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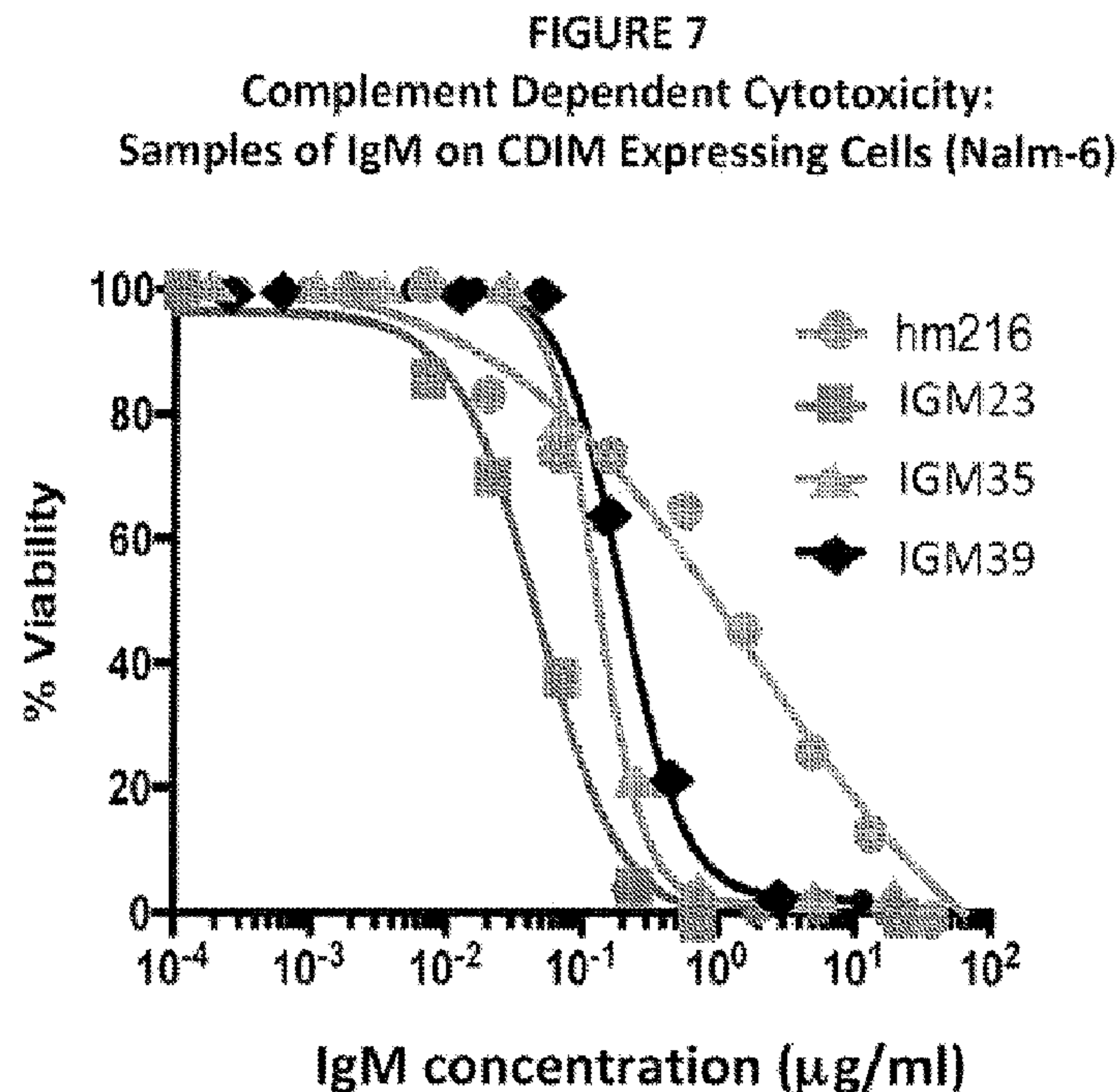
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(54) **Titre : PROTEINES SE LIANT AUX CDIM ET LEURS UTILISATIONS**

(54) **Title: CDIM BINDING PROTEINS AND USES THEREOF**



(57) **Abrégé/Abstract:**

The present disclosure relates to Cell Death Inducing Molecule ("CDIM") binding proteins and pharmaceutical compositions thereof. Particularly, the disclosure provides CDIM binding proteins that are useful in the selective depleting and killing of B cells, including neoplastic B cells as well as neoplastic cells that are not of B-cell origin that express CDIM-like antigens. In addition, the disclosure encompasses polynucleotides encoding the disclosed antigen binding proteins, and expression systems for producing the same. Further the present disclosure encompasses methods of treating patients with B cell proliferative and mediated diseases by administering the CDIM binding proteins as well as diagnostic assays for identifying proteins that bind to CDIM. The disclosure further contemplates diagnostic assays for identifying patient populations that can be treated with the CDIM binding proteins.



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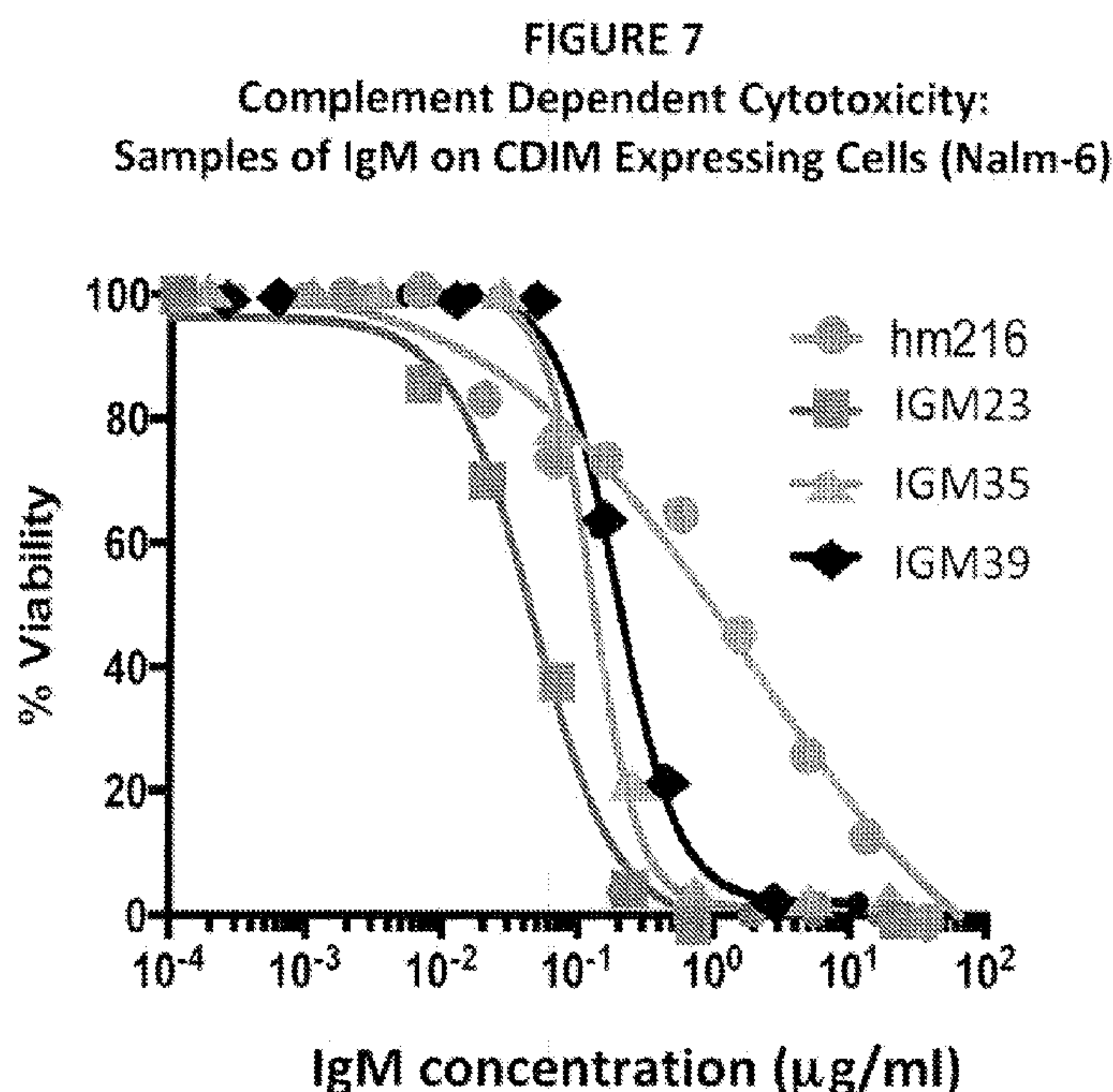
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(54) Title: CDIM BINDING PROTEINS AND USES THEREOF



(57) Abstract: The present disclosure relates to Cell Death Inducing Molecule ("CDIM") binding proteins and pharmaceutical compositions thereof. Particularly, the disclosure provides CDIM binding proteins that are useful in the selective depleting and killing of B cells, including neoplastic B cells as well as neoplastic cells that are not of B-cell origin that express CDIM-like antigens. In addition, the disclosure encompasses polynucleotides encoding the disclosed antigen binding proteins, and expression systems for producing the same. Further the present disclosure encompasses methods of treating patients with B cell proliferative and mediated diseases by administering the CDIM binding proteins as well as diagnostic assays for identifying proteins that bind to CDIM. The disclosure further contemplates diagnostic assays for identifying patient populations that can be treated with the CDIM binding proteins.

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CDIM BINDING PROTEINS AND USES THEREOF

[0001] SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 7, 2013, is named 0155-005WO1_SL.txt and is 225,619 bytes in size.

[0003] I. FIELD

[0004] The present disclosure relates to Cell Death Inducing Molecule (hereinafter "CDIM") binding proteins and pharmaceutical compositions thereof. Particularly, the disclosure provides CDIM binding proteins that are useful in the selective depleting and killing of B cells, including neoplastic B cells as well as other neoplastic cells that express CDIM or CDIM-like antigens. The disclosure also provides polynucleotides encoding the disclosed CDIM binding proteins, and expression systems for producing the same. Further encompassed in the present disclosure are methods of treating patients with B cell proliferative and B cell mediated diseases by administering the CDIM binding proteins. The disclosure further contemplates diagnostic assays for identifying patient populations that can be treated with the CDIM binding proteins.

[0005] II. BACKGROUND

[0006] The major responsibility for carrying out the functions of the immune system is born by white blood cells called lymphocytes. Lymphocytes can be categorized into two major classes, *i.e.*, T cells and B cells. T cells (*i.e.*, T-lymphocytes) originate from stem cells in the bone marrow, develop in the thymus gland and secrete lymphokines. B cells (*i.e.*, B-lymphocytes) originate from stem cells in the bone marrow and are the source of antibodies. In fact, B cells generate five different types of antibodies including IgM, IgG, IgA, IgD and IgE. These antibodies can neutralize substances that can trigger an immune response, *i.e.*, antigens, by attaching to specific sites on the antigens in order to block them. IgM is the largest antibody and the primary antibody against A and B antigens on red blood cells. Structurally, IgM forms polymers where multiple immunoglobulins are covalently linked together with disulfide bonds, primarily

as a pentamer but also as a hexamer. IgM has a molecular mass of approximately 900kDa in its pentameric form. Because each monomer has two antigen binding sites, a pentameric IgM has ten (10) binding sites.

[0007] Numerous diseases are associated with altered or dysfunctional B cells including, but not limited to, autoimmune diseases and cancer. The proliferation and differentiation of B cells is regulated by receptors localized on the cell surface. The engagement of these receptors induces the activation of intracellular signaling proteins that transmit the receptor signals to specific targets inside the cell that control the cellular responses. Many signaling proteins are the products of oncogenes and many oncogenes are associated with tumorigenesis. The molecular mechanisms of signaling pathways that control the proliferation and differentiation of B cells are still being studied (Jumaa *et al.* (2005) *Annu. Rev. Immunol.* 23:415-445).

[0008] An example of a disease involving neoplastic B lymphocytes is acute lymphoblastic leukemia (ALL). Some progress in combating this disease is due to intensification of chemotherapy, as well as better supportive care for both, pediatric and adult ALL. While the risk of relapse is lower in the pediatric population, both pediatric and adult patients face dire outcomes if the disease recurs. Less than one third of children and few adults with relapsed ALL survive this disease despite the use of aggressive regimens and stem cell transplantation. Novel therapies are therefore needed that reach beyond conventional chemotherapy. For ALL, there is preclinical and early clinical data with a variety of monoclonal antibodies including rituximab, epratuzumab and gemtuzumab, suggesting that the use of monoclonal antibodies alone or in combination with standard chemotherapy is a viable treatment option.

[0009] U.S. Patent No. 5,593,676 describes ways of inducing cell death in neoplastic B cells by using reagents that bind a specific B cell epitope called cell death inducing molecule (CDIM). Herein, the B cell specific oligosaccharide epitope CDIM is used as a neoplastic B cell marker. IgM antibodies specific for this marker are administered to a host *in vivo* to induce death in neoplastic B cells. The same concept can be applied in *ex vivo* clinical situations to selectively remove B cells. A human monoclonal antibody (*i.e.*, MAb 216), which recognizes

the B cell epitope CDIM is cytotoxic to neoplastic and normal B cells and binds all CD19+ and CD20+ B lymphocytes in human peripheral blood and spleen.

Furthermore, MAb 216 does not distinguish B cells by the isotype expressed, binding IgG+ and IgM+ cells with equal intensity. MAb 216 also binds all B cells regardless of their CD5 expression. Hence, MAb 216, is useful in diagnosis and therapy. See, also Bhat *et al.* (2000), *Scand. J. Immunol.* 51:134-140.

[00010] However, there remains a need in the art to identify antibodies that are specific for B cells to selectively kill and/or remove them from the host with reduced off-target binding and/or tissue damaging side effects. Cancer therapy still has a tremendous need for such therapeutic antibodies. The present application addresses this need.

[00011] III. BRIEF DESCRIPTION OF THE FIGURES

[00012] The present disclosure is best understood when read in conjunction with the accompanying figures, which serve to illustrate the embodiments. It is understood, however, that the disclosure is not limited to the specific embodiments disclosed in the figures.

[00013] FIGS. 1A-D depict amino acid sequences of heavy chain variable regions (SEQ ID NOS:1-22) that are representative of the CDIM binding proteins disclosed herein. The three heavy chain complementarity determining regions (CDRH1, CDRH2, and CDRH3) and framework regions of the heavy chain variable region (FR1, FR2, and FR3), and J_H (joining region) are shown.

[00014] FIG. 1E depicts amino acid sequences of light chain variable regions (SEQ ID NOS:23 and 24) that are representative of the CDIM binding proteins disclosed herein. The three light chain complementarity determining regions (CDRL1, CDRL2, and CDRL3) and framework regions of the light chain variable region (FR1, FR2, and FR3), and J_L (joining region) are shown.

[00015] FIG. 1F depicts amino acid sequences of a heavy chain constant region (Ig μ) (SEQ ID NO:25), and two light chain constant regions (Ig λ and Ig κ , respectively) (SEQ ID NOS:26 and 27) utilized in representative examples disclosed herein.

[00016] **FIGS. 2A-2V** depict the complete amino acid sequences of the 44 anti-CDIM antibodies disclosed herein, designated IGM1 through IGM44. The 44 disclosed antibodies are formed by combining each of the 22 disclosed heavy chains (SEQ ID NOS:28-49) with each of the two disclosed light chains (SEQ ID NOS:50 and 51).

[00017] **FIG. 3** depicts the CDR3 sequences of the representative H1 through H22 CDIM binding proteins disclosed herein. The arginine residues of the various sequences are underlined.

[00018] **FIGS. 4A-K** depict exemplary polynucleotide sequences (SEQ ID NOS:52-73) encoding the 22 heavy chains of the antigen binding proteins disclosed herein.

[00019] **FIG. 4L** depicts exemplary polynucleotide sequences (SEQ ID NOS:74 and 75) encoding the two light chains, lambda and kappa, of the antigen binding proteins disclosed herein.

[00020] **FIG. 5** depict native SDS gels of crude cell extracts from CHO cells expressing H1 through H7 (panel A), and H9 through H21 (panel B), respectively. The band at 1,048 kD represents IgM pentamers, while the band at 1,236 kD represents IgM hexamers.

[00021] **FIG. 6** illustrates the binding of CDIM binding proteins to CDIM expressed on a human B cell line and subsequent cytotoxicity results for the disclosed antibodies. Cell cultures were harvested and analyzed by flow cytometry using (1) mean fluorescence intensity to quantitate binding and (2) propidium iodine uptake to distinguish live from dead cells. As shown in **FIG. 6A**, all antibodies tested bind to the CDIM expressing human B cell line, NALM-6 across a broad dose range. **FIG. 6B** shows the cytotoxicity results following binding of the antibodies to the CDIM epitope.

[00022] **FIG 7** shows cytotoxicity results following binding of the antibodies to the CDIM epitope.

[00023] **FIG. 8, panels A-E** depict ELISA based binding data that is representative of the CDIM binding proteins to antigens other than CDIM. Results using the antigens single stranded DNA (ssDNA), double stranded DNA

(dsDNA), lipid A, cardiolipin, and maleonaldehyde LDL (MDA-LDL) are shown in panels A-E, respectively. As shown, MAb 216 binds to all of the antigens across a broad dose range in comparison with all the disclosed antibodies which demonstrate markedly reduced binding or total lack of binding to these select antigens.

[00024] **FIG. 9, panels A-F** depict ELISA based binding data that is representative of the CDIM binding proteins to antigens other than CDIM. Results using the antigens single stranded DNA (ssDNA), double stranded DNA (dsDNA), lipopolysaccharide, cardiolipin, chondroitin and heparan, are shown in panels A-F, respectively. As shown, MAb 216 binds to all of the antigens across a broad dose range in comparison with all the disclosed antibodies which demonstrate markedly reduced binding or total lack of binding to these select antigens.

[00025] **IV. DETAILED DESCRIPTION OF THE EMBODIMENTS**

[00026] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00027] Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[00028] Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present application are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g.,* Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001), Ausubel *et al.*, Current Protocols in Molecular

Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[00029] It should be understood that this invention is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such may vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the disclosed, which is defined solely by the claims.

[00030] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." The term "about" when used in connection with percentages may mean +/-1%.

[00031] *General Overview*

[00032] The present disclosure provides materials and methods related to treating or diagnosing proliferative diseases involving cells expressing the CDIM antigen. In particular, the disclosure provides CDIM binding proteins with improved *ex vivo* and *in vivo* performance that are useful in the selective killing and/or depleting of neoplastic B cells, specifically in patients who are afflicted with a condition characterized by B cell proliferative and B cell mediated diseases. In addition, the CDIM binding proteins are useful for treating solid tumors that express the CDIM antigen. The disclosed CDIM binding proteins may be used alone, or in combination with small molecules chemotherapeutics. As a result of a unique pore inducing effect of the disclosed CDIM binding proteins,

i.e., membrane wounding, the targeted cells become more accessible to chemotherapeutic molecules. Therefore, the disclosed binding proteins are particularly suitable to treat cells otherwise resistant to small molecule compounds in combination with the same.

[00033] Definitions

[00034] The following terms used herein shall have the meaning as indicated below.

[00035] The term “antigen” refers to any substance capable of inducing a specific immune response and of reacting with a specific antibody.

[00036] The “antigen binding protein” or “CDIM binding protein,” as used herein is a scaffold protein having an antibody like binding activity or an antibody, *i.e.*, an anti-CDIM antibody.

[00037] The term “CDIM” (“Cell Death Inducing Molecule”), as used herein, refers to a poly n-acetyl lactosamine glycoform attached to cell surface molecules. The CDIM epitope is found on nearly all peripheral B lymphocytes and splenic B lymphocytes and on certain cultured B cell lymphoma lines. The epitope is also found on primary B cell lymphomas of various histopathologic classifications, and on the cells of some solid tumors.

[00038] In more specific terms, the CDIM epitope is a linear B cell lactosamine antigen (*i.e.*, a poly-N-acetyl lactosamine type 2 determinant, with or without a terminal sialic acid) that has a three-dimensional structural conformation and is sensitive to the enzyme endo-beta-galactosidase. The epitope has no branching or substitutions and it can be attached to a glycolipid or a glycoprotein. On glycoproteins, the epitope could branch off a mannose frame work (*e.g.*, enzyme MGAT4), or could be a long chain branching off a “large I” structure, but is normally at least about four hexose moieties in a straight chain (*i.e.*, type 2) after the branch Gal β 1-4 GlcNac β 1-3 Gal β 1-4 Glc β 1; at least about six hexoses for good affinity; and least about twelve hexoses in the longest form. The chain is made by enzymes (*e.g.*, B3GNT1, B4GALT1), which add alternate sugars to the eptitope. Notably, the glycosylated epitope CDIM is

present on multiple proteins ranging from molecular weights of about 20KD to greater than about 200KD proteins.

[00039] The CDIM epitope has been further elucidated in that the glycoform of the antigen is capped with sialic acid, making it a more mature type of glycosylation.

[00040] The term “epitope” generally refers to part of an antigen (*i.e.*, the antigenic determinant of a molecule), which is recognized by the immune system. An epitope can be composed of sugars, lipids, and/or amino acids or mixtures thereof. The epitope is recognized by immune cells such as specific T cells, B cells, and/or antibodies produced by B cells. When immune cells recognize and are activated by specific epitopes, they mount an immune response. Alternatively, when antibodies recognize and bind specific epitopes, the cells carrying the epitopes may be depleted, killed, deactivated, wounded, removed, and/or altered.

[00041] The term “scaffold protein”, or “antigen binding protein,” as used herein, means a polypeptide or protein with exposed surface areas in which amino acid insertions, substitutions or deletions are highly tolerable. Examples of scaffold proteins that can be used in accordance with the present invention are protein A from *Staphylococcus aureus*, the bilin binding protein from *Pieris brassicae* or other lipocalins, ankyrin repeat proteins, and human fibronectin (reviewed in Binz and Plückthun (2005) *Curr. Opin. Biotechnol.* 16:459-69). Engineering of a scaffold protein can be regarded as grafting or integrating an affinity function onto or into the structural framework of a stably folded protein. Affinity function means a protein binding affinity according to the present invention. A scaffold can be structurally separable from the amino acid sequences conferring binding specificity. In general, proteins appearing suitable for the development of such artificial affinity reagents may be obtained by rational, or most commonly, combinatorial protein engineering techniques such as panning against CDIM, either purified protein or protein displayed on the cell surface, for binding agents in an artificial scaffold library displayed *in vitro*, skills which are known in the art (Skerra, A. (2000) *J. Mol. Recogn.* 13:167-187; Binz and Plückthun, *supra*). In addition, a scaffold protein having an antibody like binding

activity can be derived from an acceptor polypeptide containing the scaffold domain, which can be grafted with binding domains of a donor polypeptide to confer the binding specificity of the donor polypeptide onto the scaffold domain containing the acceptor polypeptide. Said inserted binding domains may be, for example, the complementarity determining region (CDR) of an antibody, in particular an anti-CDIM antibody. Insertion can be accomplished by various methods known to those skilled in the art including, for example, polypeptide synthesis, nucleic acid synthesis of an encoding amino acid as well by various forms of recombinant methods well known to those skilled in the art.

Importantly, the term “heavy chain” or “light chain” is to be understood broadly to be a scaffold protein, embedding one or several of the disclosed CDRs, rather than limited to the traditional meaning of the term in the context of antibody technology.

[00042] Moreover, the term “antibody” or “CDIM-binding antibody,” as used herein, means a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody (Jones *et al.* (1986) *Nature* 321:522-525; Riechmann *et al.* (1988) *Nature* 332:323-329; and Presta (1992) *Curr. Op. Struct. Biol.* 2:593-596), a chimeric antibody (Morrison *et al.* (1984) *Proc. Natl. Acad. Sci. U.S.A.* 81:6851-6855), a multispecific antibody (*e.g.*, a bispecific antibody) formed from at least two antibodies, or an antibody fragment thereof. The term “antibody fragment” comprises any portion of the afore-mentioned antibodies, preferably their antigen binding or variable regions. Examples of antibody fragments include Fab fragments, Fab' fragments, F(ab')₂ fragments, Fv fragments, diabodies (Hollinger *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6444-6448), single chain antibody molecules (Plückthun in: *The Pharmacology of Monoclonal Antibodies* 113, Rosenberg and Moore, EDS, Springer Verlag, N.Y. (1994), 269-315) and other fragments as long as they exhibit the desired capability of binding to CDIM.

[00043] In addition, the term “antibody” or “CDIM binding antibody,” as used herein, may include antibody-like molecules that contain engineered sub-domains of antibodies or naturally occurring antibody variants. These antibody-like molecules may be single-domain antibodies such as V_H-only or V_L-only domains derived either from natural sources such as camelids (Muyldermans *et al.* (2001) *Reviews in Molecular Biotechnology* 74:277-302) or through *in vitro* display of

libraries from humans, camelids or other species (Holt *et al.* 2003 *Trends Biotechnol.* 21:484-90).

[00044] In accordance with the present invention, the “Fv fragment” is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain (heavy chain CDRH1, CDRH2, and CDRH3; light chain CDRL1, CDRL2, and CDRL3) interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDR's confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDR's specific for an antigen) has the ability to recognize and bind the antigen. The “Fab fragment” also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. The “Fab fragment” differs from the “Fab' fragment” by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. The “F(ab')₂ fragment” originally is produced as a pair of “Fab' fragments” which have hinge cysteines between them. Methods of preparing such antibody fragments, such as papain or pepsin digestion, are known to those skilled in the art.

[00045] In some embodiment of the present invention, the anti-CDIM antibody is of the IgA-, IgD-, IgE, IgG- or IgM-type, preferably of the IgG- or IgM-type including, but not limited to, the IgG1-, IgG2-, IgG3-, IgG4-, IgM1- and IgM2-type. In most embodiments, the antibody is of the IgM type. The light chain may be either a lambda-1, lambda-2, or a kappa. A J chain may be included or omitted.

[00046] IgG has several subtypes, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgA subtypes include IgA1 and IgA2. In humans, the IgA isotype contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains ten or twelve heavy chains and ten or twelve light chains (pentameric or hexameric). In naturally occurring IgM molecules, the J chain stabilizes the pentameric configuration.

[00047] The heavy chain C region typically comprises one or more domains that may be responsible for effector function. The number of heavy chain

constant region domains will depend on the isotype. In one embodiment, the CDIM binding proteins are of the IgM subtype. In full-length light and heavy chains, the variable and constant regions may be joined by a “J” region of about twelve or more amino acids, with the heavy chain also including a “D” region of about ten more amino acids. (*See, e.g.,* Fundamental Immunology, 2nd ed., Ch. 7 (Paul, W., ed.) (1989) New York: Raven Press).

[00048] *The CDIM Binding Proteins*

[00049] A first aspect of the present disclosure relates to an isolated binding protein that binds to the CDIM epitope on human peripheral B lymphocytes, splenic B lymphocytes, neoplastic B lymphocytes, and some solid tumors.

[00050] In one embodiment, the antigen binding protein comprises a heavy chain comprising at least one of a CDRH1, CDRH2, and CDRH3 having a sequence shown in any of SEQ ID NOS:1-22, and/or a light chain comprising at least one of a CDRL1, CDRL2, and CDRL3 shown in SEQ ID NOS:23 or 24. In one embodiment, the antigen binding protein comprises a heavy chain comprising at least a CDRH3 shown in SEQ ID NOS:1-22, and a light chain. In yet another embodiment, the antigen binding protein comprises each a CDRH1, CDRH2, and CDRH3 shown in SEQ ID NOS:1-22, and a light chain. In other embodiments, the antigen binding protein additionally comprises a CDRL1, a CDRL2, and a CDRL3 of SEQ ID NOS:23 or 24, embedded into the light chain. In some embodiments, the antigen binding protein additionally has a FR1 shown in SEQ ID NOS:1-22, embedded in the heavy chain.

[00051] In yet another embodiment, the antigen binding protein comprises a heavy chain variable region shown in any of SEQ ID NOS:1-22. Additionally, the disclosure includes an embodiment where the antigen binding protein comprises a light chain variable region that has the sequence shown in SEQ ID NO:23 or 24. Further, the disclosure contemplates an antigen binding protein comprising a heavy chain variable region shown in any of SEQ ID NOS:1-22, and a light chain variable region shown in SEQ ID NO:23 or 24. **FIGS. 1A-D** illustrate the 22 exemplary unique heavy chain variable regions of the CDIM binding proteins disclosed herein. **FIG. 1E** depicts two light chain variable regions (SEQ ID

NOS:23 and 24). **FIG. 1F** shows a constant region for the heavy chain (Ig μ) (SEQ ID NO:25), as well as constant regions for the light chains (Ig λ and Ig κ) (SEQ ID NOS:26 and 27). SEQ ID NO: 108 represents MAb 216 (Bhat *et al*, 2000, *supra*), a CDIM binding antibody, which was used as experimental reference antibody in assessing potency and specificity. *See, Examples, infra*.

[00052] Each of the heavy chain variable regions may be attached to a heavy chain constant region to form a full heavy chain, and each light chain variable region may be attached to a light chain constant region to form a full light chain, respectively. The amino acid sequences of the exemplary full heavy chains disclosed herein have a sequence shown in SEQ ID NOS:28-49. The amino acid sequences of the exemplary light chains disclosed herein have an amino acid sequence shown in SEQ ID NOS:50 and 51. As explained, *supra*, two heavy chain and two light chain sequences may form a full antibody tetramer. Disclosed herein are, *inter alia*, exemplary CDIM binding antibody tetramers, designated IGM1, IGM2, IGM3, IGM4, IGM5, IGM6, IGM7, IGM8, IGM9, IGM10, IGM11, IGM12, IGM13, IGM14, IGM15, IGM16, IGM17, IGM18, IGM19, IGM20, IGM21, IGM22, IGM23, IGM24, IGM25, IGM26, IGM27, IGM28, IGM29, IGM30, IGM31, IGM32, IGM33, IGM34, IGM35, IGM36, IGM37, IGM38, IGM39, IGM40, IGM41, IGM42, IGM43, and IGM44 (collectively also referred to herein as “IGM1-IGM44”). As shown in **FIGS. 2A-2V**, these 44 disclosed CDIM binding proteins are comprised of the heavy chains of SEQ ID NOS:28-49, each combined with either of the light chains of SEQ ID NOS:50-51. TABLES 3, *infra*, show the correlation between the various polypeptide and polynucleotide SEQ ID NOS and the IGM1-IGM44 antigen binding proteins.

[00053] In one embodiment, the isolated antigen binding protein binds to CDIM, and comprises a heavy chain CDR3 sequence $X_1X_2X_3AX_4GX_5SX_6X_7$, wherein:

X_1 is an G, A, or an R;

X_2 is an R, a G, or an A;

X_3 is an M, an T, or a R;

X_4 is an R, a W, or a Y;

X_5 is an A, an S or a G;

X_6 is an I, a V, or a Y; and

X₇ is an N, or no amino acid;
 and wherein there is one, and not more than one, Arginine within positions 1 through 3 (relative to heavy chain variable region, positions 98 through 100, position 97 being the invariable Arginine preceding the CDR3 region).

[00054] In another embodiment, , the isolated antigen binding protein binds to CDIM, and comprises a heavy chain CDR3 sequence X₁X₂X₃AX₄GX₅SX₆X₇, wherein:

X₁ is an G, A, or an R;

X₂ is an R, a G, or an A;

X₃ is an M, an T, or a R;

X₄ is an R, or a W;

X₅ is an A, or an S;

X₆ is an I, or a V; and

X₇ is an N, or no amino acid;

and wherein there is one, and not more than one, Arginine within positions 1 through 3 (relative to heavy chain variable region, positions 98 through 100, position 97 being the invariable Arginine preceding the CDR3 region).

[00055] In accordance with the present invention, it is to be understood, that the amino acid sequence of the binding protein of the invention is not limited to the twenty conventional amino acids (*See*, Immunology - A Synthesis (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference). For example, the amino acids may include stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids. Examples of unconventional amino acids, which may also be suitable components for the binding protein of the invention, include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids, *e.g.*, 4-hydroxyproline.

[00056] Furthermore, in accordance with the present invention, minor variations in the amino acid sequences shown in SEQ ID NOS:1-51 are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75%, more preferably at least 80%, 90%, 95%, and most preferably 99% of the sequences shown in SEQ ID NOS:1-51. The variations may occur within the framework regions (*i.e.*, outside the CDRs), within the CDRs, or within the framework regions and the CDRs. Preferred variations in the amino acid sequences shown in SEQ ID NOS:1-51, *i.e.*, deletions, insertions and/or replacements of at least one amino acid, occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other binding proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. *See, e.g.*, Bowie *et al.* (1991) *Science* 253:164; Proteins, Structures and Molecular Principles (Creighton, Ed., W. H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.* 1991 *Nature* 354: 105, which are all incorporated herein by reference. Thus, those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

[00057] Especially preferred variations in the amino acid sequences shown in SEQ ID NOS:1-51, are those that lead to a reduced susceptibility to proteolysis or oxidation, alter glycosylation patterns or alter binding affinities or confer or modify other physicochemical or functional properties of the binding protein. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Preferred amino acid families are the following: acidic family = aspartate, glutamate; basic family = lysine, arginine, histidine; non-polar family = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and uncharged polar family = glycine,

asparagine, glutamine, cysteine, serine, threonine, tyrosine. More preferred families are: aliphatic-hydroxy family = serine and threonine; amide-containing family = asparagine and glutamine; aliphatic family = alanine, valine, leucine and isoleucine; and aromatic family = phenylalanine, tryptophan, and tyrosine. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting binding protein, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional binding protein, *i.e.*, in an antigen binding protein that binds to CDIM can be readily determined by assaying in ELISA or FACS.

[00058] In some embodiments, the CDIM binding protein is a “scaffold protein” having an antibody like binding activity, where one or several CDRs of SEQ ID NOS:1-24 are embedded in a scaffold as defined, *supra*. In some embodiments at least CDRH3 and CDRL3 are embedded in the scaffold. In some embodiments all six CDRs are embedded in the scaffold. Whether the scaffold protein has CDIM binding activity can be readily determined by assaying in ELISA or FACS competition for binding with MAb 216, which is a naturally occurring CDIM binding antibody, or *in vitro* or *in vivo* functional assays.

[00059] Furthermore, according to the present invention, it is appreciated that the CDIM binding antibody of the invention is a fully human or humanized antibody. Human antibodies avoid certain of the problems associated with xenogeneic antibodies, for example antibodies that possess murine or rat variable and/or constant regions. The presence of xenogeneic-derived proteins such murine or rat derived proteins can lead to the generation of an immune response against the antibody by a patient, subsequently leading to the rapid clearance of the antibodies, loss of therapeutic utility through neutralization of the antibody and/or severe, even life-threatening, allergic reactions.

[00060] The antigen binding proteins described herein may be antibodies or may be derived from antibodies. In certain embodiments, the polypeptide structure of the antigen binding proteins is based on antibodies, including, but

not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), and fragments thereof. The antigen binding proteins provided herein have been shown to bind CDIM epitopes on all B cells, including neoplastic B cells and some solid tumor cells. As demonstrated in the examples, the ability of injured B cells to repair themselves and survive is reduced or inhibited. As a consequence, the disclosed antigen binding proteins are capable of depleting and killing B cells, including tumor cells. The antigen binding proteins that are disclosed herein have a variety of utilities. Some of the antigen binding proteins, are, for example, useful in specific binding assays, affinity purification of CDIM expressing cells, and in screening assays to identify CDIM expressing cells including solid tumor cells, cells of B cell origin. In addition, the disclosed antigen binding proteins may be used for the diagnosis and/or treatment of disease, such as B cell proliferative disorders and autoimmune diseases. To that end, the disclosed antigen binding proteins may be used alone, or in combination with small molecules chemotherapeutics.

[00061] In one embodiment, the antigen binding protein is a polyvalent CDIM binding protein (*i.e.*, CDIM binding proteins with two or more binding sites for the CDIM epitope). As such, the binding proteins function as receptors with a specific affinity and avidity for the CDIM epitope, generally at least about 10^{-6} M, and more preferably at least about 10^{-7} M. The polyvalent nature of the receptor allows the simultaneous binding of at least two CDIM epitopes on the cell membrane surface. Antibodies can be used from any of the immunoglobulin families, such as IgA, IgD, IgE, IgG, and IgM; it is not a requirement that the antibody be associated with various cytotoxic processes associated with particularly Fc-initiated processes. In one embodiment, the antibody will be IgM, since the pentameric or hexameric structure of this molecule allows cross-linking unhindered by steric interference. In some embodiments, the antibody composition is a mixture of IgM pentamers and IgM hexamers, including at least 20% hexamers, or at least 30% hexamers, at least 40% hexamers, at least 50% hexamers, or at least 60% hexamers, or at least 70% hexamers, or at least 80%

hexamers. Alternatively, fragments of antibodies may be used or synthetic alternatives thereof that act like antibodies. For example, small synthetic molecules can be devised which will allow for specific binding and cross-linking of the CDIM epitope.

[00062] In one embodiment, the antibody has the J chain, in another embodiment the antibody lacks the J chain.

[00063] In one aspect, the antigen binding protein is a recombinant antibody constructed based on the VH4-34 germ line sequence. The VH4-34 gene (variable heavy region) is one of the 53 identified human functional antibody germline genes. The VH4-34 gene is present in all haplotypes, and no sequence variation was found in germline DNA that was isolated from unrelated individuals. Anti-B cell VH4-34 antibodies are cytotoxic to B cells (Bhat *et al.* (1997) *Clin. Exp. Immunol.* 108:151 and Bhat *et al.* (2001) *Crit. Rev. Oncol. Hematol.* 39:59). As alluded to above, the plasma membrane defects or pores induced by the antibodies are larger than those formed by other well-known pore-forming proteins. By permeabilizing the cells, the disclosed CDIM binding proteins effect significant depletion of the targeted cells (*see*, also Patent Publication Number 20100322849). B cells that have been permeabilized are more susceptible to the action of additional cytotoxic agents, including, but not limited to, radioactive isotopes, cytotoxic antibodies, immunoconjugates, ligand conjugates, immunosuppressants, cell growth regulator and/or inhibitors, toxins, and/or mixtures thereof. The compromised cell membrane allows entry of cytotoxic agents such as chemotherapeutic agents, thus increasing the efficacy of the chemotherapeutic agents, even in cells that are resistant or impermeable to such agents. Any B cell or cancer cell that expresses the CDIM epitope or CDIM-like epitope, respectively, can be treated with the CDIM binding proteins and is subject to depletion and killing *via* the disclosed antigen binding proteins.

[00064] The CDIM binding proteins of the present disclosure recognize the CDIM epitope on human peripheral B lymphocytes, splenic B lymphocytes and on neoplastic B lymphocytes, and some solid tumors. Many IgM antibodies are polyreactive, *i.e.*, they can bind to a variety of different and structurally unrelated self and non-self foreign antigens. However, the antigen binding proteins

disclosed herein were found to have less polyreactivity than some naturally occurring CDIM antibodies. As such, the disclosed antigen binding proteins are subject to less off-target binding, making them better therapeutic and diagnostic candidates for *in vivo* applications. Their reduced polyreactivity is illustrated in **FIGS. 5A-5E**, which shows examples of the disclosed antigen binding proteins that have reduced or lost their binding affinity for multiple non-CDIM antigens, specifically ssDNA, dsDNA, lipid A, cardiolipin and MDA-LDL. This suggests that the disclosed CDIM binding proteins are safer for therapeutic applications because the dose required to bind the target cells will be lower since there is no “antigen sink” for the antibody (binding to antigens other than CDIM). The affinity of a polyreactive antibody for different antigens varies by as much as 1000-fold and is generally lower than that of a monoreactive antibody for its antigen. Many of the polyreactive antibodies are usually germline or near germline although some have a small number of substitutions. Polyreactive antibodies may be cleared from the circulation faster than monoreactive antibodies. The rapid clearance of the polyreactive antibodies may be due to the binding of these antibodies to endogenous host antigens (*see, also Zhou et al. (2007) J. Autoimmun. 29(4):219–228*). Many of the natural antibodies are polyreactive antibodies, which have broad antibacterial activity. This partly explains the antibacterial activity in the sera of newborns in the absence of known antigenic stimulation (*see, also Zhou et al. (2007), supra*). However, for therapeutic purposes, it is generally desirable to employ antibodies that are mono-specific and are not cleared too rapidly so as to accomplish binding and killing to B cells and cancer cells that express the CDIM epitope.

[00065] In specific therapeutic applications, for example, in treating an autoimmune disease it is desirable that the CDIM binding proteins bind B cells and kill them selectively as B cells contribute to multiple autoimmune diseases by a variety of mechanisms (*Browning, J.L. (2006) Nature (Reviews) 5:564-576*). The rapid depletion of the B cells reduces the activity of the immune system which in turn reduces many associated side-effects such as inflammation and tissue damage. In cancer treatment it is desirable to kill selective cell populations, such as neoplastic B cells or cancer cells in order to stop hyper-proliferation of these cells and the spread of cancer to other organs. Herein, the

combination therapy with other agents and cancer drugs can be beneficial in directing the killing of specific cells. Thus, the CDIM binding proteins find therapeutic application in both autoimmune disease and cancer treatment.

[00066] As discussed above, binding of the disclosed antigen binding proteins to its linear lactosamine ligand leads to disruption of the plasma membrane and formation of large membrane pores resulting in cell lysis. The combination of vincristine, for example, and the disclosed antigen binding proteins results in an enhanced degree of cytotoxicity to B cells when compared to the additive effect of each single agent alone. Hence, the CDIM binding proteins can be administered to patients alone and in combination with other agent and/or cancer drugs to assess tumor targeting and efficacy. Furthermore, the CDIM binding proteins can be administered to patients alone and in combination with other agents and/or cancer drugs to treat and/or diagnose various diseases including cancer and autoimmune diseases. Examples of other agents that could be used in combination with CDIM binding proteins are shown in TABLE 1 below:

TABLE 1		
COMPOUND	ACTION	EFFECT
Etoposide (VP-16)	Topoisomerase II Inhibitor	Additive Effect
Paclitaxel (Taxol)	Freezes Microtubules	Possible/Undermined Effect
Ara-C (Cytarabine)	Analog	Additive Effect
Vincristine, Nocodazole, Colchicine	Depolymerize Microtubules	Synergistic Effect
Daunorubicin	Anthracyclines	Additive Effect

[00067] In some embodiments, an antigen binding protein of the invention is coupled to a labeling group. Such a binding protein is particularly suitable for diagnostic applications. As used herein, the term "labeling group" refers to a detectable marker, *e.g.*, a radiolabeled amino acid or biotinyl moiety that can be detected by conjugated avidin (*e.g.*, streptavidin bound to a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Various methods for labeling polypeptides and glycoproteins, such as antibodies, are known in the art and may be used in performing the present invention.

Examples of suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic groups (*e.g.*, horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In certain respects, it may be desirable that the labeling groups are attached by spacer arms of various lengths to reduce potential steric hindrance.

[00068] Alternatively, an antigen binding protein disclosed herein may be coupled to an effector group in another preferred embodiment of the invention. Such a binding protein is especially suitable for therapeutic applications. As used herein, the term "effector group" refers to a cytotoxic group such as a radioisotope or radionuclide, a toxin, a therapeutic group or other effector group known in the art. Examples for suitable effector groups are radioisotopes or radionuclides (*e.g.*, ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), calicheamicin, dolastatin analogs such as auristatins, and chemotherapeutic agents such as geldanamycin and maytansine derivatives, including DM1. In certain respects, it may be desirable that the effector groups are attached by spacer arms of various lengths to reduce potential steric hindrance.

[00069] *Polynucleotides Encoding CDIM Binding Proteins And Expression Systems*

[00070] Another aspect of the present invention relates to an isolated nucleic acid molecule encoding a binding protein of the invention. Within the context of the present invention, the term "isolated nucleic acid molecule" means a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin, the "isolated nucleic acid molecule" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence. Further, the term "nucleic acid molecule", as referred to herein,

means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide, such as nucleotides with modified or substituted sugar groups and the like. The term also includes single and double stranded forms of DNA.

[00071] Exemplary complete nucleic acid sequences encoding the heavy chain sequences of IGM1-IGM44 (SEQ ID NOS:52-73) are provided in **FIGS. 3A-K**. Exemplary complete nucleic acid sequences encoding the light chain sequences of IGM1-IGM44 (SEQ ID NOS:74 and 75) are provided in **FIG. 3L**. Of course, due to the degeneracy of the genetic code, other nucleic acids encoding the CDIM binding proteins described herein can be contemplated.

[00072] In a one embodiment of the present invention, a nucleic acid molecule of the invention is operably linked to a control sequence. The term "control sequence", as used herein, refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism. In prokaryotes, such control sequences generally include promoters, ribosomal binding sites, and transcription termination sequences. In eukaryotes, generally, such control sequences include promoters and transcription termination sequences. In accordance with the present invention, the term "control sequence" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. Furthermore, the term "operably linked", as used herein, refers to positions of components so described which are in a relationship permitting them to function in their intended manner. Moreover, according to the present invention, an expression control sequence operably linked to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the expression control sequence.

[00073] A further aspect of the present invention is a vector comprising a nucleic acid molecule that encodes a binding protein of the invention. The nucleic acid molecule can be operably linked to a control sequence.

Furthermore, the vector may additionally contain a replication origin or a selection marker gene. Examples of vectors that may be used in accordance with the present invention are, *e.g.*, plasmids, cosmids, phages, viruses, etc.

[00074] Another aspect of the present invention relates to a host cell transformed with a nucleic acid molecule or vector of the invention. Transformation could be done by any known method for introducing polynucleotides into a host cell, including for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455, which patents are hereby incorporated herein by reference. Particularly, methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. Examples of host cells that may be used according to the present invention are hybridomas eukaryotic cells such as mammalian cells, *e.g.*, hamster, rabbit, rat, pig, mouse or other animal cells; plant cells and fungal cells, *e.g.*, corn, tobacco, *Saccharomyces cerevisiae*, *Pichia pastoris*; prokaryotic cells such as *E. coli*; and other cells used in the art for the production of antibodies. Especially mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and a number of others.

[00075] *Pharmaceutical Compositions of CDIM Binding Proteins and Methods of Treatment and Diagnosis*

[00076] A further aspect of the present disclosure are pharmaceutical compositions and of the CDIM binding proteins. The binding proteins are formulated as pharmaceuticals to be used in the methods of the disclosure. Any composition or compound that can stimulate a biological response associated

with the binding of the CDIM binding proteins to the CDIM epitope of B lymphocytes can be used as a pharmaceutical in the disclosure. General details on techniques for formulation and administration are well described in the scientific literature (*see*, "Remington's Pharmaceutical Sciences", Maack Publishing Co, Easton Pa.). CDIM binding protein pharmaceutical formulations can be prepared according to any method known in the art for the manufacture of pharmaceuticals. The CDIM binding proteins can be formulated for administration in any conventionally acceptable way including *via* intravenous injection, intramuscular, intraperitoneal, orally, topically or through other routes. Illustrative examples are set forth below.

[00077] Pharmaceutical formulations for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical formulations to be formulated in unit dosage forms as tablets, pills, powder, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, and the like, suitable for ingestion by the patient. Pharmaceutical preparations for oral use can be obtained through combination of the CDIM binding proteins with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or pills. Suitable solid excipients are carbohydrate or protein fillers which include, but are not limited to, sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate. Pharmaceutical preparations of the present disclosure that can also be used orally are, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the CDIM binding proteins mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the CDIM binding proteins may be dissolved or

suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[00078] Aqueous suspensions of the disclosure contain the CDIM binding proteins in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethylene oxyethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (*e.g.*, polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[00079] Oil suspensions can be formulated by suspending CDIM binding proteins in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid.

[00080] Dispersible powders and granules of the disclosure suitable for preparation of an aqueous suspension by the addition of water can be formulated from the CDIM binding proteins in admixture with a dispersing, suspending and/or wetting agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[00081] The CDIM binding protein pharmaceutical formulations can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening and flavoring agents. Syrups and elixirs can be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations can also contain a demulcent, a preservative, a flavoring or a coloring agent.

[00082] When the CDIM binding proteins are delivered by intravenous injection, the pharmaceutical formulations can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

[00083] The methods of the present disclosure treat human and non-human patients who suffer from lymphoid cancer or leukemia (*e.g.*, B-cell acute lymphoblastic leukemia or ALL), any form of autoimmune disease involving B cells (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus or SLE), any form of B cell hyper-proliferation such as lymphomas and myelomas (*e.g.*, non-Hodgkin's lymphomas), certain forms of solid tumors that express the CDIM antigen, and/or related conditions. The amount of CDIM binding protein that is

adequate to accomplish this is considered the therapeutically effective dose. Alternatively, the amount of CDIM binding protein in combination with another agent or another drug that is adequate to accomplish this is also considered a therapeutically effective dose. Other agents are, for example, cytotoxic agents including, but not limited to, a radioactive isotope, a cytotoxic antibody, an immunoconjugate, a ligand conjugate, an immunosuppressant, a cell growth regulator and/or inhibitor, a toxin, or mixtures thereof. A chemotherapeutic agent or compound (*see*, also TABLE 1) is often an agent that interferes with the polymerization or depolymerization of microtubules such as a taxane, vinca alkaloid or colchicine, or mixtures thereof. The vinca alkaloid includes vinblastine, vincristine, vindesine, or vinorelbine, or mixtures thereof. The taxane includes, but is not limited to, paclitaxel, docetaxel, or mixtures thereof. The cytotoxic antibody that can be administered in combination with the disclosed antigen binding proteins usually has specific binding for a cell surface receptor on a B cell, including CD11a, CD19, CD20, CD21, CD22, CD25, CD34, CD37, CD38, CD40, CD45, CD52, CD80, CD 86, IL-4R, IL-6R, IL-8R, IL-13, IL-13R, α -4/ β -1 integrin (VLA4), BLYS receptor, cell surface idiotype Ig, tumor necrosis factor (TNF), or mixtures thereof. As such, the cytotoxic antibody can be efalizumab (RAPTIVA), rituximab (RITUXAN), daclizumab (ZENAPAX), epratuzumab, basiliximab (SIMULECT), anti-CD52 (CAMPATH), natalizumab, infliximab (REMICADE), and the like. The immunosuppressant includes, but is not limited to, a glucocorticoid, a calcineurin inhibitor, an antiproliferative/antimetabolic agent, or an immunosuppressive antibody. In one embodiment, the agents are etoposide (VP-16), paclitaxel (taxol), ara-C (cytarabine), vincristine, nocodazole, colchicine, daunorubicin, cytochalasin, jasplakinolide, and the like.

[00084] In one embodiment of the present invention, at least one binding protein disclosed herein contained in the pharmaceutical composition is coupled to an effector, such as calicheamicin, Auristatin-PE, a radioisotope or a toxic chemotherapeutic agent such as geldanamycin and maytansine. In particular, these binding protein conjugates are useful in targeting cells, *e.g.*, cancer cells, expressing CDIM for elimination.

[00085] Moreover, linking the binding proteins disclosed herein to

radioisotopes provides advantages to tumor treatments. Unlike chemotherapy and other forms of cancer treatment, radioimmunotherapy or the administration of a radioisotope-binding protein combination directly targets the cancer cells with minimal damage to surrounding normal, healthy tissue. With this "magic bullet", the patient can be treated with much smaller quantities of radioisotopes than other forms of treatment available today. Certain radioisotopes include yttrium⁹⁰ (⁹⁰Y), indium¹¹¹ (¹¹¹In), ¹³¹I, ^{99m}Tc, radiosilver-111, radiogold-199, and Bismuth²¹³. The linkage of radioisotopes to binding proteins may *e.g.*, be performed with conventional bifunctional chelates. Since silver and gold can exist in a monovalent state, for radiosilver-111 and radiogold-199 can utilize sulphur-based linkers may be used (Hazra *et al.* (1994) *Cell Biophys.* 24-25:1-7). Linkage of silver radioisotopes may involve reducing the immunoglobulin with ascorbic acid. Furthermore, tiuxetan is an MX-DTPA linker chelator attached to ibritumomab to form ibritumomab tiuxetan (Zevalin) (Witzig, T.E. (2001) *Cancer Chemother. Pharmacol.* 48 Suppl 1:91-5). Ibritumomab tiuxetan can react with radioisotopes such as indium¹¹¹ (¹¹¹In) or ⁹⁰Y to form ¹¹¹In-ibritumomab tiuxetan and ⁹⁰Y-ibritumomab tiuxetan, respectively.

[00086] Furthermore, a binding protein disclosed herein, particularly when used to treat cancer, may be conjugated with toxic chemotherapeutic drugs such as calicheamicin (Hamann *et al.* (2002) *Bioconjug. Chem.* 13:40-46, geldanamycin (Mandler *et al.*, (2002) *J. Natl. Cancer Inst.*, 92:1549-1951) and maytansine, for example, the maytansinoid drug, DM1 (Liu *et al.* (1996) *Proc. Natl. Acad. Sci. U.S.A.* 93:8618-8623). Different linkers that release the drugs under acidic or reducing conditions or upon exposure to specific proteases may be employed with this technology. According to the present invention, a binding protein disclosed herein may be conjugated as described in the art.

[00087] Auristatin-PE, *e.g.*, is an antimicrotubule agent that is a structural modification of the marine, shell-less mollusk peptide constituent dolastatin 10. Auristatin-PE has both anti-tumor activity and anti-tumor vascular activity (Otani *et al.* (2000) *Jpn. J. Cancer Res.* 91:837-44). For example, auristatin-PE inhibits cell growth and induces cell cycle arrest and apoptosis in pancreatic cancer cell lines (Li *et al.* (1999) *Int. J. Mol. Med.* 3:647-653). Accordingly, to specifically target the anti-tumor activity and anti-tumor vascular activities of

auristatin-PE to particular tumors, auristatin-PE may be conjugated to the binding protein disclosed herein.

[00088] The dosage schedule and amounts effective for this use, *i.e.*, the "dosing regimen," will depend upon a variety of factors, including the stage of the disease or condition, the severity of the disease or condition, the severity of the adverse side effects, the general state of the patient's health, the patient's physical status, age and the like. In calculating the dosage regimen for a patient, the mode of administration is also taken into consideration. The dosage regimen must also take into consideration the pharmacokinetics, *i.e.*, the rate of absorption, bioavailability, metabolism, clearance, and the like (*see, for example, Liedtke et al. (2012) Haematologica 97(1):30-37*).

[00089] The state of the art allows the clinician to determine the dosage regimen for each individual patient. CDIM binding proteins can be administered alone or in combination with other compounds. If administered in combination with other compounds, better patient responses and more durable outcomes would be expected. The combined compounds may act synergistically, or additively.

[00090] As an illustrative example, the guidelines provided below for CDIM binding proteins can be used as guidance to determine the dosage regimen, *i.e.*, dose schedule and dosage levels, of any CDIM binding protein administered when practicing the methods disclosed herein. The clinical efficacy of CDIM binding proteins may be enhanced by the co-administration of a second compound such as vincristine or similar agent. Likewise, the efficacy of a small molecule chemotherapeutic may be enhanced by the co-administration with the CDIM antigen binding protein. CDIM binding proteins are effective in a dose range of about between 0.25mg/kg to 100mg/kg. Single or multiple administrations of CDIM binding protein formulations may be administered depending on the dosage and frequency as required and tolerated by the patient who suffers from lymphoid cancer or leukemia (*e.g.*, B-cell acute lymphoblastic leukemia or ALL), any form of autoimmune disease involving B cells (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus or SLE), or any form of B cell hyperproliferation such as lymphomas and myelomas (*e.g.*, non-Hodgkin's

lymphomas) and/or related conditions. The formulations should provide a sufficient quantity of CDIM binding protein to effectively ameliorate the condition. For example, any one of the 44 antigen binding proteins disclosed herein may be administered to a patient through monotherapy (*i.e.*, with no other medications) or in combination therapy with, for example, vincristine or other agents, *see, supra*). The antigen binding proteins having specific binding for the CDIM epitope on a B cell can be administered at a dose of from about 2.5 to about 3000mg/m², or more preferably, from about 25 to 1000mg/m², or in particular, about 75, 150, 300 or 600mg/m². In additional aspects, the antibody is administered at a dose of from about 0.25mg/kg to about 100mg/kg, and more preferably, at about 1.25, 2.5, 5, 10, or 20mg/kg. The anti-CDIM antibody is typically administered on a weekly basis, and in some embodiments, more frequently than once per week, as often as once per day. Additional cytotoxic antibodies can be administered in an amount of 10-375mg/m² per week for four weeks, or 0.4-20mg/kg per week for 2 to 10 weeks in form of a combination therapy. In one embodiment, CDIM binding proteins are currently administered to a patient daily as monotherapy in an amount from about 0.25mg/kg to about 100mg/kg. In another embodiment, CDIM binding proteins are administered to a patient daily in combination therapy with a second agent selected from the group consisting of vinblastine, vincristine, vindesine, vinorelbine, or mixtures thereof in an amount from about from about 0.15mg/kg to about 50mg/kg.

[00091] Notably, the dosages of selective CDIM binding proteins administered to a patient may vary depending on age, degree of illness, drug tolerance, and concomitant medications and conditions. The CDIM binding proteins may be administered to the patient in combination with another drug in order to potentiate the effect of the CDIM binding proteins and in order to reduce adverse side effects. Using a second drug, the activity of co-administration of CDIM binding proteins may be enhanced by between 10% and 90% and the combination therapy will continue until the combination treatment is no longer deemed beneficial or necessary. The CDIM binding proteins may be administered to a patient simultaneously or within specific time frames of one another. Different CDIM binding proteins can be administered to the patient simultaneously in separate pills or tablets or in the form of a combination pill.

[00092] *Disorders and Diseases*

[00093] The CDIM binding proteins of the present disclosure can be used to treat patients who suffer from lymphoid cancer or leukemia, any form of autoimmune disease involving B, or any form of B cell hyperproliferation such as acute or chronic leukemia, lymphomas and myelomas, and/or related disorders. Any condition that is characterized by a hyperproliferation of B cells including lymphoid cancer, viral infection, immunodeficiency, or autoimmune disease can be treated with the CDIM binding proteins. Similarly, any tumor cell or cancer cell that expresses the CDIM epitope or a CDIM-like antigen can be treated with the CDIM binding proteins.

[00094] The disclosure provides improved CDIM binding proteins for selective B cell killing and depleting in disorders related to autoimmunity including, but not limited to, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), Myasthenia gravis, Pemphigus vulgaris, Grave's disease and autoimmune thrombocytopaenia. Autoreactive B cells secrete autoantibodies directed against self-proteins. B lymphocytes not only produce autoantibodies but also play an important regulatory role independent of their function as antibody-producing cells. This is relevant with respect to autoimmunity, since autoreactive B cells have the ability to activate pathogenic T cells to produce pro-inflammatory cytokines. Myasthenia gravis, Pemphigus vulgaris, Grave's disease and autoimmune thrombocytopaenia are good examples of conditions in which pathogenic antibodies drive the clinical phenotype (*see*, Browning, J.F, *supra*). In addition, autoimmune disorders lead to overactive and increased numbers of B cells that should be removed in order to prevent massive inflammation and tissue damage. Thus, the depletion of B lymphocytes is useful in the treatment of such autoimmune diseases. Since the treatment of many rheumatic autoimmune diseases such as rheumatoid arthritis relies primarily on the use of cytotoxic immunosuppressants and corticosteroids patients often suffer additional severe side effects. In addition, patient relapse rates remain high. There is a need for safer and more effective drugs such as the CDIM binding proteins of the present disclosure.

[00095] A lymphoid cancer is any acute or chronic leukemia or lymphoma of B cell origin, including, but not limited to, acute lymphocytic leukemia (ALL), non-Hodgkins lymphoma (NHL), Burkitt's lymphoma, B progenitor ALL, adult ALL, chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinaemia. The CDIM binding proteins bind to the epitope CDIM, which is found on cancerous B cells.

[00096] In order to allow prediction of patients who will respond to treatment with the disclosed CDIM antigen binding proteins, *in vitro* or *in vivo* analysis may be performed. *In vivo* imaging may be performed prior to treatment by administering CDIM antigen binding proteins as a conjugate which allows visualization of the CDIM antigen on the tissue of interest. A particular level of reactivity may be established that would allow prediction of patient response to therapy. Alternatively, this type of analysis may help in establishing dosing parameters based on tumor load. *In vitro* analysis may be performed on samples of patient's lymphoid cells (peripheral blood, bone marrow or other) prior to treatment. Cells will be stained with CDIM antigen binding proteins using standard flow cytometric analysis. A cut-off will be established that allows prediction of positive outcome following therapy. For example, a minimal mean fluorescence intensity may be established which predicts positive outcome.

[00097] V. EXAMPLES

[00098] The following specific examples are intended to illustrate the disclosure and should not be construed as limiting the scope of the claims.

[00099] Example 1: Generation and Sequence Determination of Exemplary CDIM Binding Proteins

[000100] *Plasmid DNA construction.* All the H series mu chain constructs variable heavy regions (designated H1-H22) were synthesized by Genscript with Xba1-Kpn1 sites on the 5' and 3' ends respectively. All the H series Mu chain constructs were assembled by isolating each of heavy chain variable regions as Xba1-Kpn1 fragments and joining them in a three-part ligation with a Kpn1-BamH1 fragment spanning the constant mu region together with the expression vector AB11 that had been digested with Xba1 and BamH1. The ligated plasmids were transformed into competent bacteria. The resulting cloned plasmids were

confirmed by direct sequencing. Plasmid midi-preps were generated using Qiagen, to provide adequate amounts of DNA for transfection into CHO-S cells.

[000101] The light chain plasmid were constructed in a similar fashion. The lambda insert was cloned in a three part ligation; the variable lambda region was designed as a XbaI-EcoRI fragment, which was mixed with the EcoRI-BamHI lambda constant region fragment and ligated into the AB2 vector between XbaI and BamHI sites. The L2 kappa insert was isolated as a XbaI-BamHI fragment and ligated into the AB2-Kappa vector.

[000102] *Transfection of CHO-S cells with the H1-H22/L2 plasmid DNA.* DNA corresponding to heavy and light chains, was prepared for co-transfection (equal amounts of L2 and of H1-22) using the PEI technique. CHO-S cells ($1E^8$ of log phase growth) used for transfection were grown in RPMI1640 media. DNA:PEI was mixed 1:2 and this DNA:PEI mixture was added to CHO-S cells in CD OptiCHO supplemented with 0.5x Pen/Strep, Glutamax and HT. After overnight incubation in shaker flask, the media was exchanged into CD OptiCHO with 0.5x P/S, Glu. On day 7 post-transfection, the cell culture supernatant (100 ml) was harvested by centrifugation of the cells. For characterization of these IgM examples, 15 ml of cell culture supernatant was concentrated 10x by Centricon.

[000103] The amino acid sequences of the 22 distinct heavy chain variable regions are depicted in **FIGS. 1A-D**. The amino acid sequences of the 2 distinct light chain variable regions are depicted in **FIG. 1E**. The amino acid sequences of the constant regions of the heavy and light chains are shown in **FIG. 1F**. It is understood that either kappa or lambda constant regions can be utilized. The amino acid sequences that are representative of the identified and isolated CDIM binding proteins, IGM1-IGM44, shown in **FIGS 2A-2V**. The CDR3 sequences of H1 through H22 are depicted in **FIGURE 3**.

[000104] Examples of polynucleotide sequences that could be used to encode the 44 disclosed CDIM binding proteins are depicted in **FIGS. 4A-L**. It is understood that due to degeneracy in the genetic code, other sequences could be utilized to encode the exact amino acid sequence. The sequences of the various complementarity determining regions (CDRHs) and framework (FR) regions of

the heavy chain variable region of the antibodies were determined include framework 1 (FR1), complementarity determining region 1 (CDRH1), framework 2 (FR2), complementarity determining region 2 (CDRH2), framework 3 (FR3) and complementarity determining region 3 (CDRH3).

[000105] Example 2: Making of CDIM Binding Proteins

[000106] This example describes how some of the disclosed binding proteins were made. Sequences consisted of heavy and light chain variable region variants (both kappa and lambda constant regions were encoded). Specific combinations of heavy and light chain variants were transfected into CHO cells, *i.e.*, DG44 CHO cells and transient transfections were made. Expression levels of 10-100 µg/ml were obtained from the initial transfections. IgM antibodies were purified by affinity chromatography, evaluated by gel electrophoresis and tested for bioactivity by cell binding, cytotoxicity assays and ELISA testing for binding to multiple biomolecules. Results obtained from the functional assays were used to guide lead candidate selection. Once selected, the lead candidates were stably transfected into CHO cells and sub-cloned into 20 plates (approximately 2000 wells) and screened by ELISA for highest level of secretion. The top 50 clones were expanded to T75 flasks followed expansion of the best 24 clones being transferred into shaker flasks. IgM from these 24 clones were purified and quantified and the top six clones (selected by IgM antibody secretion levels) were grown under further selection in methotrexate (50 nM, 100 nM, 200 nM, 400 nM) to facilitate outgrowth of high secreting cell lines.

[000107] Example 3: Evaluation of IgM Expression using Non-Reduced SDS-PAGE

[000108] Non-reducing gel electrophoresis is a separation method typically used in proteomics and resolves proteins based on molecular mass and oligomeric structures. Under non-reducing conditions, protein disulfide bonds are left intact and so the IgM oligomer can be resolved as pentameric or hexameric structures.

[000109] To confirm IgM antibody expression by transient transfection of CHO-S cell supernatant, we performed non-reducing SDS polyacrylamide gel electrophoresis as described in Vorauer-Uhl, et al, J Immunol. Methods 359 (2010): 21-27. This example describes how transiently transfected IgM mAbs were investigated for purity and multimeric structure. Protein sample of interest is

incubated with NuPage SDS sample buffer for 5 minutes at room temperature. After incubation, the molecular weight standards and test samples are loaded onto the gel and run at 100V constant voltage for approximately 2 hours until dye front reaches the bottom of the gel. After electrophoresis, the gel is removed from XCell Mini-Cell apparatus, fixed and stained with Colloidal Blue dye.

[000110] To demonstrate pentamer and hexamer formation, non-reducing SDS PAGE of concentrated supernatant of CHO cells, transfected with the various CDIM binding protein samples (L1-L7, and L9-L21, respectively), was performed using SDS PAGE, Life Technologies' (Carlsbad, CA) Native Page Novex 3-12% Bis-Tris gels.

[000111] **Fig. 5** shows the SDS gel stained according to the Colloidal Blue Staining protocol (Life Technologies, Carlsbad, CA), with a prominent band at 1,048 kD, which represents the IgM pentamers, and a prominent band at 1,236 kD, which represents the IgM hexamers. As can be seen in the figure, pentamer formation for the IgM examples (solid arrow) is more dominant compared with hexamer formation. Similarly, the isolated human IgM 216 is predominately of pentameric form (dashed arrow), however, it appears as a lower molecular weight due to the smaller lambda light chains included in this IgM format.

[000112] **Example 4: Binding of CDIM Binding Proteins to CDIM Antigen**

[000113] This example describes how the binding properties of the disclosed antibodies were investigated. The antibodies were prepared by affinity chromatography. In **FIG. 6A**, the human pro-B cell line, NALM-6, which expresses the CDIM antigen on the cell surface was stained with the series of recombinant IgM antibodies. The antibodies were used to determine the dose response beginning at 20 µg/tube diluted stepwise by 2, to a final concentration at 0.039 µg. Cells were stained in a 100 µl volume in 3% FBS/PBS on ice for 1 hour followed by a subsequent staining with DyLight-488 conjugated anti-human IgM (Jackson Immuno), 1 µg/ml for 20 minutes at 4 C.

[000114] Analysis of CDIM binding was performed on FACScan flow cytometer using CellQuest analysis software. Results are shown as raw data

points with Mean Fluorescence Intensity (MFI) on Y-axis and concentration of primary antibody ($\mu\text{g}/100\ \mu\text{l}$) on X-axis.

[000115] The data were re-analyzed using GraphPad analysis program to fit the results using non-linear regression curve fit. EC_{50} ($\mu\text{g}/100\ \mu\text{l}$) for each antibody was (a) 10.6 for IGM1, (b) 2.2 for IGM23, (c) 2.2 for IGM34, and (d) 1.7 for IGM36.

[000116] Example 5: Cytotoxicity Resulting from Cellular Binding of CDIM Binding Proteins

[000117] This example describes how the cytotoxicity of the CDIM binding proteins was investigated. The human pro-B cell line NALM-6 was stained identically as described in **FIG. 6A** above. In **FIG. 6B**, cell killing was evaluated by measuring cell viability after 1 hour of staining. By quantifying the proportion of cells that did not uptake propidium iodine, the percentage of viable cells was calculated. Results are shown as raw data with % viability on Y-axis and concentration ($\mu\text{g}/100\ \mu\text{l}$) on X-axis.

[000118] Identical results were graphed using GraphPad analysis program and data fit using non-linear regression curve fitting. The EC_{50} was calculated for each antibody using the same approach described above. EC_{50} ($\mu\text{g}/100\ \mu\text{l}$) for each antibody was (a) 3.0 for IGM1, (b) 0.6 for IGM 23, (c) 0.6 for IGM34, and (d) 0.3 for IGM36.

[000119] Results from **FIGS. 6A and 6B** show that the disclosed antibodies bind human B cells across a broad dose range and that these antibodies are cytotoxic for B cells resulting in cellular death.

[000120] Example 6: Cytotoxicity Resulting from Human Complement Dependent Cytotoxicity Assay of CDIM Binding Proteins

[000121] "Complement-dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies, which are bound to their cognate antigen. To assess complement activation, a CDC assay, as described in Hinton et al, J. Immunol. 2006 Jan 1; 176(1):346-56, may be performed. Briefly, this example describes how the cytotoxicity of the CDIM binding proteins was

investigated. Human pro-B NALM-6 cells (50,000) were plated in a 96-well flat bottom microtiter plate. Human complement is added at the optimal tested dilution with or without a serial dilution of supernatant containing expressed antibody of interest. After 24 hours, a colorimetric substrate CCK8 was added for 3 hours and then the optical density (OD) was measured at 450nm wavelength on a Microtiter Plate Reader. Quantification of the increase in OD is directly proportional to viable proliferating NALM-6 cells. The OD of untreated Nalm6 without supernatant is then used to calculate 100%, with supernatant OD values normalized accordingly to obtain viability percentages. In Figure 8, the results are shown as percent viability on plotted on the Y-axis versus antibody containing concentration of supernatant (ug/ml) on X-axis. These results were analyzed using the GraphPad program and data were modeled using four parameter, non-linear regression curve fitting. The IC50 was calculated for each antibody using the same approach as described above.

[000122] Example 7: Binding of CDIM Binding Proteins to non-CDIM Antigens

[000123] This example describes the binding specificity of the CDIM binding proteins for antigens other than CDIM. The antibodies were purified by affinity chromatography. Antibodies were tested across a broad dose range against a panel of antigens available in commercially available ELISA kits. ELISA plates pre-coated with the antigens, ssDNA (Inova Diagnostics, Inc, San Diego, CA), dsDNA (Inova Diagnostics, Inc., San Diego, CA.), cardiolipin (Inova Diagnostics, Inc., San Diego, CA.) MDA-LDL (malondialdehyde modified low density lipoprotein) (Rocky Mountain Diagnostics, Colorado Springs, CO.) were purchased from various vendors. Lipid A (Avanti Polar Lipids, Alabaster, AL) was purchased as an antigen, dissolved in ethanol and diluted in 100mM Na carbonate buffer at pH 9.5 prior to coating onto ELISA plates. Anti-CDIM antibodies were used at concentrations indicated and ELISA was performed according to manufacturers recommendations. Briefly, plates were blocked with BSA-milk powder for 1 hour, followed by washing. The disclosed antibodies were added at the concentrations indicated. The antibodies were allowed to bind for 1.5 hours at room temperature followed by a wash step. The HRP-conjugated anti-human IgM antibody was added, followed by substrate addition.

Results were quantified using absorbance at 450nm (Bio-Tek Synergy HT). As shown in **FIGS. 8 and 9**, MAb 216 binds to all the antigens tested while each of the disclosed antibodies show either decreased binding (*i.e.*, ssDNA) or complete elimination of specificity for the antigen (*i.e.*, cardiolipin). These results demonstrate that the disclosed antibodies have more restricted antigen binding specificities than MAb 216.

[000124] TABLE 2 summarizes the potency and specificity characteristics of the various CDIM binding proteins disclosed herein.

TABLE 2
Summary of Name and Characteristics of the Various Samples

Example	ELISA (μ g/ml)	Cytotoxicity IC ₅₀ (ng/ml)	LPS	ss DNA	ds DNA	Cardio- lipin	Chondroitin Sulfate	Heparan Sulfate
hm216	71	1762	++++	++++	++++	+++	++++	++++
H1	66	47	+	+	+	+	+	+
H2	61	49	-	-	-	-	+	+
H3	27	1762	-	-	-	-	+	++
H4	44	66	-	-	-	-	+	-
H5	82	190	-	-	-	-	+	+
H7	88	60	-	+	-	-	+	+
H8	50	150	-	+	++	++	++	++
H9	201	29	+	+	-	+	+	++
H12	223	46	-	+	-	+	-	+
H13	74	128	-	+	-	+++	++	+++
H14	72	184	+	+	-	++	+	++
H16	79	30	-	-	-	+	-	-
H17	46	194	+	-	+	++	+	+
H18	185	33	+	+	-	+	+	++
H21	136	42	-	-	-	+	-	+

[000125] TABLE 2 summarizes the data shown in **FIG. 6** and **FIG. 7** for the CDIM binding proteins comprising variable heavy chains H1, H2, H3, H4, H5, H6, H7, H9, H10, H11, H12, H13, H14, H15, H16, H17, H18, H19, H20, and H21, respectively. The ELISA value refers to the concentration of IgM determined in the conditioned media following transient transfection of IgM heavy and light chains. The cytotoxicity IC₅₀ is the half-maximal concentration of IgM antibody

that results in 50% cell death upon incubation of antibodies, with human complement and Nalm-6 cells (*see*, also **Fig. 6**). The IC₅₀ value represents the potency of the various CDIM binding proteins disclosed herein.

[000126] The additional binding to other antigens (LPS, ssDNA, dsDNA, etc.) is the binding observed in ELISA format (*see*, also, **FIGS. 9A-9F**). The relative reactivity of IgM samples to various antigens is based on the maximal reaction (OD₄₅₀ nm) when the IgM is at 10 µg/ml. The values shown represent the values of non-specificity of the various CDIM binding proteins. The scoring of relative reactivity is as follows: OD₄₅₀ is 0 to 0.3, the score is given as (-)minus. The (+), (++) , (+++) and (++++) scores are given for maximal ELISA values of 0.3 to 1, 1 to 2, 2 to 3 and above 3, respectively.

[000127] Various modifications and variations of the present disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific embodiments, it should be understood that the claims should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure, which are understood by those skilled in the art are intended to be within the scope of the claims.

TABLE 3A: CDIM BINDING PROTEIN: POLYPEPTIDES

Name of Antibody	Heavy Chain Variable Region Polypeptide Sequence ID Number (SEQ ID NO)	Light Chain Variable Region Polypeptide Sequence ID Number (SEQ ID NO)	Heavy Chain Constant Region Polypeptide Sequence ID Number (SEQ ID NO)	Light Chain Constant Region Polypeptide Sequence ID Number (SEQ ID NO)	Complete Heavy Chain Polypeptide Sequence ID Number (SEQ ID NO)	Complete Light Chain Polypeptide Sequence ID Number (SEQ ID NO)
IGM1	1	23	25	26 (lambda)	28	50
IGM2	2	23	25	26 (lambda)	29	50
IGM3	3	23	25	26 (lambda)	30	50
IGM4	4	23	25	26 (lambda)	31	50
IGM5	5	23	25	26 (lambda)	32	50
IGM6	6	23	25	26 (lambda)	33	50
IGM7	7	23	25	26 (lambda)	34	50
IGM8	8	23	25	26 (lambda)	35	50
IGM9	9	23	25	26 (lambda)	36	50
IGM10	10	23	25	26 (lambda)	37	50
IGM11	11	23	25	26 (lambda)	38	50
IGM12	12	23	25	26 (lambda)	39	50
IGM13	13	23	25	26 (lambda)	40	50
IGM14	14	23	25	26 (lambda)	41	50
IGM15	15	23	25	26 (lambda)	42	50
IGM16	16	23	25	26 (lambda)	43	50
IGM17	17	23	25	26 (lambda)	44	50
IGM18	18	23	25	26 (lambda)	45	50
IGM19	19	23	25	26 (lambda)	46	50
IGM20	20	23	25	26 (lambda)	47	50
IGM21	21	23	25	26 (lambda)	48	50
IGM22	22	23	25	26 (lambda)	49	50
IGM23	1	24	25	27 (kappa)	28	51
IGM24	2	24	25	27 (kappa)	29	51
IGM25	3	24	25	27 (kappa)	30	51
IGM26	4	24	25	27 (kappa)	31	51
IGM27	5	24	25	27 (kappa)	32	51
IGM28	6	24	25	27 (kappa)	33	51
IGM29	7	24	25	27 (kappa)	34	51
IGM30	8	24	25	27 (kappa)	35	51
IGM31	9	24	25	27 (kappa)	36	51
IGM32	10	24	25	27 (kappa)	37	51
IGM33	11	24	25	27 (kappa)	38	51
IGM34	12	24	25	27 (kappa)	39	51
IGM35	13	24	25	27 (kappa)	40	51
IGM36	14	24	25	27 (kappa)	41	51
IGM37	15	24	25	27 (kappa)	42	51
IGM38	16	24	25	27 (kappa)	43	51
IGM39	17	24	25	27 (kappa)	44	51
IGM40	18	24	25	27 (kappa)	45	51
IGM41	19	24	25	27 (kappa)	46	51
IGM42	20	24	25	27 (kappa)	47	51
IGM43	21	24	25	27 (kappa)	48	51
IGM44	22	24	25	27 (kappa)	49	51

TABLE 3B: HEAVY CHAIN CDR SEQUENCES

Antibody/ Heavy Chain Designation	Heavy Chain CDR1 Sequence	Heavy Chain CDR1 SEQ ID NO)\	Heavy Chain CDR2 Sequence	Heavy Chain CDR2 SEQ ID NO	Heavy Chain CDR3 Sequence	Heavy Chain CDR3 SEQ ID NO
IGM1 (H1)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRMAWGASVN	78
IGM2 (H2)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRRAWGASVN	79
IGM3 (H3)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRMARGASVN	80
IGM4 (H4)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRRARGASVN	81
IGM5 (H5)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGMAWGASVN	82
IGM6 (H6)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRMAWGASVN	83
IGM7 (H7)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGMARGASVN	84
IGM8 (H8)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGRARGASVN	85
IGM9 (H9)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRGARGASVN	86
IGM10 (H10)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	AGRAWGASVN	87
IGM11 (H11)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGRAWGASVN	88
IGM12 (H12)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARTAWGSSI	89
IGM13 (H13)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARRAWGSSI	90
IGM14 (H14)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARTARGSSI	91
IGM15 (H15)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARRARGSSI	92
IGM16 (H16)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RATAWGSSI	93
IGM17 (H17)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRTAWGSSI	94
IGM18 (H18)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RATARGSSI	94
IGM19 (H19)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RARARGSSI	95
IGM20 (H20)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRTARGSSI	97
IGM21 (H21)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GARAWGSSI	98
IGM22 (H22)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RARAWGSSI	99
IGM23 (H1)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRMAWGASVN	78
IGM24 (H2)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRRAWGASVN	79
IGM25 (H3)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRMARGASVN	80
IGM26 (H4)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GRRARGASVN	81
IGM27 (H5)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGMAWGASVN	82
IGM28 (H6)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRMAWGASVN	83
IGM29 (H7)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGMARGASVN	84
IGM30 (H8)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGRARGASVN	85
IGM31 (H9)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRGARGASVN	86
IGM32 (H10)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	AGRAWGASVN	87
IGM33 (H11)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RGRAWGASVN	88
IGM34 (H12)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARTAWGSSI	89
IGM35 (H13)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARRAWGSSI	90
IGM36 (H15)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARTARGSSI	91
IGM37 (H15)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	ARRARGSSI	92
IGM38 (H16)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RATAWGSSI	93
IGM39 (H17)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRTAWGSSI	94
IGM40 (H18)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RATARGSSI	94
IGM41 (H19)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RARARGSSI	95
IGM42 (H20)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RRTARGSSI	97
IGM43 (H21)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	GARAWGSSI	98
IGM44 (H22)	FSGYYWS	76	EINHSGSTNYNPSLKS	77	RARAWGSSI	99

TABLE 3C: LIGHT CHAIN CDR SEQUENCES						
Light Chain SEQ IG NO.	Light Chain CDR1 Sequence	Light Chain CDR1 SEQ ID NO	Light Chain CDR2 Sequence	Light Chain CDR2 SEQ ID NO	Light Chain CDR3 Sequence	Light Chain CDR3 SEQ ID NO
23 (Used with lambda light chain constant region)	TGTSSDVGGYNYVS	100	GVSNRFS	102	SSYTSSSTL	104
24 (Used with kappa light chain region)	RASQSISSYLN	101	AASSLQS	103	QQSYSTP	105

TABLE 4: POLYNUCLEOTIDES		
Name of Antibody	Heavy Chain Variable Region Polynucleotide Sequence ID Number (SEQ ID NO)	Light Chain Variable Region Polynucleotide Sequence ID Number (SEQ ID NO)
IGM1	52	74
IGM2	53	74
IGM3	54	74
IGM4	55	74
IGM5	56	74
IGM6	57	74
IGM7	58	74
IGM8	59	74
IGM9	60	74
IGM10	61	74
IGM11	62	74
IGM12	63	74
IGM13	64	74
IGM14	65	74
IGM15	66	74
IGM16	67	74
IGM17	68	74
IGM18	69	74
IGM19	70	74
IGM20	71	74
IGM21	72	74
IGM22	73	74
IGM23	52	75
IGM24	53	75
IGM25	54	75
IGM26	55	75
IGM27	56	75
IGM28	57	75
IGM29	58	75
IGM30	59	75
IGM31	60	75
IGM32	61	75
IGM33	62	75
IGM34	63	75
IGM35	64	75
IGM36	65	75
IGM37	66	75
IGM38	67	75
IGM39	68	75
IGM40	69	75
IGM41	70	75
IGM42	71	75
IGM43	72	75
IGM44	73	75

CLAIMS**WHAT IS CLAIMED IS:**

1. An isolated antigen binding protein that binds to CDIM, comprising:
a heavy chain comprising a complementarity determining region 3 (CDRH3) having a sequence shown in any of SEQ ID NOS: 78-99.
2. The antibody of claim 1, further comprising a light chain comprising a complementarity determining region 3 (CDRL3) having a sequence shown in any one of SEQ ID NOS:104 or 105.
3. The isolated antigen binding protein of claim 1 or 2, which does not substantially cross-react with (ssDNA), double stranded DNA (dsDNA), lipopolysaccharide, cardiolipin, chondroitin and heparan.
4. The isolated antigen binding protein of claim 1, 2 or 3, further comprising:
a heavy chain comprising a framework 1 (FR1) shown in any of SEQ ID NOS: 1-22.
5. The isolated antigen binding protein of claim 1, 2, 3 or 4, further comprising:

(a) a heavy chain comprising a CDRH1 having a sequence as shown in SEQ ID NO:76, and a CDRH2 having a sequence shown in SEQ ID NOS:77; and

(b) a light chain comprising a CDRL1 having a sequence shown in SEQ ID NO:100 or 102, and a CDRL2 having a sequence shown in SEQ ID NOS:101 or 103.
6. The isolated antigen binding protein of claim 5, further comprising a heavy chain comprising a FR1 having the sequence shown in any one of SEQ ID NOS: 1-22.

7. An isolated antigen binding protein that binds to CDIM, comprising a heavy chain variable region selected from the group consisting of SEQ ID NOS: 1-22.
8. An isolated antigen binding protein that binds to CDIM, comprising a light chain variable region selected from the group consisting of SEQ ID NOS:23 or 24.
9. An isolated antigen binding protein that binds to CDIM, comprising a heavy chain sequence selected from the group consisting of SEQ ID NOS: 1-22, and a light chain sequence selected from the group consisting of SEQ ID NOS:23 or 24.
10. An isolated antigen binding protein that binds to CDIM, comprising a heavy chain CDR3 sequence $X_1X_2X_3AX_4GX_5SX_6X_7$,

wherein:

- X_1 is an G, A, or an R;
- X_2 is an R, a G, or an A;
- X_3 is an M, an T, or a R;
- X_4 is an R, a W, or a Y;
- X_5 is an A, an S or a G;
- X_6 is an I, a V, or a Y; and
- X_7 is an N, or no amino acid;

and wherein there is one, and not more than one, Arginine within positions 1 through 3 (relative to heavy chain variable region, positions 98 through 100, position 97 being the invariable Arginine preceding the CDR3 region).

11. The isolated binding protein of claim 10,

wherein:

- X_1 is an G, A, or an R;
- X_2 is an R, a G, or an A;
- X_3 is an M, an T, or a R;
- X_4 is an R, or a W;
- X_5 is an A, or an S;

X₆ is an I, or a V; and

X₇ is an N, or no amino acid.

12. The isolated antigen binding protein of claim 10 or 11, further comprising a heavy chain CDR2 sequence: EINHSGSTNYNPSLKS, numbered (50-65), and wherein His53 may be substituted with Tyrosine at position 53.

13. The isolated antigen binding protein of claim 12, further comprising a heavy chain CDR1 sequence: FSGYYWS, numbered (29-35), and wherein Ser35 may be substituted with Threonine at position 35.

14. The isolated antigen binding protein of any of claims 1-13, which does not substantially cross-react with (ssDNA), double stranded DNA (dsDNA), lipopolysaccharide, cardiolipin, chondroitin and heparin.

15. An isolated antigen binding protein that binds to CDIM, comprising

(a) a heavy chain variable region selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:12, and SEQ ID NO:14; and

(b) a light chain variable region selected from the group consisting of SEQ ID NO:23 and SEQ ID:24.

16. An isolated antigen binding protein which competes with an antibody comprising any of SEQ ID NOS 1-22 variable heavy chain sequences for binding to CDIM.

17. The isolated antigen binding protein of any of claims 1-16, having a binding potency to CDIM five times stronger than MAb 216.

18. An isolated antigen binding protein of any of claims 1-16, having a binding potency to CDIM ten times stronger than MAb 216.

19. The isolated antigen binding protein of claim 1-18, said antigen binding protein having a reduced binding of twofold with (ssDNA), double stranded DNA (dsDNA), lipopolysaccharide, cardiolipin, chondroitin and/or heparin than MAb 216.

20. The isolated antigen binding protein of any of claims 1-19, wherein said antigen binding protein is a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multi-specific antibody, or an antibody fragment thereof.

21. The isolated antigen binding protein of any of claims 1- 20, wherein said antibody fragment is a Fab fragment, a Fab' fragment, a F(ab)₂ fragment, a Fv fragment, a diabody, or a single chain antibody molecule.

22. The isolated antigen binding protein of claim 20, wherein said antigen binding protein is a human antibody.

23. The isolated antigen binding protein of claim 20, wherein said antigen binding protein is a monoclonal antibody.

24. The isolated antigen binding protein of claims 20, wherein said antigen binding protein is selected from the group consisting of IgA, IgD, IgM, IgG, and IgE.

25. The isolated antigen binding protein of claim 24, wherein said antigen binding protein is an IgM.

26. The isolated antigen binding protein of claim 25, wherein said antigen binding protein is coupled to a labeling group.

27. The isolated antigen binding protein of claim 26, wherein said labeling group is a radioisotope, a radionuclide, a fluorescent group, an enzymatic group, a

chemiluminescent group, a biotinyl group, or a predetermined polypeptide group.

28. The isolated antigen binding protein of claim 10, wherein said antigen binding protein is coupled to an effector group.

29. The isolated antigen binding protein of claim 28, wherein said effector group is a radioisotope, a radionucleotide, a toxin, a therapeutic group, or a chemotherapeutic group.

30. The isolated antigen binding protein of claim 29, wherein the therapeutic or chemotherapeutic group is selected from the group consisting of calicheamicin, auristatin-PE, geldanamycin, maytansine and derivatives thereof.

31. The isolated antigen binding protein of claim 20, wherein said antigen binding protein is characterized by (a) the presence of a J chain; or (b) the absence of a J chain.

32. A mixture of antigen binding proteins according to claim 25, wherein said mixture is a mixture comprising pentamers and hexamers.

33. A pharmaceutical composition comprising as an active agent of at least one isolated binding protein of Claim 1, and a pharmaceutically acceptable carrier, diluent or adjuvant.

34. The composition of claim 33 for therapeutic use.

35 The composition of claim 33 for diagnostic use.

36. A kit comprising the isolated binding protein of claim 1.

37. The kit of claim 36, comprising a further therapeutic agent.

38. The kit of claim 37, wherein the further therapeutic agent is an anti-neoplastic agent.

39. The kit of claim 33, wherein the anti-neoplastic agent is an anti-tumor antibody or a chemotherapeutic agent.

40. A method for treating a disease related to abnormal B-cell proliferation, comprising administering the pharmaceutical composition of claim 33 to a patient in need thereof.

41. The method of claim 40, wherein the disease is selected from the group consisting of lymphoid cancer and leukemia.

42. The method of claim 41, wherein the leukemia is B-cell acute lymphoblastic leukemia (ALL).

43. The method of claim 33, wherein the disease is an autoimmune disease involving B cells.

44. The method of claim 40, wherein the disease is rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, or a form of B cell hyperproliferation.

45. The method of claim 44, wherein the form of B cell hyperproliferation includes acute or chronic leukemia, lymphoma, myeloma, and non-Hodgkin's lymphoma.

46. The method of claim 45, wherein the disease is any condition that is characterized by a hyperproliferation of B cells including lymphoid cancer, viral infection, immunodeficiency, and autoimmune disease.

47. The method of claim 29, wherein a chemotherapeutic compound selected from the group consisting of Etoposide (VP-16), Paclitaxel (Taxol), Ara-C (Cytarabine), Vincristine, Nocodazole, Colchicine, Daunorubicin, Cytochalasin, and Jasplakinolide is co-administered with said pharmaceutical composition.

48. The method of claim 40, wherein the disease is characterized by a solid tumor that binds the antigen binding protein of claim 10.

49. A method for the diagnosis of a disease related to abnormal B-cell proliferation, comprising contacting a patient sample containing B-cells with an antigen binding protein of claim 10.

50. A polynucleotide encoding the antigen binding protein of claims 10.

51. A recombinant expression system which comprises the encoding polynucleotide of claim 45 operably linked to sequences effective for its expression.

52. Recombinant host cells that comprise the expression system of claim 51.

53. The recombinant host cells of claim 52, wherein said host cells are eukaryotic host cells.

54. The recombinant host cells of claim 53, wherein said host cells are yeast cells or Chinese Hamster Ovary (CHO) cells.

55. A method to prepare an antigen binding protein which comprises culturing the cells of claim 44 and recovering said protein.

Heavy Chain Variable Region of IGM1 and IGM23 (SEQ ID NO:1)

FR1	CDRH1	FR2	CDRH2	FR3
QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
CDRH3	JH			
GRMANGASVN	FDYWGQGT	TLVT	VSS	

Heavy Chain Variable region of IGM2 and IGM24 (SEQ ID NO:2)

QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
GRRANGASVN	FDYWGQGT	TLVT	VSS	

Heavy Chain Variable region of IGM3 and IGM25 (SEQ ID NO:3)

QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
GRMARGASVN	FDYWGQGT	TLVT	VSS	

Heavy Chain Variable region of IGM4 and IGM26 (SEQ ID NO:4)

QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
GRRARGASVN	FDYWGQGT	TLVT	VSS	

Heavy Chain Variable region of IGM5 and IGM27 (SEQ ID NO:5)

QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RGMANGASVN	FDYWGQGT	TLVT	VSS	

Heavy Chain Variable region of IGM6 and IGM28 (SEQ ID NO:6)

QVQLQQWGAGLLKPSETLSLTCAVYGG	FSGYYWS	WIRQPPGKGLEWIG	EINHSGSTNYPNPSLKS	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RRMANGASVN	FDYWGQGT	TLVT	VSS	

FIGURE 1A

Heavy Chain Variable region of IGM7 and IGM29 (SEQ ID NO:7)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RGMARGASVN FDYWGQGTLVTVSS

Heavy Chain Variable region of IGM8 and IGM30 (SEQ ID NO:8)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RGRARGASVN FDYWGQGTLVTVSS

Heavy Chain Variable region of IGM9 and IGM31 (SEQ ID NO:9)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RRGARGASVN FDYWGQGTLVTVSS

Heavy Chain Variable region of IGM10 and IGM32 (SEQ ID NO:10)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
AGRAWGASVN FDYWGQGTLVTVSS

Heavy Chain Variable region of IGM11 and IGM33 (SEQ ID NO:11)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RGRANGASVN FDYWGQGTLVTVSS

Heavy Chain Variable region of IGM12 and IGM34 (SEQ ID NO:12)

QVQLQQWGAGLLKPSETLSLTCAVYGGG FSGYYWS WIRQPPGKGLEWIG EINHSGSTNYPNPSLKS RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
ARTAWGSSI FDYWGQGTLVTVSS

FIGURE 1B

Heavy Chain Variable region of IGM13 and IGM35 (SEQ ID NO:13)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
ARRANGSSI FDYWGQGTLLVTVSS

Heavy Chain Variable region of IGM14 and IGM36 (SEQ ID NO:14)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
ARTARGSSI FDYWGQGTLLVTVSS

Heavy Chain Variable region of IGM15 and IGM37 (SEQ ID NO:15)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
ARRARGSSI FDYWGQGTLLVTVSS

Heavy Chain Variable region of IGM16 and IGM38 (SEQ ID NO:16)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RATANGSSI FDYWGQGTLLVTVSS

Heavy Chain Variable region of IGM17 and IGM39 (SEQ ID NO:17)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RRTANGSSI FDYWGQGTLLVTVSS

Heavy Chain Variable region of IGM18 and IGM40 (SEQ ID NO:18)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RATARGSSI FDYWGQGTLLVTVSS

FIGURE 1C

Heavy Chain Variable region of IGM19 and IGM41 (SEQ ID NO:19)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RARARGSSI FDYWGQGT¹⁹LVTVSS

Heavy Chain Variable region of IGM20 and IGM42 (SEQ ID NO:20)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RRTARGSSI FDYWGQGT²⁰LVTVSS

Heavy Chain Variable region of IGM21 and IGM43 (SEQ ID NO:21)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
GARAWGSSI FDYWGQGT²¹LVTVSS

Heavy Chain Variable region of IGM22 and IGM44 (SEQ ID NO:22)

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
RARAWGSSI FDYWGQGT²²LVTVSS

FIGURE 1D

Light Chain Variable region of IGM1 through IGM22 (SEQ ID NO:23) (used with lambda light chain constant region)

FR1	CDRL1	FR2	CDRL2	FR3
DIQMTQSPSTLSASVGDRVITTC	TGTSSDVGGYNYVS	WYQQHPGKAPKLMIIY	GVSNRFS	GSKSGNTASLTISGLAAEDEADYYC
CDRL3	JL			
SSYTSSSTL	VVFGGGTKLTVLG			

Light Chain Variable region of IGM23 through IGM44 (SEQ ID NO:24) (used with kappa light chain constant region)

FR1	CDRL1	FR2	CDRL2	FR3
DIQMTQSPSSLSASVGDRVITTC	RASQSISSYLN	WYQQKPGKAPKLLIIY	AASSLQS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
CDRL3	JL			
QQSYSTP	ITFGQGTRLEIKR			

FIGURE 1E

Constant Region for IGM Heavy Chain (SEQ ID NO:25)

GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAEL
PPKVSFVFPFRDGFPGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSGVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLGQSMFTCRVDHRGLTFQQNASSMCVPDQ
DTAIRVFAIPPSFASIFLTKSTKLTCLVTDLTYYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPLKQTISRPKGVALH
RPDVYLLPPAREQLNLRESATITCLVTGFSPADVVFQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVAHDALPNRVTERTVDKSTGKPT
LYNVSLVMSDTAGTCY

Constant Region for IGλ Light Chain (SEQ ID NO:26)

QPKAAPSVTL FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE
GSTVEKTVAP TECS

Constant Region for IGκ Light Chain (SEQ ID NO:27)

TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYLSST LTLKADYEK HKVYACEVTH QGLSSPVTKS
FNRGEC

IGM1:

SEQ ID NO:28

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGMAWGASVNF
DYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFP
SVLRGGKYAATSQVLLPSKDVMQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVS
VFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLT
IKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT
KSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWNSGERFTCT
VTHTDLPSP
LKQTI
SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV
TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGD
RVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAA
EDEADYYCSSYTS
SSSTLVVFEGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNNKYAASSYLSLTPEQWKS
HRSYSCQVTHEGSTVEKTVAPTECS

IGM2:

SEQ ID NO:29

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGRRAWGASVNF
DYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFP
SVLRGGKYAATSQVLLPSKDVMQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVS
VFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLT
IKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT
KSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWNSGERFTCT
VTHTDLPSP
LKQTI
SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV
TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGD
RVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAA
EDEADYYCSSYTS
SSSTLVVFEGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNNKYAASSYLSLTPEQWKS
HRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2A

IGM3:

SEQ ID NO:30

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARGRMARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVQVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRYSQCQVTHEGSTVEKTVAPTECS

IGM4:

SEQ ID NO:31

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARGRRARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVQVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRYSQCQVTHEGSTVEKTVAPTECS

FIGURE 2B

IGM5:

SEQ ID NO:32

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGMAWGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVQVQWQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS

IGM6:

SEQ ID NO:33

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRMAWGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVQVQWQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2C

IGM7:

SEQ ID NO:34

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGMARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKHTNISESHPNATFSAVGEASICEDDWNSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM8:

SEQ ID NO:35

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGRARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYYDSVTISWTRQNGEAVKHTNISESHPNATFSAVGEASICEDDWNSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2D

IGM9:

SEQ ID NO:36

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRRGARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWSNGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM10:

SEQ ID NO:37

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARAGRAWGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWSNGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2E

IGM11:

SEQ ID NO:38

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGRAWGASVNFYWGQGTlVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSgvTTDQVQAEAKESGPTTYKVTSTLTIKESDwLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM12:

SEQ ID NO:39

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARARTAWGSSIFDYWGQGTlVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSgvTTDQVQAEAKESGPTTYKVTSTLTIKESDwLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2F

IGM13:

SEQ ID NO:41

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARARRAWGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQ TISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRV TITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYICSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM14:

SEQ ID NO:41

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARARTARGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQ TISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRV TITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYICSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2G

IGM15:

SEQ ID NO:42

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARARRARGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM16:

SEQ ID NO:43

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRATAWGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2H

IGM17:

SEQ ID NO:44

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRRTAWGSSIFDYWGQGTILVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT KSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM18:

SEQ ID NO:45

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRATARGSSIFDYWGQGTILVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT KSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVITITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 21

IGM19:

SEQ ID NO:46

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRARARGSSIFDYWGQGTSLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

IGM20:

SEQ ID NO:47

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRRTARGSSIFDYWGQGTSLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRRESATITCLVTGFSPADV FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2J

IGM21:

SEQ ID NO:48

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARGARAWGSSIFDYWGQGTlVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGESPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFEGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWkSHRSYSCQVTHEGSTVEKTVAPTECS

IGM22:

SEQ ID NO:49

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRARAWGSSIFDYWGQGTlVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNsGERFTCTVTHTDLPsPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGESPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:50

LIGHT CHAIN

DIQMTQSPSTLSASVGDRVTITCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYGVSNRFSGSKSGNTASLTISGLAAEDEADYYCSSYTSSTLVVFEGGGTKLTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWkSHRSYSCQVTHEGSTVEKTVAPTECS

FIGURE 2K

IGM23:

SEQ ID NO:28

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKS RVTISVDT SKNQFSLKLSSVTAADTAVYYCARGMAWGASVNF DYWGQGT LVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVS VFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSGVT TDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT KSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQTISR PKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGD RVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAPSVFI FPPS
DEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM24:

SEQ ID NO:29

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKS RVTISVDT SKNQFSLKLSSVTAADTAVYYCARGRRAWGASVNF DYWGQGT LVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVS VFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSGVT TDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLT KSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWN SGERFTCTVTHTDLP SPLKQTISR PKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGD RVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTPITFGQGTRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2L

IGM25:

SEQ ID NO:30

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARGRMARGASVNFYWGQGTlVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCL
VTDLTtyDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVfVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM26:

SEQ ID NO:31

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARGRRARGASVNFYWGQGTlVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTkSTKLTCL
VTDLTtyDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVfVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2M

IGM27:

SEQ ID NO:32

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRGMAWGASVNFYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM28:

SEQ ID NO:33

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRRMAWGASVNFYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2N

IGM29:

SEQ ID NO:34

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGMARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYSVTISWTRQNGEAVKHTNISESHPNATFSAVGEASICEDDWSGERFTCTVHTDLPSPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM30:

SEQ ID NO:35

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYPNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRGRARGASVNFQYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGE
FGNPRKSKLICQATGFSRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTYKVTSTLTIKESDWLSQSMFTCRVDHRLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTYSVTISWTRQNGEAVKHTNISESHPNATFSAVGEASICEDDWSGERFTCTVHTDLPSPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 20

IGM31:

SEQ ID NO:36

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSITCAVYGGSFSGYYWSWIRQPPGKLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRRGARGASVNFYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLTCL
VTDLTITYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWNSEGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPS
DEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM32:

SEQ ID NO:37

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSITCAVYGGSFSGYYWSWIRQPPGKLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARAGRAWGASVNFYWGQGTILVTVSS
GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCVKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRD
GFFGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTGSTKLT
CLVTDLTITYDSVTISWTRQNGEAVKHTHTNISESHPNATFSAVGEASICEDDWNSEGERFTCTVTHTDLPSPKQTI SRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQW
MQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2P

IGM33:

SEQ ID NO:38

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSITCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQPSLKLSSVTAADTAVYYCARRGRAWGASVNF
DYWGQGTILVTVSSG
SASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFP
SVLRGGKYAATSQVLLPSKDV
MQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
FGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLT
IKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKST
KLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTV
THTDLP
SPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV
FVQWMQ
RGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV
TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTIS
SLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI
PPS
DEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM34:

SEQ ID NO:39

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSITCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQPSLKLSSVTAADTAVYYCARARTAWGSSIFDYWGQGTILVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFP
SVLRGGKYAATSQVLLPSKDV
MQGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLT
IKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKST
KLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWSGERFTCTV
THTDLP
SPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV
FVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV
TERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTIS
SLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI
PPSD
EQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2Q

IGM35:

SEQ ID NO:40

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARARRAWGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRG
GKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDG
FFGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLT
IKESDWLSQSMFTRVDHRLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNSGERFTCTV
THTDLP SPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQW
MQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVT
ERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFRSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM36:

SEQ ID NO:41

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNP
SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARARTARGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRG
GKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDG
FFGNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLT
IKESDWLSQSMFTRVDHRLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCL
VTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNSGERFTCTV
THTDLP SPLKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADV FVQW
MQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVT
ERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
RFRSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2R

IGM37:

SEQ ID NO:42

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARARRARGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSP LKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM38:

SEQ ID NO:43

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRATAWGSSIFDYWGQGLTVTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDV MQGTDEHV VCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSP LKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2S

IGM39:

SEQ ID NO:44

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRRTAWGSSIFDYWGQGTLLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM40:

SEQ ID NO:45

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARRATARGSSIFDYWGQGTLLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFI FPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2T

IGM41:

SEQ ID NO:46

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRARARGSSIFDYWGQGTSLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM42:

SEQ ID NO:47

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRRTARGSSIFDYWGQGTSLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2U

IGM43:

SEQ ID NO:48

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARGARAWGSSIFDYWGQGTLLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

IGM44:

SEQ ID NO:49

HEAVY CHAIN

QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYKSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRTVISVDTSKNQFSLKLSSVTAADTAVYYCARRARAWGSSIFDYWGQGTLLTVSSGS
ASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMOGTDEHVVCKVQHPNGNKEKNVPLPVIAELPPKVSFVPPRDGFF
GNPRKSKLICQATGFSPRQIQVSWLREGKQVGSVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLV
TDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNNGERFTCTVTHTDLPSPKQTISRPGVALHRPDVYLLPPAREQLNLRRESATITCLVTGFSPADVFVQWMQR
GQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTGKPTLYNVSLVMSDTAGTCY

SEQ ID NO:51

LIGHT CHAIN

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGRLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSSITLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

FIGURE 2V

CDR3 Variants of H1 through H22

H1	GRMAWGASVN	H2	ARTAWGSSI
H3	GRRAWGASVN	H14	ARRAWGSSI
H5	GRMARGASVN	H4	ARTARGSSI
H6	GRRARGASVN	H15	ARRARGSSI
H7	RGMAWGASVN	H16	RATAWGSSI
H8	RRMAWGASVN	H17	RRTAWGSSI
H9	RGMARGASVN	H18	RATARGSSI
H10	RGRARGASVN	H19	RARARGSSI
H11	RRGARGASVN	H20	RRTARGSSI
H12	AGRAWGASVN	H21	GARAWGSSI
H13	RGRAWGASVN	H22	RARAWGSSI

FIGURE 3

SEQ ID NO:52

HEAVY CHAIN OF IGM1 AND IGM23

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGGTAGAATGGCCTGGGGCGCTTCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAAATAGCCCGTCGGATACGAGCAGCGTGGCGGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACC CCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAAGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGCCCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTACTTCGCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:53

HEAVY CHAIN OF IGM2 AND IGM24

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGGTAGAAGGGCTGGGGCGCTTCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAAATAGCCCGTCGGATACGAGCAGCGTGGCGGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACC CCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAAGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGCCCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTACTTCGCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

FIGURE 4A

SEQ ID NO:54

HEAVY CHAIN OF IGM3 AND IGM25

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGTAGAATGGCCAGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGGCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:55

HEAVY CHAIN OF IGM4 AND IGM26

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGTAGAAGGGCCAGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGGCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

FIGURE 4B

SEQ ID NO:56

HEAVY CHAIN OF IGM5 AND IGM27

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACCTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCGCGACACTGCCGTCTACTACTGTGCTCGTGGGGAATGGCCTGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCAGTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCCTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCCTCTTCCAGTGATTGCTGAGCTGCCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACAGGT
GCAGGTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:57

HEAVY CHAIN OF IGM6 AND IGM28

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACCTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCGCGACACTGCCGTCTACTACTGTGCTCGTGGGGAATGGCCTGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCAGTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCCTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCCTCTTCCAGTGATTGCTGAGCTGCCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACAGGT
GCAGGTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

FIGURE 4C

SEQ ID NO:58

HEAVY CHAIN OF IGM7 AND IGM29

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGGGAATGGCCAGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGC
ACAGGGCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:59

HEAVY CHAIN OF IGM8 AND IGM30

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGGGAAGGGCCAGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGC
ACAGGGCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTGTCCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

FIGURE 4D

SEQ ID NO:60

HEAVY CHAIN OF IGM9 AND IGM31

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTTGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGAGAGGGGCCAGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGC
ACAGGCCCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTTGTCGCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:61

HEAVY CHAIN OF IGM10 AND IGM32

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCTTGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCGCCGACACTGCCGTCTACTACTGTGCTCGTGGCAGAGCCTGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCTTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGCTGAGGCCAAAGAGTCTGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGC
ACAGGCCCCGATGTCTACTTGCTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTTGTCGCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGGTAAGTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

FIGURE 4E

SEQ ID NO:62

HEAVY CHAIN OF IGM11 AND IGM33

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGAAGTCCCGCCGACACTGCGGTCTACTACTGTGCTCGTAGAGGACGGGCTGGGGCGCTTCCGTGAATTTGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGT
TCCGCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCGGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTG
GAAATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGACGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAG
ACGAACACGTGGTGTGCAAAGTCCAGCACC CCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTC
TTCGGCAACCCCGCAAGTCCAAGTCTATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGGTGCTGCTGCGGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGT
GCAGGTGAGGGCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGA
CCTTCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTG
GTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGG
TGAGGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGC
ACAGGCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAG
AGGGGGCAGCCCTTGTCGCCGAGAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGAGGCCGTACTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGG
GGAGACCTACACCTGCGTGGTGGCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAG
CTGGCACCTGCTAC

SEQ ID NO:63

HEAVY CHAIN OF IGM12 AND IGM34

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGAAGTCCCGCCGACACTGCGGTCTACTACTGTGCTCGTAGAACCCTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTCC
GCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCGGTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACC CGGGCTTCCCATCAGTCTGAGAGGGGGCAAGTACGACGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACC CCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGTCTATCTGCCAGGCCACGGGTTTCAGTCCCCGGCAGATTCAAGGTGCTGCTGCGGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGGCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCAGCTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACTGCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCTTTGCCAGCATCTTCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCGCCGAGAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCCGAGGCCGTACTTCGCCCCACAGCATCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 4F

SEQ ID NO:64

HEAVY CHAIN OF IGM13 AND IGM35

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGCTAGAGGGCTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCTGCAGGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

SEQ ID NO:65

HEAVY CHAIN OF IGM14 AND IGM36

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGCTAGAACCGCTAGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCTGCAGGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 4G

SEQ ID NO:66

HEAVY CHAIN OF IGM15 AND IGM37

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGTAGAGAGCTAGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAGACG
AACACGTGGTGTGCAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCAGCGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGCCCAGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTACAGCGCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCTCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCAGGCCGCTACTTCGCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

SEQ ID NO:67

HEAVY CHAIN OF IGM16 AND IGM38

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAGCAACCGTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTATGCAGGGCACAGACG
AACACGTGGTGTGCAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCAGCGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGCCCAGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTACAGCGCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCTCCCGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCAGGCCGCTACTTCGCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 4H

SEQ ID NO:68

HEAVY CHAIN OF IGM17 AND IGM39

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAAGAACCGCTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTGATGCAGGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

SEQ ID NO:69

HEAVY CHAIN OF IGM18 AND IGM40

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAGCAACCGCTAGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTGATGCAGGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 41

SEQ ID NO:70

HEAVY CHAIN OF IGM19 AND IGM41

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAGCAAGAGCTAGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCAATGCAGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCAGCGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

SEQ ID NO:71

HEAVY CHAIN OF IGM20 AND IGM42

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAAGAACAGCTAGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCAATGCAGGGCACAGACG
AACACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCAGCGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGGCCACGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAGCGCCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGTGTGCCACCAGCCCGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGCCCCAGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 4J

SEQ ID NO:72

HEAVY CHAIN OF IGM21 AND IGM43

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTGGAGCAAGAGCTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCAATGCAGGGCACAGACG
AACACGTGGTGTGCAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTCAAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGCCCAGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTACAGCGCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCTCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCAGGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

SEQ ID NO:73

HEAVY CHAIN OF IGM22 AND IGM44

CAGGTGCAGCTCCAGCAGTGGGGAGCAGGACTCTTGAAACCCCTCTGAGACTTTGAGCCTCACATGCGCTGTCTATGGCGGATCTTTCTCCGGCTACTATTGGTCCTGGATACGACAGCCCC
AGGCCAAAGGACTCGAGTGGATTGGGGAAATCAACCACTCTGGTAGCACTAACTATAATCCAAGCCTGAAGTCCCGTGTAACAATTAGTGTGATACATCCAAGAACCAATTTTCCCTGAAAC
TGAGCTCAGTGACTGCCCGGACACTGCCGTCTACTACTGTGCTCGTAGAGCAAGAGCTTGGGGAAGCTCCATCTTCGACTACTGGGGACAGGGTACCCTGGTCACTGTCTCTTCAGGTTC
GCATCCGCCCCAACCCCTTTTCCCCCTCGTCTCCTGTGAGAATAGCCCGTCGGATACGAGCAGCGTGGCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAA
ATACAAGAACAACCTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAAGTACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCAATGCAGGGCACAGACG
AACACGTGGTGTGCAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCCAGTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTCTTC
GGCAACCCCGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCGGCAGATTCAAGGTGTCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCAGGTGCA
GGCTGAGGCCAAAGAGTCTGGGCCCAGACCTACAAGGTGACCAGCACACTGACCATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTACCTGCCGCGTGGATCACAGGGGCTGACCT
TCCAGCAGAATGCGTCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGGGTCTTCGCCATCCCCCATCCTTTGCCAGCATCTTCCTCACCAGTCCACCAAGTTGACCTGCCTGGTC
ACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAATGGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTACAGCGCGTGGGTGA
GGCCAGCATCTGCGAGGATGACTGGAATAGCGGGGAGAGGTTACGTGCACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCAAGGGGGTGGCCCTGCACA
GGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTGCGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTGCAGTGGATGCAGAGG
GGGCAGCCCTTGTCCTCCCGGAGAAGTATGTGACCAGCGCCCCAATGCCTGAGCCCCAGGCCAGGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGAGGAATGGAACACGGGGGA
GACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCAACAGGGTCACCGAGAGGACCGTGGACAAGTCCACCGGTAAACCCACCCCTGTACAACGTGTCCCTGGTCATGTCCGACACAGCTG
GCACCTGCTAC

FIGURE 4K

SEQ ID NO:74

LIGHT CHAIN OF IGM1 THROUGH IGM22

GACATACAGATGACCCAGTCCCCAAGCACCCCTGTCTGCATCTGTGGGAGATCGCGTGACCATCACCTGCACTGGAAGTAGCTCCGACGTAGGAGGCTATAATTATGTTTCCTGGTATCAGCA
ACATCCTGGAAAGGCTCCAAAGCTGATGATCTACGGTGTTTCCAACCGGTCAGTGGCTCTAAGAGTGGTAACACCGCATCTCTGACCATTAGTGGCCTGGCAGCCGAAGATGAGGCGGACT
ACTACTGCTCCTCCTATAACAAGCAGCTCAACCCTCGTGGTGTTTGGTGGCGGTACCAAGCTGACCGTCCTAGGTGAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCACCCCTCCTCTGAG
GAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACC
CTCCAAACAAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAAGTCCCACAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGTGGAGAAGA
CAGTGGCCCCCTACAGAATGTTCATAG

SEQ ID NO:75

LIGHT CHAIN OF IGM23 THROUGH IGM44

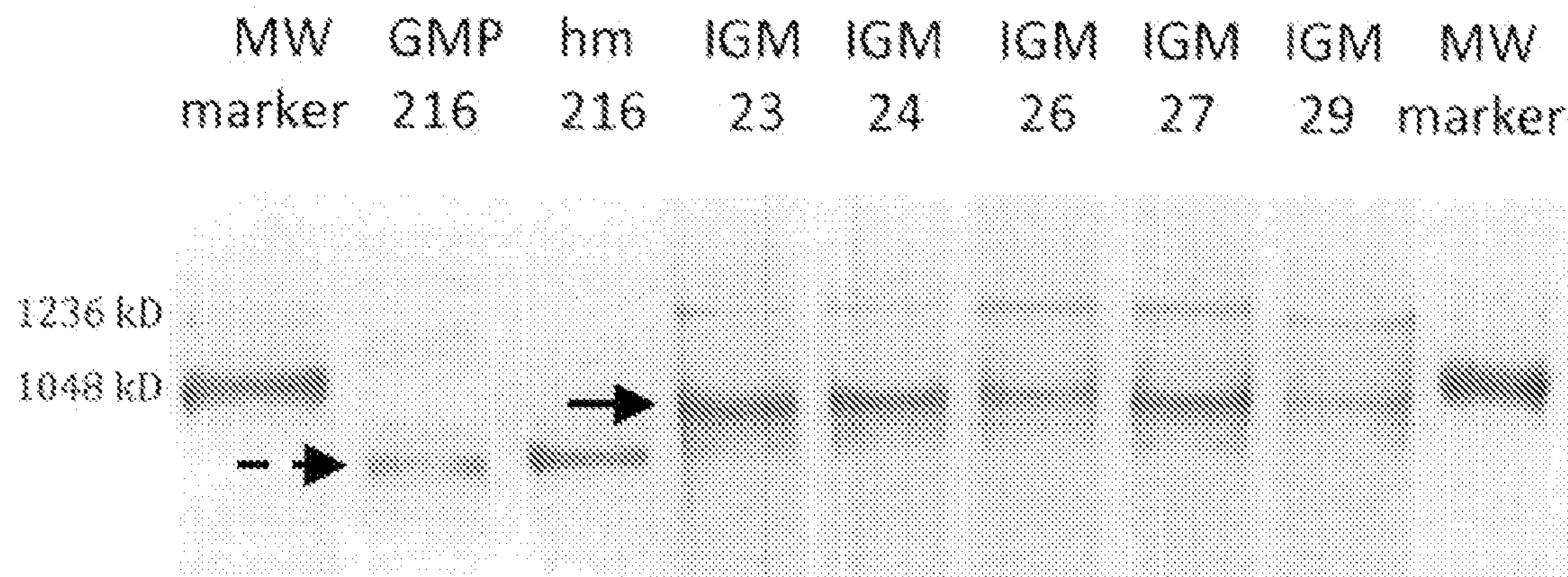
GATATCCAGATGACCCAGTCAACCCTCAAGCCTGAGCGCAAGCGTGGGGGACCGAGTGACTATTACATGTTCGAGCTTCTCAGTCAATCAGCTCCTACCTGAAGTGGTATCAGCAGAAACCTGG
AAAAGCCCCAAAAGTGCCTTATCTAGCAGCCAGTTCCTTGCAAAGTGAGTGCCCTCCCGATTGAGTGGCTCAGGAAGTGGGACTGACTTCACTCTGACTATCAGTAGTCTGCAACCAGAAG
ACTTTGCCACCTACTATTGCCAGCAGAGCTACAGCACCCCTATTACCTTCGGCCAGGGTACCCGACTAGAGATCAAACGTACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGT
CACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGC
CCGTCACAAAGAGCTTCAACAGGGGAGAGTGTAG

FIGURE 4L

FIGURE 5

Non-reducing SDS-PAGE: Panel A showing IGM23 through IGM29 and Panel B showing IGM31 through IGM43.

Panel A



Panel B

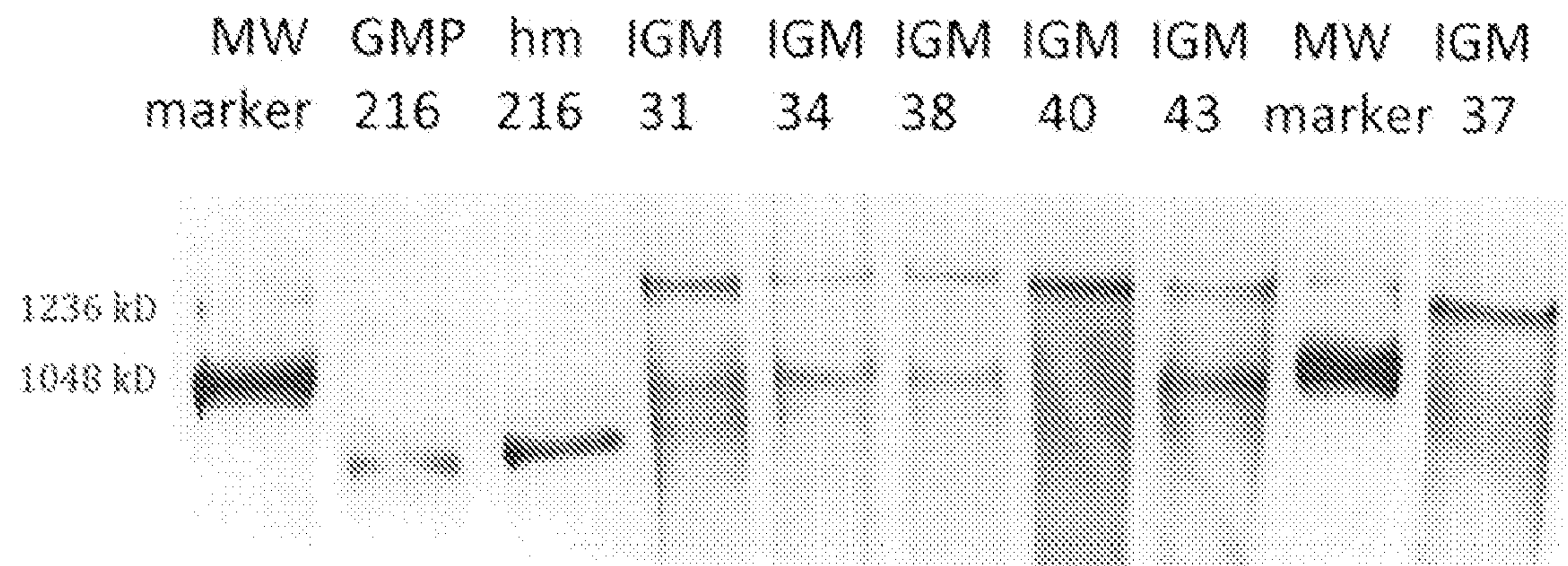


FIGURE 6A:
CDIM Binding on Nalm-6 Cells

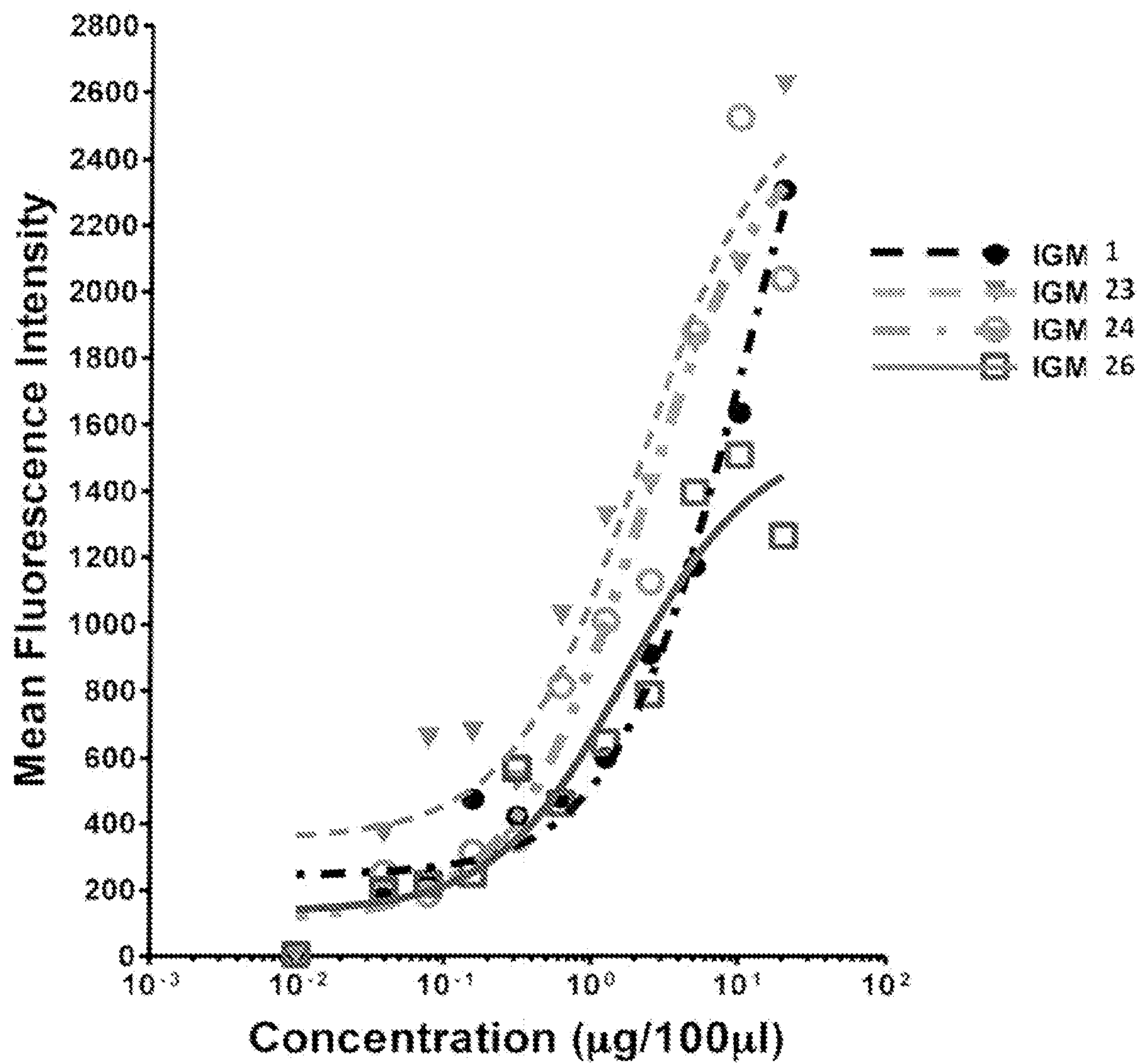


FIGURE 6B:
Cytotoxicity on Nalm-6 Cells

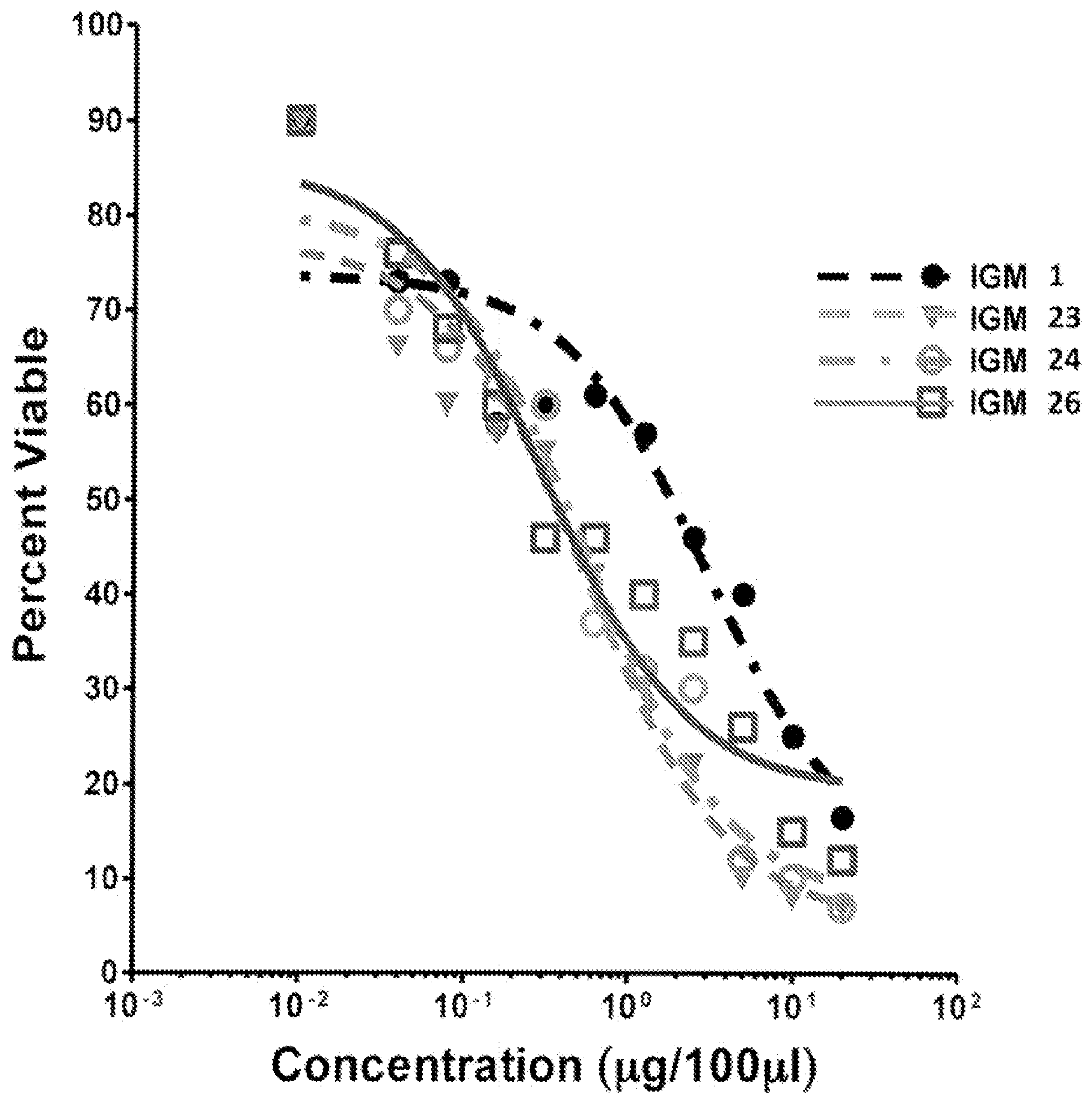


FIGURE 7
Complement Dependent Cytotoxicity:
Samples of IgM on CDIM Expressing Cells (Nalm-6)

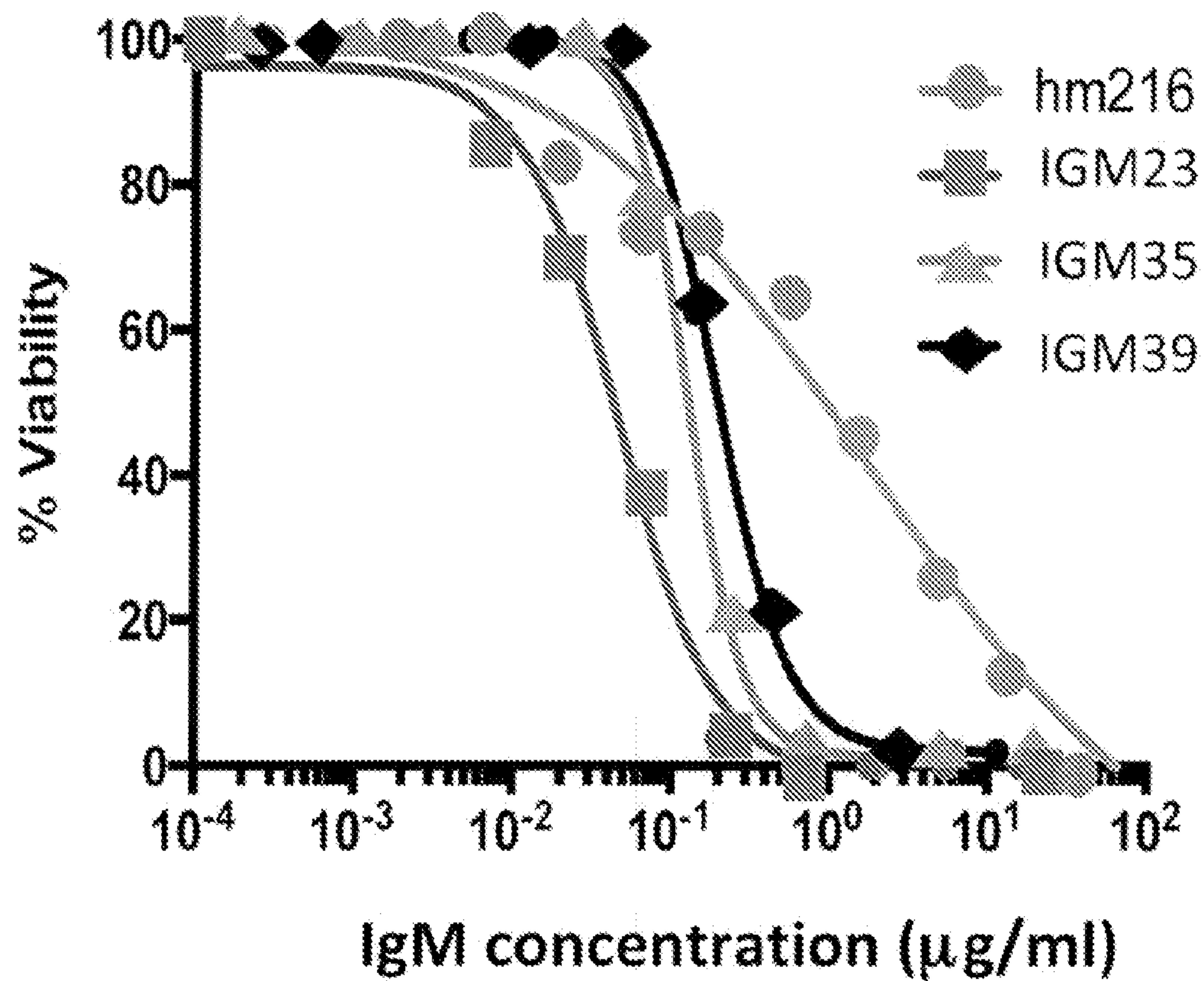


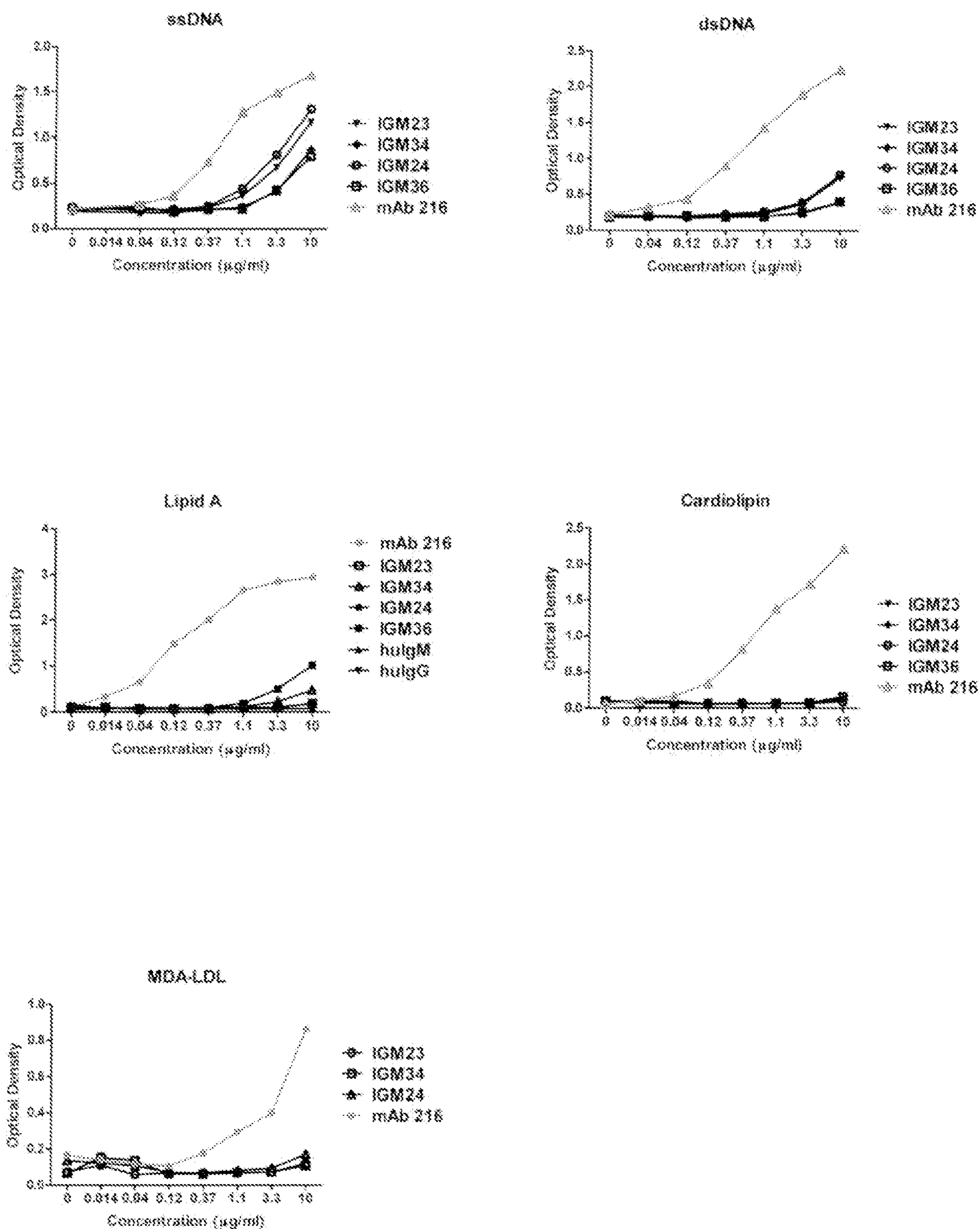
FIGURE 8: Panels A, B, C, D and E

FIGURE 9: Panels A, B, C, D, E and F

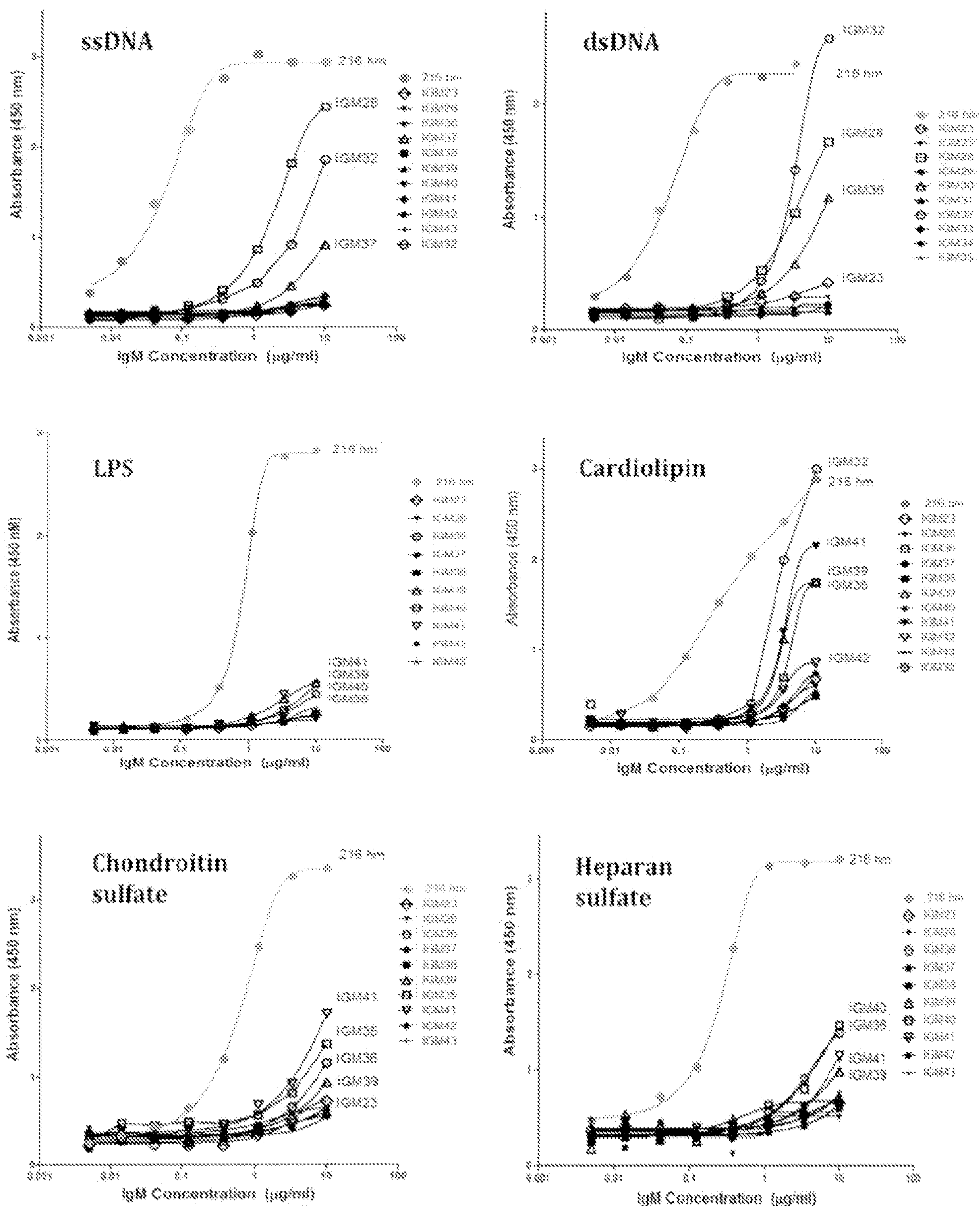


FIGURE 7

**Complement Dependent Cytotoxicity:
Samples of IgM on CDIM Expressing Cells (Nalm-6)**

