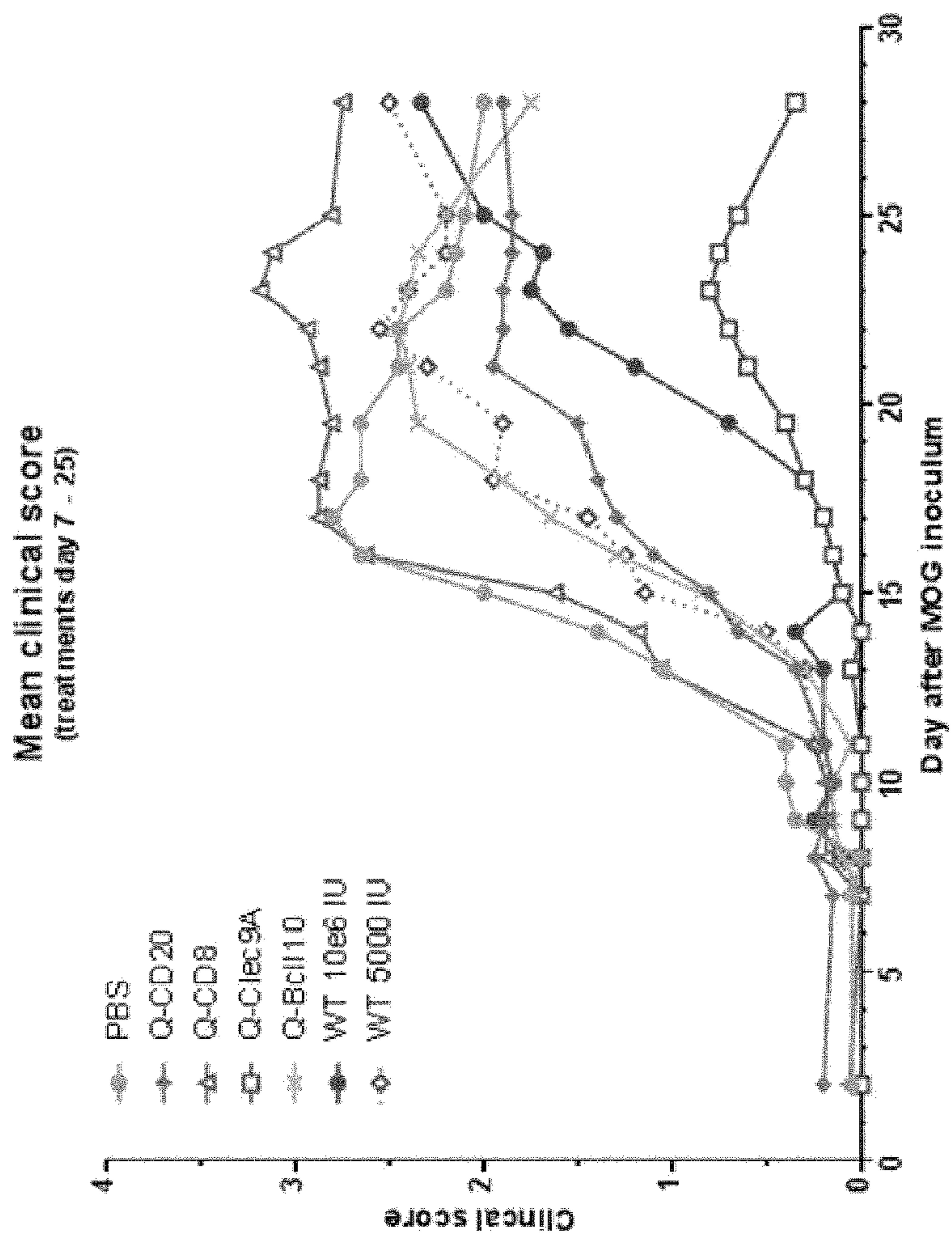


FIGURE 10 (Continued)
B.

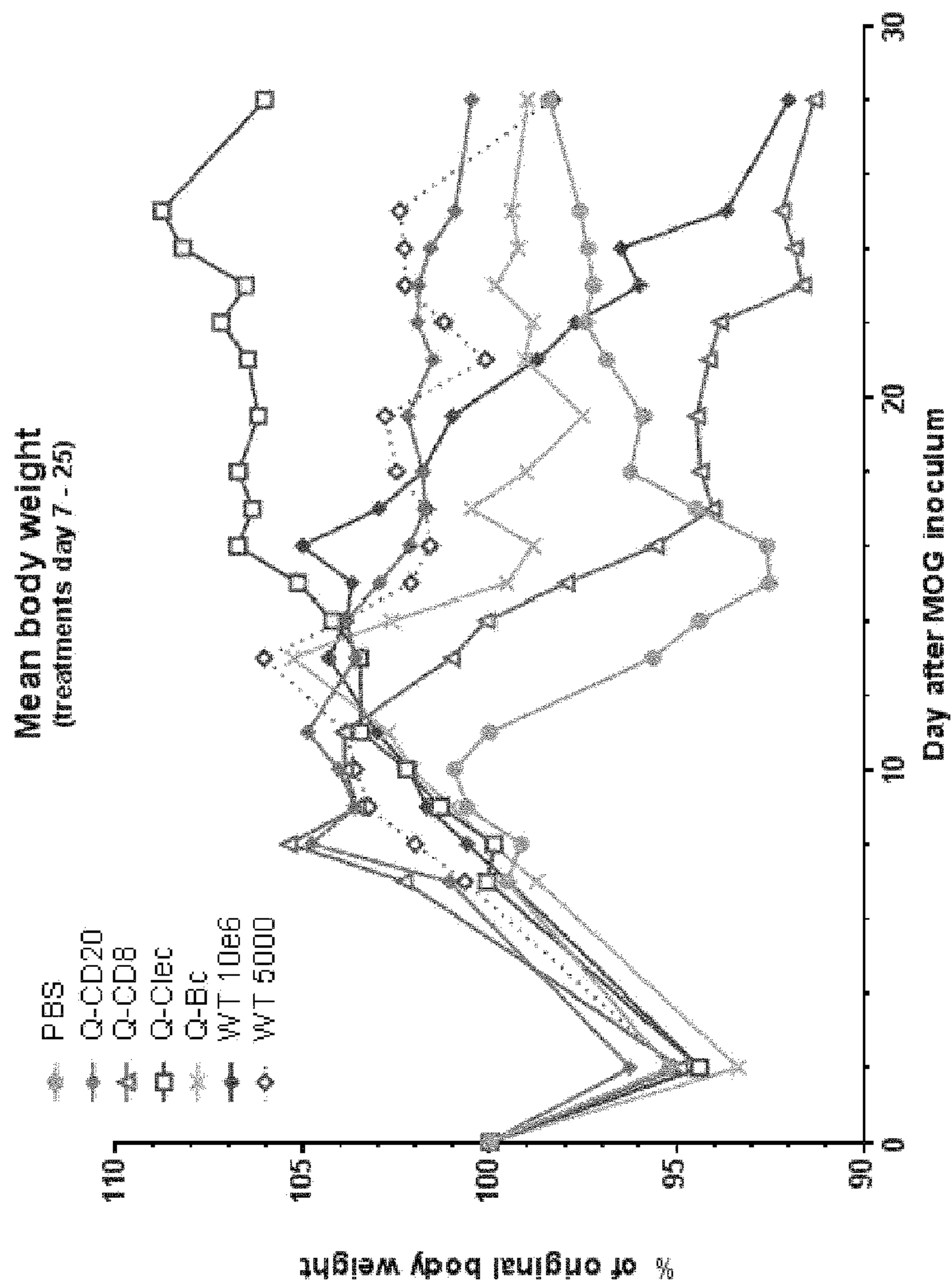


FIGURE 11

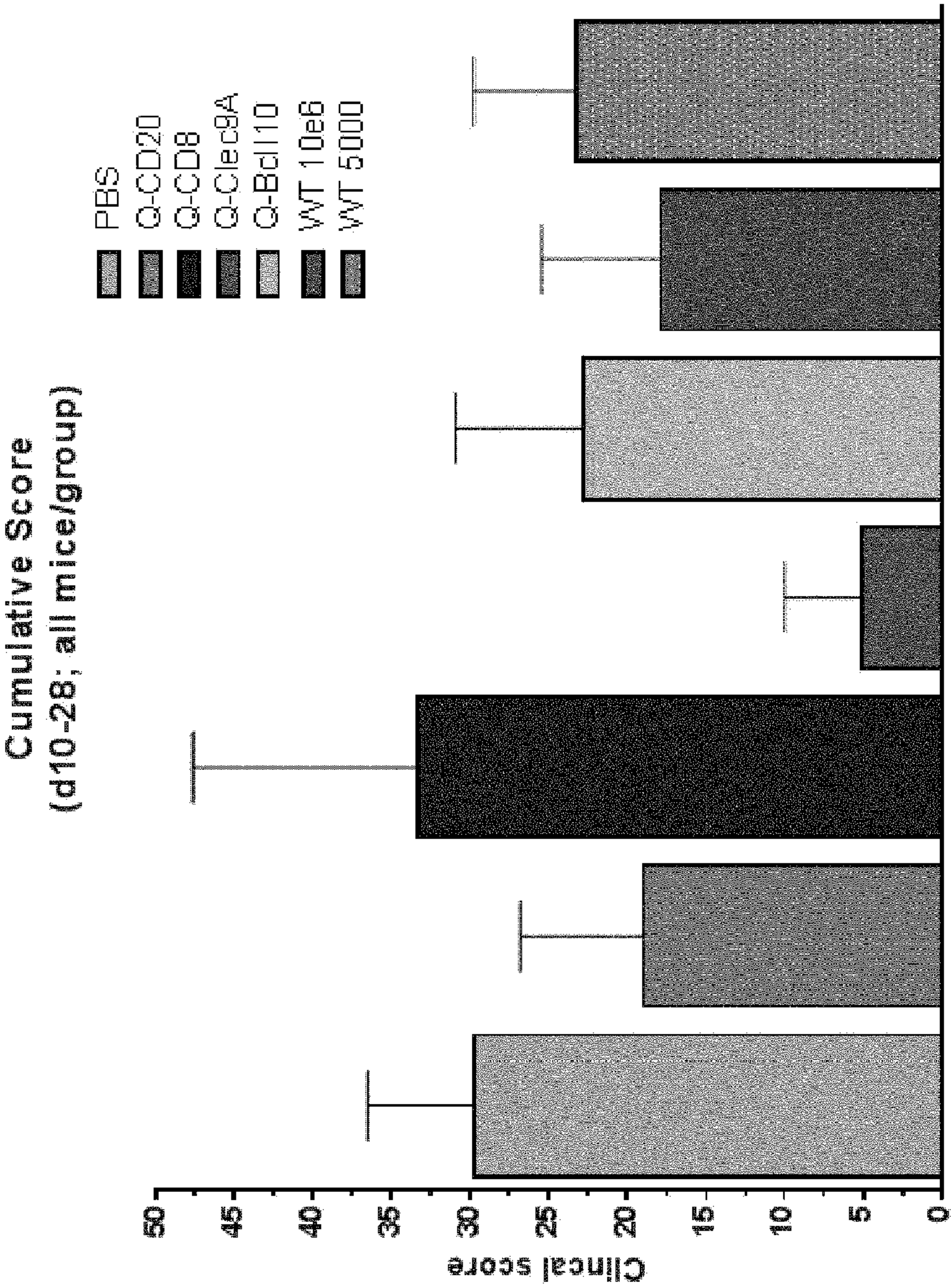


FIGURE 12

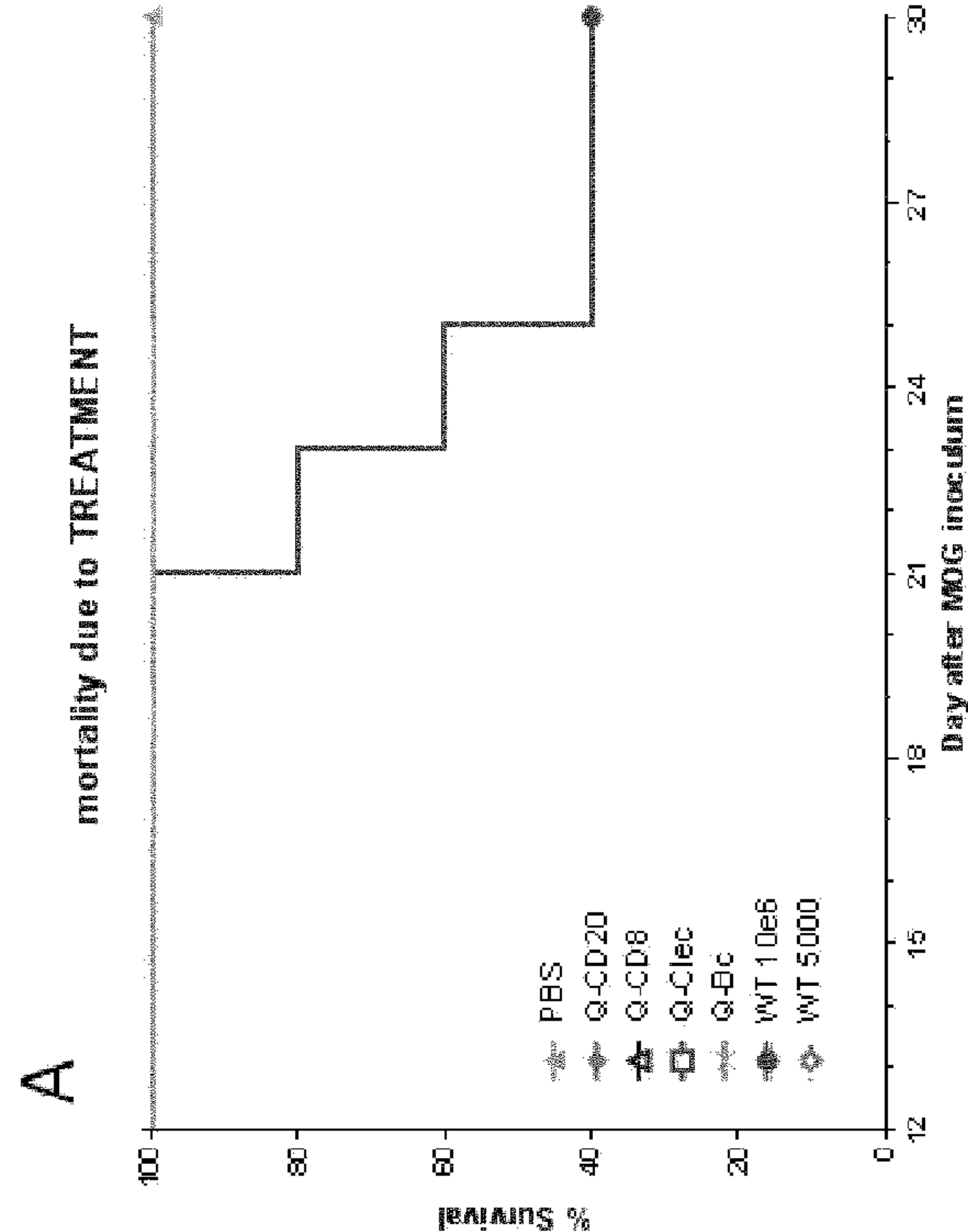


FIGURE 12 (Continued)

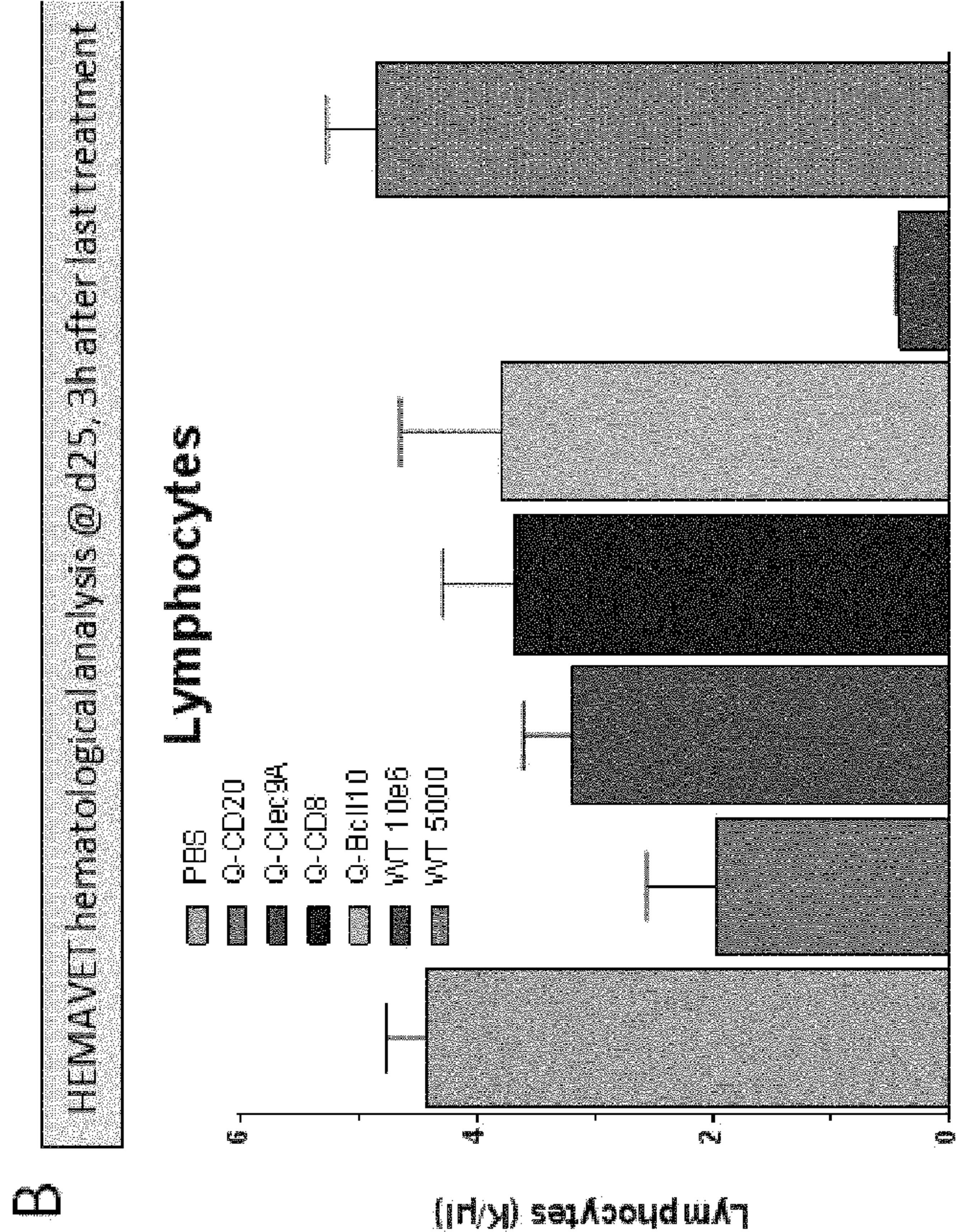


FIGURE 12 (Continued)

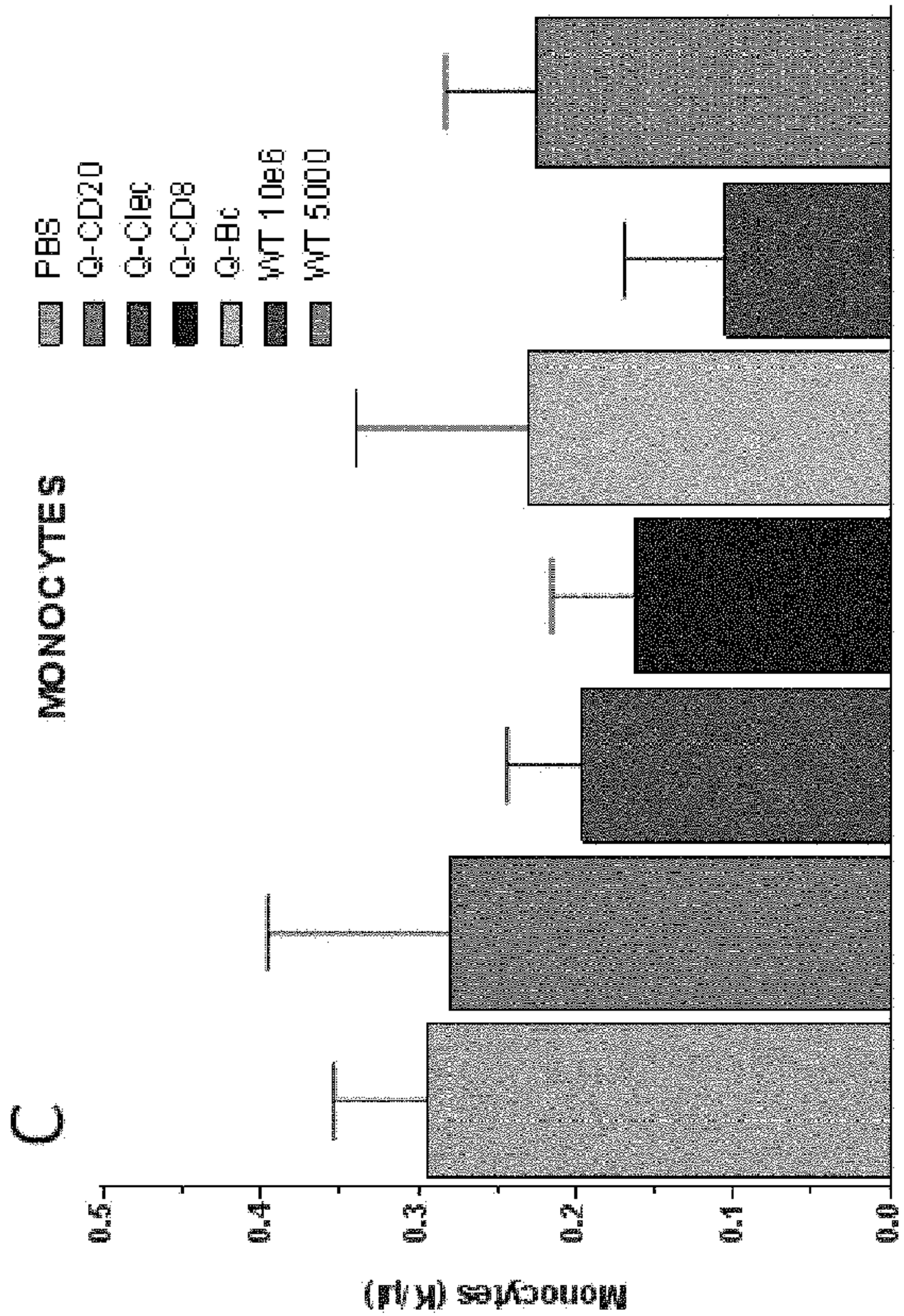


FIGURE 12 (Continued)

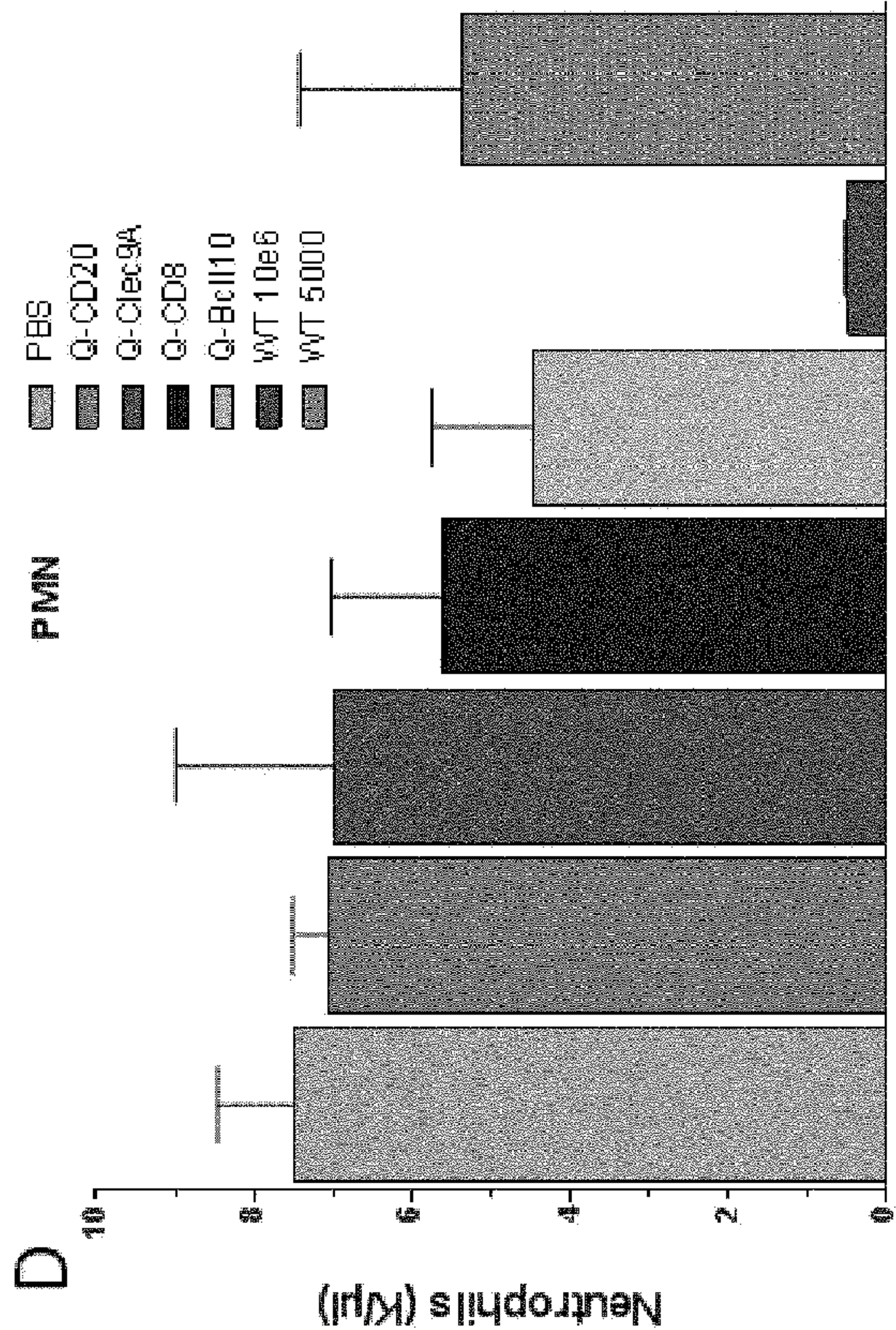
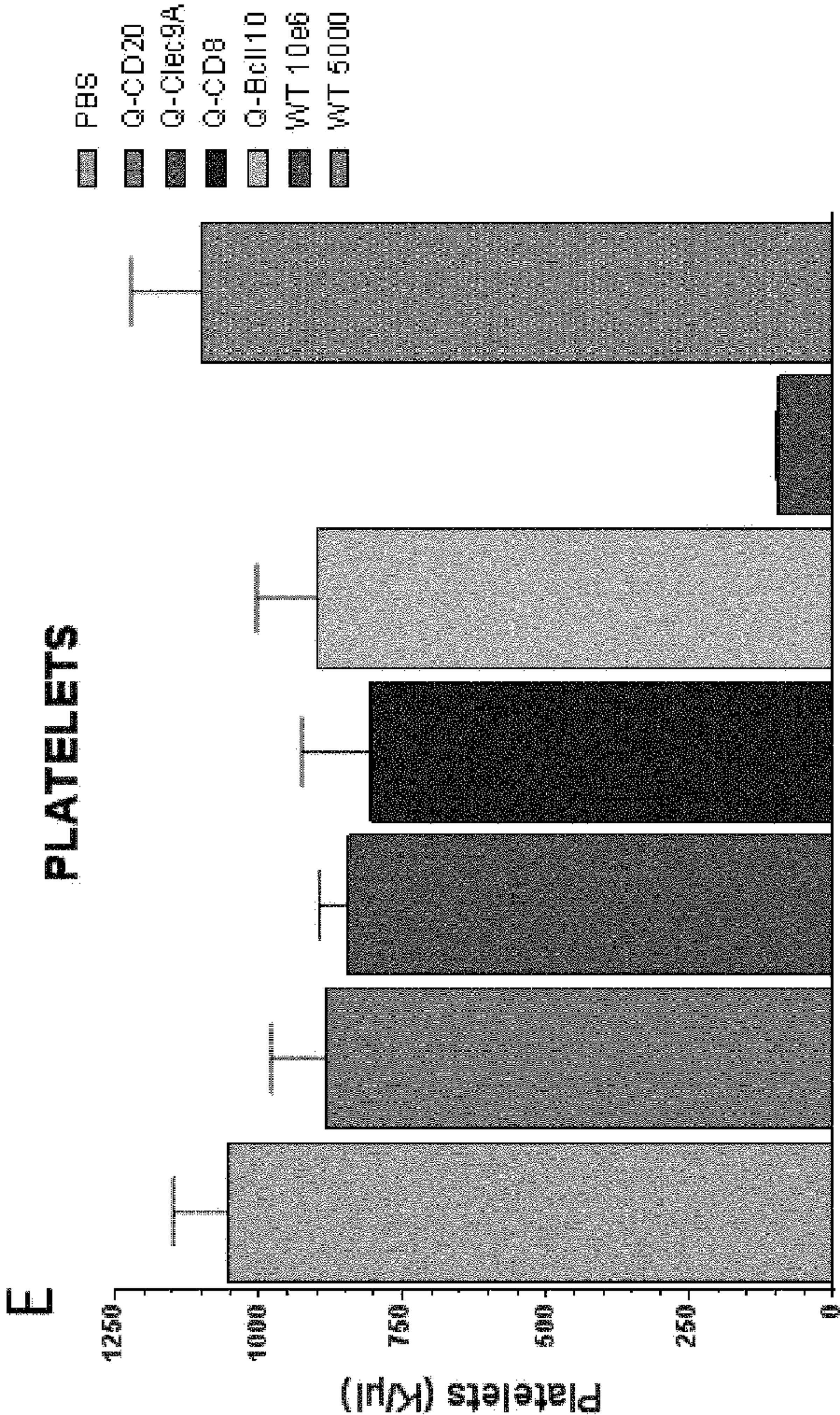


FIGURE 12 (Continued)



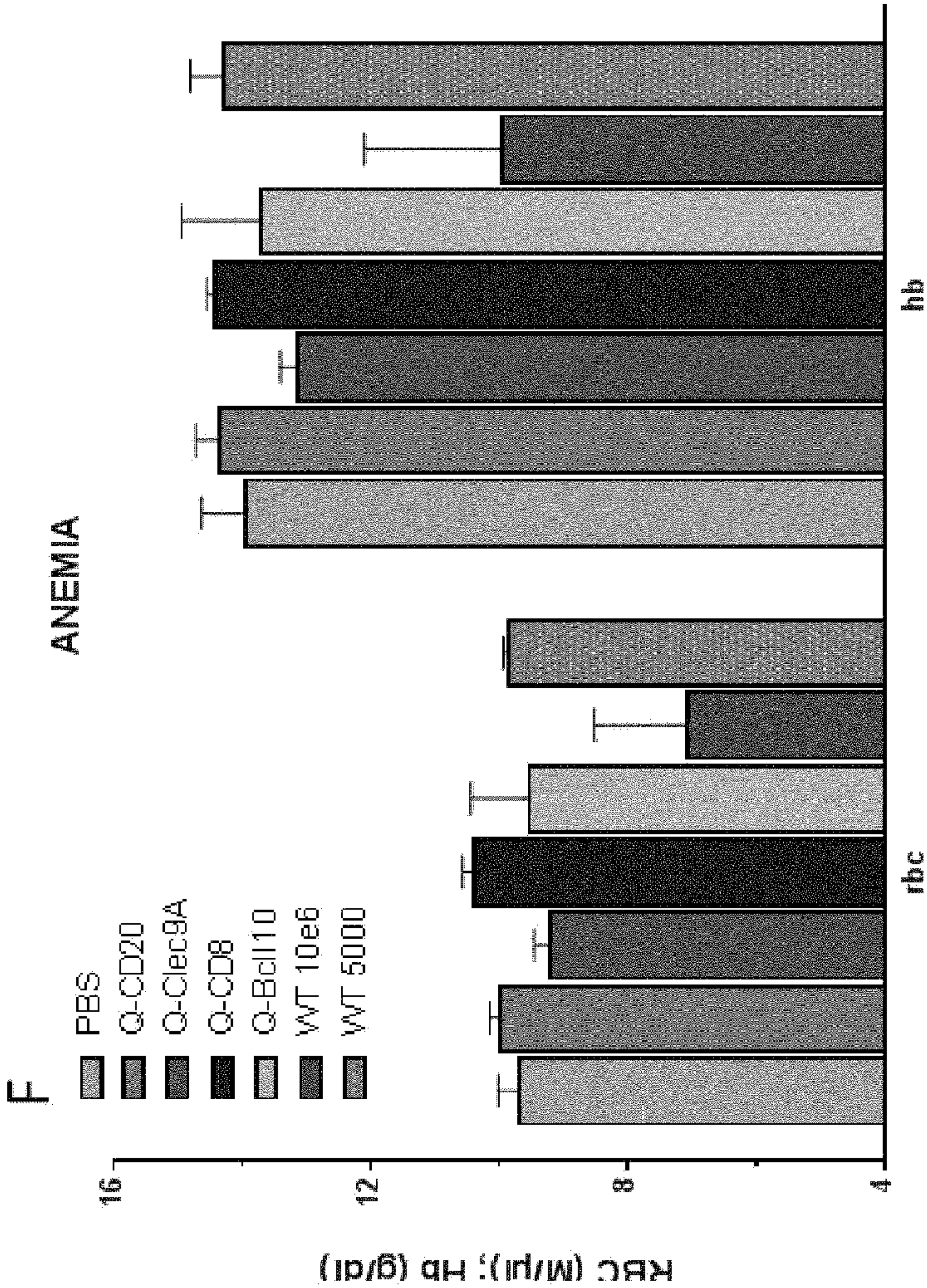


FIGURE 12 (Continued)

FIGURE 13

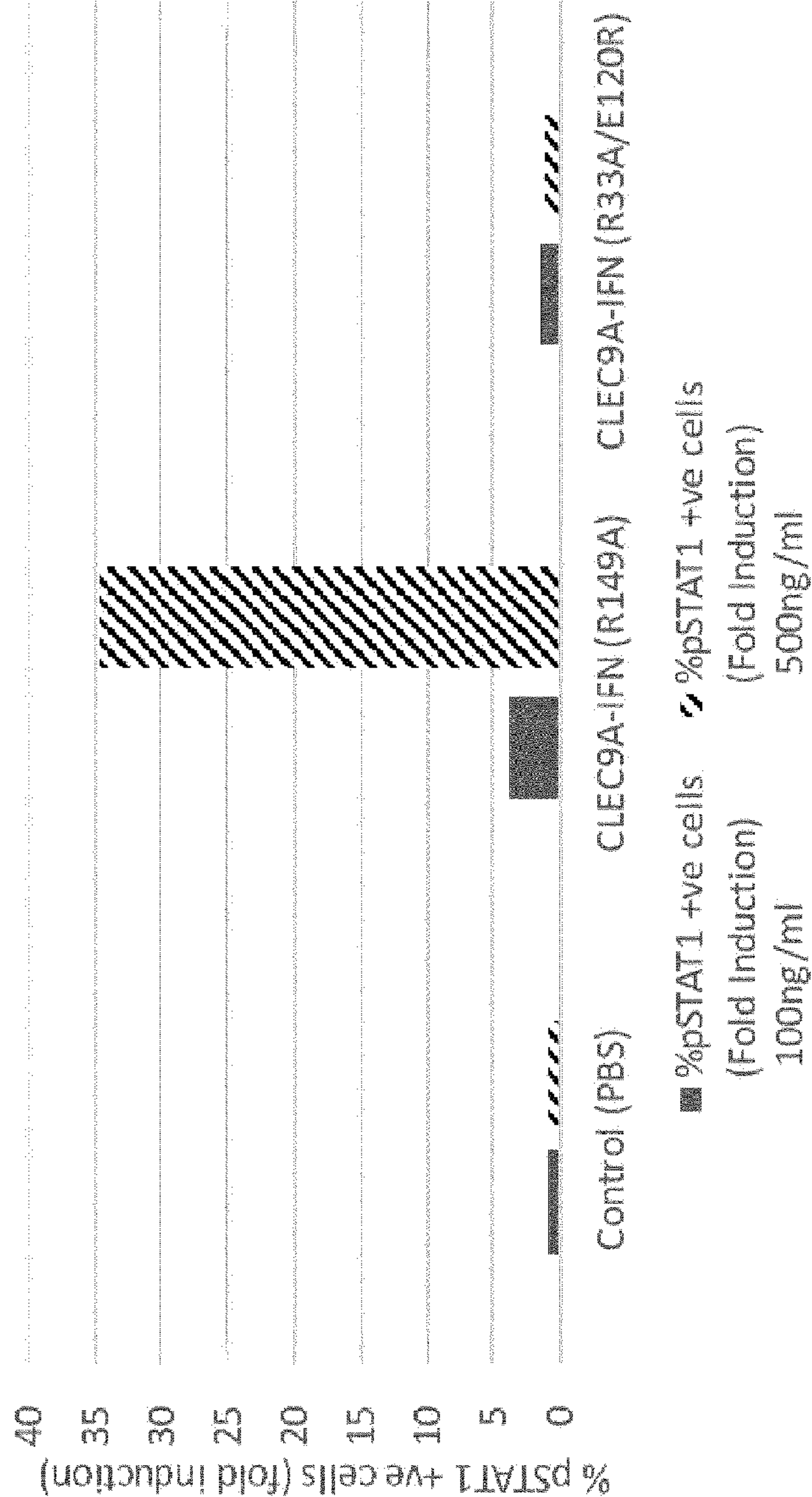


FIGURE 14

