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(54) **Titre : ANTICORPS NEUTRALISANTS DIRIGES CONTRE LE COMPLEXE D'INTEGRINE αVβ8 POUR L'IMMUNOTHERAPIE**
(54) **Title: NEUTRALIZING ANTIBODIES TO THE αVβ8 INTEGRIN COMPLEX FOR IMMUNOTHERAPY**

VH	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
(Mouse Hybridoma Name)							
B13C4 15-8	EVQLQQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
B13C4 15-10	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
B13H3.2	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETDEPTYADDFKE	RFAFSLETSASTANLQIINLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B13C1231015	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFNG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B15B11Vh	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B2B2 15-9	QIQLLQSGPELKKPGETVKISCLASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFGG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
R11D12715.3	EVQLVESGGGLVQPGGSLKLSCAASGF	TFSSFGMS	WVRQTPDKRLELVA	TINSNGGSTYYPDNMKG	RFTISRDNAKNTLYLQMSSLKSEDTAMYYCAS	ACYRYGAFFDY	WGQGTTLTVSS
(Produced Rabbit IgG clone name)							
RSDLVH-1	EVQLLESGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTVTVSS
RSDLVH-3	QVQLMQSGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFNG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
RSDLVH-16	QIQLQQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
(scFv clone from Yeast Display library)							
29	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
44	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
A1=B4=F9	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDT	WGQGTTLSVSS
A5=C6	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTALTVSS
D4=E6	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
Final clone for in vivo/in vitro Functional test in IgG format							
C6D4	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTTLTVSS

(57) **Abrégé/Abstract:**
Provided is an antibody that specifically binds human αvββ and blocks binding of TGFp peptide to αvββ, wherein the antibody binds to the specificity determining loop (SDL) of human β8. In some embodiments, the antibody further binds to one, two, or all three of the human av-head domain, the al helix of human β8, or the al helix of human β8. In some embodiments, the antibody is humanized or chimeric. In some embodiments, the antibody is linked to a detectable label. Also provided is a method of enhancing an immune response in a human individual, comprising administering a sufficient amount of the antibody to the individual, thereby enhancing an immune response. Also provided are pharmaceutical compositions comprising the anti-αvββ antibodies or antigen-binding molecules thereof.

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ABSTRACT

Provided is an antibody that specifically binds human αvββ and blocks binding of TGFp peptide to αvβ8, wherein the antibody binds to the specificity determining loop (SDL) of human β8. In some embodiments, the antibody further binds to one, two, or all three of the human av-head domain, the a1 helix of human β8, or the a1 helix of human β8. In some embodiments, the antibody is humanized or chimeric. In some embodiments, the antibody is linked to a detectable label. Also provided is a method of enhancing an immune response in a human individual, comprising administering a sufficient amount of the antibody to the individual, thereby enhancing an immune response. Also provided are pharmaceutical compositions comprising the anti-αvßß antibodies or antigen-binding molecules thereof.

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Neutralizing antibodies to the αvβ8 integrin complex for immunotherapy

SEQUENCE LISTING

[0001] This application contains a sequence listing in electronic form in ASCII text format. A copy of the sequence listing is available from the Canadian Intellectual Property Office.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with government support under grant no. U54 HL119893, awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Transforming growth factor β (TGFβ) was originally characterized as an oncogene capable of inducing a transformed phenotype in non-neoplastic cells. A number of TGFβ family members have since been characterized, based on the presence of similar amino acid domains.

[0004] Some TGF-β isoforms are expressed ubiquitously in mammals (TGF-β 1-3), but are maintained in an inactive form by non-covalent interaction with a propeptide, the latency associated domain of TGF-β (LAP). For TGFβ to signal, it must be released from its inactive complex by a process called TGFβ activation. The latent TGF complex includes 3 components: the active (mature) TGFβ dimmer, LAP (latency associated peptide) and LTBP (latent TGFβ binding protein). LAP is a dimer, linked by a disulfide bond, that represents the N-terminal end of the TGFβ precursor protein. The mature TGFβ protein represents the C terminal end (about 25kD) of the precursor. The bond between the TGFβs and LAP is proteolytically cleaved within the Golgi, but the TGF-β propeptide remains bound to TGFβ by non-covalent interactions. The complex of TGFβ and LAP is called the small latent complex (SLC). It is the association of

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LAP and TGFβ that confers latency. LAP-TGFβ binding is reversible and the isolated purified components can recombine to form an inactive SLC. Both the SLC and the larger complex are referred to herein as latent TGFβ, as both are inactive.

[0005] In general, integrins are adhesion molecules and mediate the attachment of cells to extracellular matrix proteins. Integrin αvβ8 binds to the LAP of TGF-β and mediates the activation of TGF-β1 and 3 (Mu *et al.* (2002) *J. Cell Biol.* 159:493). Integrin αvβ8-mediated activation of TGF-β is required for *in vivo* activation of TGF-β (*i.e.*, release of the mature TGF-β polypeptide), thus αvβ8 is a gatekeeper of TGF-β function. Integrin αvβ8 is expressed in normal epithelia (*e.g.*, airway epithelia), mesenchymal cells, and neuronal tissues.

[0006] The integrin β8 (Itgb8) has been associated with forkhead box P3 (Foxp3)-positive T cells and T-regulatory-specific epigenetic remodeling. See, *e.g.*, Vandenbon, *et al.*, *Proc. Natl. Acad. Sci. USA* vol. 113 no. 17 pp. E2393–E2402 (2016). FoxP3 is a transcription factor involved in the development of T-regulatory (Treg) cells. Human and mouse effector Treg cells express functional TGF-β-activating integrin αvβ8. *See*, Worthington, *Immunity* Volume 42, Issue 5, pp. 903–915 (May 2015). Treg cell integrin αvβ8-mediated TGF-β activation is not needed for T cell homeostasis and integrin αvβ8 expression by Treg cells suppresses active inflammation.

DEFINITIONS

[0007] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, *e.g.*, Lackie, DICTIONARY OF CELL AND MOLECULAR BIOLOGY, Elsevier (4th ed. 2007); Sambrook *et al.*, MOLECULAR CLONING, A LABORATORY MANUAL, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989). Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0008] The terms "anti-αvβ8 antibody," "αvβ8 specific antibody," "αvβ8 antibody," and "anti-αvβ8" are used synonymously herein to refer to an antibody that specifically binds to αvβ8. Similarly, an anti-β8 antibody (and like terms) refer to an antibody that specifically binds

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to β8. The anti-αvβ8 antibodies and anti-β8 antibodies described herein bind to the protein expressed on αvβ8 expressing cells.

[0009] An αvβ8-associated disorder is a condition characterized by the presence of αvβ8-expressing cells, either cells expressing an increased level of αvβ8, or increased number of αvβ8-expressing cells relative to a normal, non-diseased control. TGFβ-associated disorders (disorders characterized by higher than normal TGFβ activity) include αvβ8-associated disorders, as αvβ8 is involved in activating TGFβ in certain circumstances, as described herein.

[0010] "Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term "polynucleotide" refers to a linear sequence of nucleotides. The term "nucleotide" typically refers to a single unit of a polynucleotide, *i.e.*, a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA, and hybrid molecules having mixtures of single and double stranded DNA and RNA.

[0011] The words "complementary" or "complementarity" refer to the ability of a nucleic acid in a polynucleotide to form a base pair with another nucleic acid in a second polynucleotide. For example, the sequence A-G-T is complementary to the sequence T-C-A. Complementarity may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing.

[0012] The words "protein", "peptide", and "polypeptide" are used interchangeably to denote an amino acid polymer or a set of two or more interacting or bound amino acid polymers. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers, those containing modified residues, and non-naturally occurring amino acid polymer.

[0013] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function similarly to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-

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phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *e.g.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs may have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions similarly to a naturally occurring amino acid.

[0014] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0015] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical or associated, *e.g.*, naturally contiguous, sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode most proteins. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to another of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes silent variations of the nucleic acid. One of skill will recognize that in certain contexts each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, silent variations of a nucleic acid which encodes a polypeptide is implicit in a described sequence with respect to the expression product, but not with respect to actual probe sequences.

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[0016] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following amino acids are typically conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (*see, e.g.,* Creighton, *Proteins* (1984)).

[0017] The terms "identical" or "percent identity," in the context of two or more nucleic acids, or two or more polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides, or amino acids, that are the same (*i.e.*, about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters, or by manual alignment and visual inspection. *See e.g.*, the NCBI web site at ncbi.nlm.nih.gov/BLAST. Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a nucleotide test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the algorithms can account for gaps and the like. Typically, identity exists over a region comprising an antibody epitope, or a sequence that is at least about 25 amino acids or nucleotides in length, or over a region that is 50-100 amino acids or nucleotides in length, or over the entire length of the reference sequence.

[0018] The term "recombinant" when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or

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protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0019] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, *e.g.*, a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (*e.g.*, a fusion protein).

[0020] The term "isolated," when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It is preferably in a homogeneous state. It can be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified. In particular, an isolated gene is separated from open reading frames that flank the gene and encode a protein other than the gene of interest. The term "purified" denotes that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. Particularly, it means that the nucleic acid or protein is at least 85% pure, more preferably at least 95% pure, and most preferably at least 99% pure.

[0021] The term "antibody" refers to a polypeptide comprising a framework region encoded by an immunoglobulin gene, or fragments thereof, that specifically bind and recognize an antigen, *e.g.*, human $\alpha v\beta 8$, a particular cell surface marker, or any desired target. Typically, the "variable region" contains the antigen-binding region of the antibody (or its functional equivalent) and is most critical in specificity and affinity of binding. See Paul, *Fundamental Immunology* (2003).

[0022] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a

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variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively.

[0023] An "isotype" is a class of antibodies defined by the heavy chain constant region. Antibodies described herein can be of any isotype of isotype class. Immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the isotype classes, IgG, IgM, IgA, IgD and IgE, respectively.

[0024] Antibodies can exist as intact immunoglobulins or as any of a number of well-characterized fragments that include specific antigen-binding activity. Such fragments can be produced by digestion with various peptidases. Pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)'$_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The F(ab)'$_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)'$_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (*see Fundamental Immunology* (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (*e.g.*, single chain Fv) or those identified using phage display libraries (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990)).

[0025] For preparation of monoclonal or polyclonal antibodies, any technique known in the art can be used (see, *e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4:72 (1983); Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, pp. 77-96. Alan R. Liss, Inc. 1985). Techniques for the production of single chain antibodies (U.S. Patent No. 4,946,778) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies. Alternatively, phage display technology can be used to identify

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antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, *e.g.*, McCafferty *et al.*, *supra*; Marks *et al.*, *Biotechnology*, 10:779-783, (1992)).

[0026] Methods for humanizing or primatizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (*see, e.g.*, Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-327 (1988); Verhoeyen *et al.*, *Science* 239:1534-1536 (1988) and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some complementary determining region ("CDR") residues and possibly some framework ("FR") residues are substituted by residues from analogous sites in rodent antibodies.

[0027] Antibodies or antigen-binding molecules of the invention further includes one or more immunoglobulin chains that are chemically conjugated to, or expressed as, fusion proteins with other proteins. It also includes bispecific antibody. A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Other antigen-binding fragments or antibody portions of the invention include bivalent scFv (diabody), bispecific scFv antibodies where the antibody molecule recognizes two different epitopes, single binding domains (dAbs), and minibodies.

[0028] The various antibodies or antigen-binding fragments described herein can be produced by enzymatic or chemical modification of the intact antibodies, or synthesized de novo using recombinant DNA methodologies (e.g., single chain Fv), or identified using phage display libraries (see, e.g., McCafferty et al., Nature 348:552-554, 1990). For example, minibodies can be generated using methods described in the art, e.g., Vaughan and Sollazzo, Comb Chem High Throughput Screen. 4:417-30 2001. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai &

Lachmann, Clin. Exp. Immunol. 79:315-321 (1990); Kostelny et al., J. Immunol. 148, 1547-1553 (1992). Single chain antibodies can be identified using phage display libraries or ribosome display libraries, gene shuffled libraries. Such libraries can be constructed from synthetic, semi-synthetic or native and immunocompetent sources.

[0029] A "monoclonal antibody" refers to a clonal preparation of antibodies with a single binding specificity and affinity for a given epitope on an antigen. A "polyclonal antibody" refers to a preparation of antibodies that are raised against a single antigen, but with different binding specificities and affinities.

[0030] As used herein, "V-region" refers to an antibody variable region domain comprising the segments of Framework 1, CDR1, Framework 2, CDR2, Framework 3, CDR3, and Framework 4. These segments are included in the V-segment as a consequence of rearrangement of the heavy chain and light chain V-region genes during B-cell differentiation.

[0031] As used herein, "complementarity-determining region (CDR)" refers to the three hypervariable regions in each chain that interrupt the four "framework" regions established by the light and heavy chain variable regions. The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found.

[0032] The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, serves to position and align the CDRs in three dimensional space.

[0033] The amino acid sequences of the CDRs and framework regions can be determined using various well known definitions in the art, *e.g.*, Kabat, Chothia, international ImMunoGeneTics database (IMGT), and AbM (*see, e.g.*, Johnson and Wu, *Nucleic Acids Res.* 2000 Jan 1; 28(1): 214–218 and Johnson *et al.*, Nucleic Acids Res., 29:205-206 (2001);; Chothia & Lesk, (1987) *J. Mol. Biol.* 196, 901-917; Chothia et al. (1989) Nature 342, 877-883; Chothia et

al. (1992) J. Mol. Biol. 227, 799-817; Al-Lazikani *et al., J.Mol.Biol* 1997, 273(4)). Unless otherwise indicated, CDRs are determined according to Kabat. Definitions of antigen combining sites are also described in the following: Ruiz et al. *Nucleic Acids Res.*, 28, 219–221 (2000); and Lefranc *Nucleic Acids Res.* Jan 1;29(1):207-9 (2001); MacCallum *et al., J. Mol. Biol.*, 262: 732-745 (1996); and Martin *et al, Proc. Natl Acad. Sci.* USA, 86, 9268–9272 (1989); Martin, *et al, Methods Enzymol.*, 203: 121–153, (1991); Pedersen *et al, Immunomethods*, 1, 126, (1992); and Rees *et al*, In Sternberg M.J.E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141–172 1996).

[0034] A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region, CDR, or portion thereof) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody (*e.g.*, an enzyme, toxin, hormone, growth factor, drug, etc.); or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity (*e.g.*, CDR and framework regions from different species).

[0035] A "humanized" antibody is an antibody that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing the remaining parts of the antibody with their human counterparts. *See, e.g.*, Morrison *et al., Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984); Morrison and Oi, *Adv. Immunol.*, 44:65-92 (1988); Verhoeyen *et al., Science*, 239:1534-1536 (1988); Padlan, *Molec. Immun.*, 28:489-498 (1991); Padlan, *Molec. Immun.*, 31(3):169-217 (1994).

[0036] The antibody binds to an "epitope" on the antigen. The epitope is the specific antibody binding interaction site on the antigen, and can include a few amino acids or portions of a few amino acids, *e.g.*, 5 or 6, or more, *e.g.*, 20 or more amino acids, or portions of those amino acids. In some cases, the epitope includes non-protein components, *e.g.*, from a carbohydrate, nucleic acid, or lipid. In some cases, the epitope is a three-dimensional moiety. Thus, for example, where the target is a protein, the epitope can be comprised of consecutive amino acids, or amino acids from different parts of the protein that are brought into proximity by protein folding (*e.g.*, a

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discontinuous epitope). The same is true for other types of target molecules that form three-dimensional structures.

[0037] The term "specifically bind" refers to a molecule (*e.g.*, antibody or antibody fragment) that binds to a target with at least 2-fold greater affinity than non-target compounds, *e.g.*, at least 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 25-fold, 50-fold, or 100-fold greater affinity. For example, an antibody that specifically binds β8 will typically bind to β8 with at least a 2-fold greater affinity than a non-β8 target (*e.g.*, a different integrin subunit, *e.g.*, β6).

[0038] The term "binds" with respect to a cell type (*e.g.*, an antibody that binds fibrotic cells, hepatocytes, chondrocytes, etc.), typically indicates that an agent binds a majority of the cells in a pure population of those cells. For example, an antibody that binds a given cell type typically binds to at least 2/3 of the cells in a population of the indicated cells (*e.g.*, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%). One of skill will recognize that some variability will arise depending on the method and/or threshold of determining binding.

[0039] As used herein, a first antibody, or an antigen-binding portion thereof, "competes" for binding to a target with a second antibody, or an antigen-binding portion thereof, when binding of the second antibody with the target is detectably decreased in the presence of the first antibody compared to the binding of the second antibody in the absence of the first antibody. The alternative, where the binding of the first antibody to the target is also detectably decreased in the presence of the second antibody, can, but need not be the case. That is, a second antibody can inhibit the binding of a first antibody to the target without that first antibody inhibiting the binding of the second antibody to the target. However, where each antibody detectably inhibits the binding of the other antibody to its cognate epitope or ligand, whether to the same, greater, or lesser extent, the antibodies are said to "cross-compete" with each other for binding of their respective epitope(s). Both competing and cross-competing antibodies are encompassed by the present invention. The term "competitor" antibody can be applied to the first or second antibody as can be determined by one of skill in the art. In some cases, the presence of the competitor antibody (*e.g.*, the first antibody) reduces binding of the second antibody to the target by at least 10%, *e.g.*, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or more, *e.g.*, so that binding of the second antibody to target is undetectable in the presence of the first (competitor) antibody.

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[0040] The term "differentially expressed" or "differentially regulated" refers generally to a protein or nucleic acid biomarker that is overexpressed (upregulated) or underexpressed (downregulated) in one sample compared to at least one other sample. In the context of the present invention, the term generally refers to overexpression of a biomarker (*e.g.*, αvβ8) on a diseased cell compared to a normal cell.

[0041] For example, the terms "overexpressed" or "upregulated" interchangeably refer to a protein or nucleic acid, generally a biomarker, that is transcribed or translated at a detectably greater than control level. The term includes overexpression due to transcription, post transcriptional processing, translation, post-translational processing, cellular localization (*e.g.*, organelle, cytoplasm, nucleus, cell surface), and RNA and protein stability. Overexpression can be detected using conventional techniques for detecting biomarkers, whether mRNA (*i.e.*, RT-PCR, hybridization) or protein (*i.e.*, flow cytometry, imaging, ELISA, immunohistochemical techniques). Overexpression can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a normal cell.

[0042] The terms "agonist," "activator," "inducer" and like terms refer to molecules that increase activity or expression as compared to a control. Agonists are agents that, *e.g.*, bind to, stimulate, increase, activate, enhance activation, sensitize or upregulate the activity of the target. The expression or activity can be increased 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% 100% or more than that in a control. In certain instances, the activation is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more in comparison to a control.

[0043] The terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance that results in a detectably lower expression or activity level as compared to a control. The inhibited expression or activity can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or less than that in a control. In certain instances, the inhibition is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more in comparison to a control.

[0044] A "control" sample or value refers to a sample that serves as a reference, usually a known reference, for comparison to a test sample. For example, a test sample can be taken from a test condition, *e.g.*, in the presence of a test compound, and compared to samples from known conditions, *e.g.*, in the absence of the test compound (negative control), or in the presence of a known compound (positive control). A control can also represent an average value gathered

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from a number of tests or results. One of skill in the art will recognize that controls can be designed for assessment of any number of parameters. For example, a control can be devised to compare therapeutic benefit based on pharmacological data (*e.g.*, half-life) or therapeutic measures (*e.g.*, comparison of benefit and/or side effects). Controls can be designed for *in vitro* applications. One of skill in the art will understand which controls are valuable in a given situation and be able to analyze data based on comparisons to control values. Controls are also valuable for determining the significance of data. For example, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant.

[0045] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (*e.g.*, as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, *e.g.*, by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any method known in the art for conjugating an antibody to the label may be employed, *e.g.*, using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego.

[0046] A "labeled" molecule (*e.g.*, nucleic acid, protein, or antibody) is one that is bound, either covalently, through a linker or a chemical bond, or noncovalently, through ionic, van der Waals, electrostatic, or hydrogen bonds to a label such that the presence of the molecule may be detected by detecting the presence of the label bound to the molecule.

[0047] The term "diagnosis" refers to a relative probability that a disorder such as cancer or an inflammatory condition is present in the subject. Similarly, the term "prognosis" refers to a relative probability that a certain future outcome may occur in the subject. For example, prognosis can refer to the likelihood that an individual will develop a TGFβ or αvβ8 associated disorder, have recurrence, or the likely severity of the disease (*e.g.*, severity of symptoms, rate of functional decline, survival, etc.). The terms are not intended to be absolute, as will be appreciated by any one of skill in the field of medical diagnostics.

[0048] "Biopsy" or "biological sample from a patient" as used herein refers to a sample obtained from a patient having, or suspected of having, a TGFβ or αvβ8 associated disorder. In

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some embodiments, the sample may be a tissue biopsy, such as needle biopsy, fine needle biopsy, surgical biopsy, etc. The sample can also be a blood sample or blood fraction, *e.g.*, white blood cell fraction, serum, or plasma. The sample can comprise a tissue sample harboring a lesion or suspected lesion, although the biological sample may be also be derived from another site, *e.g.*, a site of suspected metastasis, a lymph node, or from the blood. In some cases, the biological sample may also be from a region adjacent to the lesion or suspected lesion.

[0049] A "biological sample" can be obtained from a patient, *e.g.*, a biopsy, from an animal, such as an animal model, or from cultured cells, *e.g.*, a cell line or cells removed from a patient and grown in culture for observation. Biological samples include tissues and bodily fluids, *e.g.*, blood, blood fractions, lymph, saliva, urine, feces, etc.

[0050] The terms "therapy," "treatment," and "amelioration" refer to any reduction in the severity of symptoms. In the case of treating an inflammatory condition, the treatment can refer to reducing, *e.g.*, blood levels of inflammatory cytokines, blood levels of active mature TGFβ, pain, swelling, recruitment of immune cells, etc. In the case of treating cancer, treatment can refer to reducing, *e.g.*, tumor size, number of cancer cells, growth rate, metastatic activity, cell death of non-cancer cells, etc. As used herein, the terms "treat" and "prevent" are not intended to be absolute terms. Treatment and prevention can refer to any delay in onset, amelioration of symptoms, improvement in patient survival, increase in survival time or rate, etc. Treatment and prevention can be complete (no detectable symptoms remaining) or partial, such that symptoms are less frequent of severe than in a patient without the treatment described herein. The effect of treatment can be compared to an individual or pool of individuals not receiving the treatment, or to the same patient prior to treatment or at a different time during treatment. In some aspects, the severity of disease is reduced by at least 10%, as compared, *e.g.*, to the individual before administration or to a control individual not undergoing treatment. In some aspects the severity of disease is reduced by at least 25%, 50%, 75%, 80%, or 90%, or in some cases, no longer detectable using standard diagnostic techniques.

[0051] The terms "effective amount," "effective dose," "therapeutically effective amount," etc. refer to that amount of the therapeutic agent sufficient to ameliorate a disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of therapeutic effect at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%,

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75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0052] As used herein, the term "pharmaceutically acceptable" is used synonymously with physiologically acceptable and pharmacologically acceptable. A pharmaceutical composition will generally comprise agents for buffering and preservation in storage, and can include buffers and carriers for appropriate delivery, depending on the route of administration.

[0053] The terms "dose" and "dosage" are used interchangeably herein. A dose refers to the amount of active ingredient given to an individual at each administration. For the present invention, the dose can refer to the concentration of the antibody or associated components, *e.g.*, the amount of therapeutic agent or dosage of radiolabel. The dose will vary depending on a number of factors, including frequency of administration; size and tolerance of the individual; severity of the condition; risk of side effects; the route of administration; and the imaging modality of the detectable moiety (if present). One of skill in the art will recognize that the dose can be modified depending on the above factors or based on therapeutic progress. The term "dosage form" refers to the particular format of the pharmaceutical, and depends on the route of administration. For example, a dosage form can be in a liquid, *e.g.*, a saline solution for injection.

[0054] "Subject," "patient," "individual" and like terms are used interchangeably and refer to, except where indicated, mammals such as humans and non-human primates, as well as rabbits, rats, mice, goats, pigs, and other mammalian species. The term does not necessarily indicate that the subject has been diagnosed with a particular disease, but typically refers to an individual under medical supervision. A patient can be an individual that is seeking treatment, monitoring, adjustment or modification of an existing therapeutic regimen, etc.

[0055] An "inflammatory condition" refers to any inflammation in an individual, and can be transient (*e.g.*, in response to exposure to a pathogen or allergen) or chronic. Inflammation is characterized by inflammatory cytokines such as IFN-gamma, IL-6, and TNF-alpha that recruit and activate macrophages and other leukocytes. In some cases, inflammation can develop into a chronic, harmful condition or autoimmune condition (*e.g.*, MS, lupus, rheumatoid arthritis, Crohn's disease). Inflammation can be evident locally (*e.g.*, at a localized site of infection or

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exposure) or systemically (*e.g.*, atherosclerosis, high blood pressure). In some embodiments, the antibody compositions and methods described herein can be used to treat inflammatory conditions.

[0056] "Cancer", "tumor," "transformed" and like terms include precancerous, neoplastic, transformed, and cancerous cells, and can refer to a solid tumor, or a non-solid cancer (*see, e.g.*, Edge *et al.* AJCC Cancer Staging Manual (7th ed. 2009); Cibas and Ducatman Cytology: Diagnostic principles and clinical correlates (3rd ed. 2009)). Cancer includes both benign and malignant neoplasms (abnormal growth). "Transformation" refers to spontaneous or induced phenotypic changes, *e.g.*, immortalization of cells, morphological changes, aberrant cell growth, reduced contact inhibition and anchorage, and/or malignancy (*see*, Freshney, Culture of Animal Cells a Manual of Basic Technique (3rd ed. 1994)). Although transformation can arise from infection with a transforming virus and incorporation of new genomic DNA, or uptake of exogenous DNA, it can also arise spontaneously or following exposure to a carcinogen.

[0057] The term "cancer" can refer to carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, solid and lymphoid cancers, *etc.* Examples of different types of cancer include, but are not limited to, lung cancer (*e.g.*, non-small cell lung cancer or NSCLC), ovarian cancer, prostate cancer, colorectal cancer, liver cancer (*i.e.*, hepatocarcinoma), renal cancer (*i.e.*, renal cell carcinoma), bladder cancer, breast cancer, thyroid cancer, pleural cancer, pancreatic cancer, uterine cancer, cervical cancer, testicular cancer, anal cancer, pancreatic cancer, bile duct cancer, gastrointestinal carcinoid tumors, esophageal cancer, gall bladder cancer, appendix cancer, small intestine cancer, stomach (gastric) cancer, cancer of the central nervous system, skin cancer, choriocarcinoma; head and neck cancer, blood cancer, osteogenic sarcoma, fibrosarcoma, neuroblastoma, glioma, melanoma, B-cell lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, Small Cell lymphoma, Large Cell lymphoma, monocytic leukemia, myelogenous leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (AML), chronic myeloid leukemia (CML), and multiple myeloma. In some embodiments, the antibody compositions and methods described herein can be used for treating cancer.

[0058] The term "co-administer" refers to the simultaneous presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

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BRIEF SUMMARY OF THE INVENTION

[0059] In some aspects, an antibody is provided that specifically binds human αvβ8 and blocks binding of TGFβ peptide to αvβ8, wherein the antibody binds to an epitope on human αvβ8 comprising amino acids D148, A149, D150, G151, and Y178 of human αv as occurs in SEQ ID NO:393 and amino acids H118, S170, D171, Y172, N173 L174, D175, H200, and R201 of human β8 as occurs in SEQ ID NO:394.

[0060] In some embodiments, an antibody (optionally a chimeric or humanized antibody) is provided that comprises heavy chain CDRs SEQ ID NO:562, SEQ ID NO: 563, and SEQ ID NO; 564 and light chain CDRs SEQ ID NO:569, SEQ ID NO: 570, and SEQ ID NO: 571.

[0061] In some embodiments, an antibody (optionally a chimeric or humanized antibody) is provided that comprises:

heavy chain CDRs SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:315; and light chain CDRs SEQ ID NO:334, SEQ ID NO:335, and SEQ ID NO:336; or

heavy chain CDRs SEQ ID NO:319, SEQ ID NO:320, and SEQ ID NO:321; and light chain CDRs SEQ ID NO:340, SEQ ID NO:341, and SEQ ID NO:342; or

heavy chain CDRs SEQ ID NO:316, SEQ ID NO:317, and SEQ ID NO:318; and light chain CDRs SEQ ID NO:337, SEQ ID NO:338, and SEQ ID NO:339; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:343, SEQ ID NO:344, and SEQ ID NO:345; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:346, SEQ ID NO:347, and SEQ ID NO:348; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:349, SEQ ID NO:350, and SEQ ID NO:351; or

heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:352, SEQ ID NO:353, and SEQ ID NO:354; or

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heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:355, SEQ ID NO:356, and SEQ ID NO:357; or

heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:358, SEQ ID NO:359, and SEQ ID NO:360; or

heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:364, SEQ ID NO:365, and SEQ ID NO:366; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:376, SEQ ID NO:377, and SEQ ID NO:378; or

heavy chain CDRs SEQ ID NO:370, SEQ ID NO:371, and SEQ ID NO:372; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:382, SEQ ID NO:383, and SEQ ID NO:384; or

heavy chain CDRs SEQ ID NO:379, SEQ ID NO:380, and SEQ ID NO:381; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:508, SEQ ID NO:509, and SEQ ID NO:510; and light chain CDRs SEQ ID NO:529, SEQ ID NO:530, and SEQ ID NO:531; or

heavy chain CDRs SEQ ID NO:511, SEQ ID NO:512, and SEQ ID NO:513; and light chain CDRs SEQ ID NO:532, SEQ ID NO:533, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:514, SEQ ID NO:515, and SEQ ID NO:516; and light chain CDRs SEQ ID NO:535, SEQ ID NO:536, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:517, SEQ ID NO:518, and SEQ ID NO:519; and light chain CDRs SEQ ID NO:538, SEQ ID NO:539, and SEQ ID NO:540; or

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heavy chain CDRs SEQ ID NO:520, SEQ ID NO:521, and SEQ ID NO:522; and light chain CDRs SEQ ID NO:541, SEQ ID NO:542, and SEQ ID NO:543; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:544, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528; and light chain CDRs SEQ ID NO:547, SEQ ID NO:548, and SEQ ID NO:549; or

other antibodies described herein.

[0062] In some embodiments, the antibody is linked to a detectable label.

[0063] In some embodiments, the antibody further comprises heavy chain framework sequences FR1, FR2, FR3, and FR4 as SEQ ID NO: 558, SEQ ID NO: 559, SEQ ID NO: 560, and SEQ ID NO: 561, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 565, SEQ ID NO: 566, SEQ ID NO: 567, and SEQ ID NO: 568, respectively.

[0064] In some embodiments, the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 550, SEQ ID NO: 551, SEQ ID NO: 552, and SEQ ID NO: 553, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 554, SEQ ID NO: 555, SEQ ID NO: 556, and SEQ ID NO: 557, respectively.

[0065] In some embodiments, the antibody is humanized. In some embodiments, the humanized antibody comprises SEQ ID NO:395, SEQ ID NO:403, SEQ ID NO:411; SEQ ID NO:419, SEQ ID NO:427, SEQ ID NO:443, SEQ ID NO:451, SEQ ID NO:459, SEQ ID NO:467; SEQ ID NO:475, SEQ ID NO:484, or SEQ ID NO:500.

[0066] Also provided is an antibody that binds to $\alpha v\beta 8$ and $\alpha v\beta 6$ and comprising a light chain CDR1 comprising the sequence RGDL. In some embodiments, the antibody comprises variable regions comprising heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:544, SEQ ID NO:545, and SEQ ID NO:546; or heavy chain CDRs SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528; and light chain CDRs SEQ ID NO:547, SEQ ID NO:548, and SEQ ID NO:549.

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[0067] In some embodiments, the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 558, SEQ ID NO: 559, SEQ ID NO: 560, and SEQ ID NO: 561, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 565, SEQ ID NO: 566, SEQ ID NO: 567, and SEQ ID NO: 568, respectively.

[0068] In some embodiments, the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 550, SEQ ID NO: 551, SEQ ID NO: 552, and SEQ ID NO: 553, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 554, SEQ ID NO: 555, SEQ ID NO: 556, and SEQ ID NO: 557, respectively.

[0069] In some embodiments, the antibody is humanized.

[0070] In some embodiments, the antibody is linked to a detectable label.

[0071] Also provided is an antibody that specifically binds human αvβ8 and blocks binding of TGFβ peptide to αvβ8, wherein the antibody binds to the specificity determining loop (SDL) of human β8. In some embodiments, the antibody further binds to one, two, or all three of the human αv-head domain, the α1 helix of human β8, or the α2 helix of human β8. In some embodiments, the antibody is humanized or chimeric. In some embodiments, the antibody is linked to a detectable label.

[0072] Also provided is a pharmaceutical composition comprising an antibody as described above or elsewhere herein in a pharmaceutically acceptable excipient.

[0073] Also provided is a method of enhancing an immune response to a viral infection in a human individual. In some embodiments, the method comprises administering a sufficient amount of an antibody as described above or elsewhere herein to the individual, thereby enhancing an immune response to the viral infection.

[0074] In some embodiments, the viral infection is a hepatitis infection. In some embodiments, the viral infection is a hepatitis B infection.

[0075] Also provided is a method of enhancing an immune response to a viral infection in a human individual, the method comprising administering a sufficient amount of the antibody to

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the individual, wherein the antibody specifically binds to human αvβ8 and blocks binding of TGFβ peptide to αvβ8 or blocks activation of αvβ8 by binding of TGFβ human αvβ8, thereby enhancing an immune response to the viral infection.

[0076] Also provided is a method of enhancing an immune response to cancer in a human individual, the method comprising administering a sufficient amount of an antibody as described above or elsewhere herein to the individual, thereby enhancing an immune response to the cancer.

[0077] In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is a metastatic cancer. In some embodiments, the cancer is a primary cancer.

[0078] Also provided is a method of enhancing an immune response to *H. pyroli* in a human individual, the method comprising administering a sufficient amount of an antibody as described above or elsewhere herein to the individual, thereby enhancing an immune response to *H. pyroli*.

[0079] In some embodiments, the human individual has a peptide ulcer, gastric carcinoma or MALT lymphoma.

[0080] Also provided is an antibody that specifically binds to human αvβ8 and that comprises human heavy chain CDRs SEQ ID NO:299, SEQ ID NO:301, and SEQ ID NO:303; and light chain CDRs SEQ ID NO:307, SEQ ID NO:309, and SEQ ID NO:311. Alteratively, any antibodies having heavy chain CDRs or a heavy chain variable region as set forth in FIG. 53 and light chain CDRs or a light chain variable region from a corresponding sequence as set forth in FIG. 54 can be used

[0081] In some embodiments, the antibody is linked to a detectable label.

[0082] Also provided is a method of detecting the presence, absence, or quantity of human in a sample, the method comprising, contacting to the sample an antibody that specifically binds to human αvβ8 and that comprises human heavy chain CDRs SEQ ID NO:299, SEQ ID NO:301, and SEQ ID NO:303; and light chain CDRs SEQ ID NO:307, SEQ ID NO:309, and SEQ ID NO:311, and detecting or quantifying binding of the antibody to the sample.

[0083] In some embodiments, the sample is a formalin-fixed sample.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0084] FIG. 1 illustrates heavy chain amino acid sequences for clones used in the construction of the composite antibody C6D4. B13C4 15-8: all sequences (SEQ ID NO:1), Framework 1 (SEQ ID NO:2), CDR1 (SEQ ID NO:3), Framework 2 (SEQ ID NO:4), CDR2 (SEQ ID NO:5), Framework 3 (SEQ ID NO:6), CRD3 (SEQ ID NO:7), and Framework 4 (SEQ ID NO:8); B13C4 15-10: all sequences (SEQ ID NO:9), Framework 1 (SEQ ID NO:10), CDR1 (SEQ ID NO:11), Framework 2 (SEQ ID NO:12), CDR2 (SEQ ID NO:13), Framework 3 (SEQ ID NO:14), CRD3 (SEQ ID NO:15), and Framework 4 (SEQ ID NO:16); B13H3.2: all sequences (SEQ ID NO:17), Framework 1 (SEQ ID NO:18), CDR1 (SEQ ID NO:19), Framework 2 (SEQ ID NO:20), CDR2 (SEQ ID NO:21), Framework 3 (SEQ ID NO:22), CRD3 (SEQ ID NO:23), and Framework 4 (SEQ ID NO:24); B13C1231015: all sequences (SEQ ID NO:25), Framework 1 (SEQ ID NO:26), CDR1 (SEQ ID NO:27), Framework 2 (SEQ ID NO:28), CDR2 (SEQ ID NO:29), Framework 3 (SEQ ID NO:30), CRD3 (SEQ ID NO:31), and Framework 4 (SEQ ID NO:32); B15B11Vh: all sequences (SEQ ID NO:33), Framework 1 (SEQ ID NO:34), CDR1 (SEQ ID NO:35), Framework 2 (SEQ ID NO:36), CDR2 (SEQ ID NO:37), Framework 3 (SEQ ID NO:38), CRD3 (SEQ ID NO:39), and Framework 4 (SEQ ID NO:40); B2B2 15-9: all sequences (SEQ ID NO:41), Framework 1 (SEQ ID NO:42), CDR1 (SEQ ID NO:43), Framework 2 (SEQ ID NO:44), CDR2 (SEQ ID NO:45), Framework 3 (SEQ ID NO:46), CRD3 (SEQ ID NO:47), and Framework 4 (SEQ ID NO:48); R11D12715.3: all sequences (SEQ ID NO:49), Framework 1 (SEQ ID NO:50), CDR1 (SEQ ID NO:51), Framework 2 (SEQ ID NO:52), CDR2 (SEQ ID NO:53), Framework 3 (SEQ ID NO:54), CRD3 (SEQ ID NO:55), and Framework 4 (SEQ ID NO:56); RSDLVH-1: all sequences (SEQ ID NO:57 and SEQ ID NO:65), Framework 1 (SEQ ID NO:58 and SEQ ID NO:66), CDR1 (SEQ ID NO:59 and SEQ ID NO:67), Framework 2 (SEQ ID NO:60 and SEQ ID NO:68), CDR2 (SEQ ID NO:61 and SEQ ID NO:69), Framework 3 (SEQ ID NO:62 and SEQ ID NO:70), CRD3 (SEQ ID NO:63 and SEQ ID NO:71), and Framework 4 (SEQ ID NO:64 and SEQ ID NO:72); RSDLVH-3: all sequences (SEQ ID NO:73), Framework 1 (SEQ ID NO:74), CDR1 (SEQ ID NO:75), Framework 2 (SEQ ID NO:76), CDR2 (SEQ ID NO:77), Framework 3 (SEQ ID NO:78), CRD3 (SEQ ID NO:79), and Framework 4 (SEQ ID NO:80); RSDLVH-16: all sequences (SEQ ID NO:81), Framework 1 (SEQ ID NO:82), CDR1 (SEQ ID NO:83), Framework 2 (SEQ ID

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NO:84), CDR2 (SEQ ID NO:85), Framework 3 (SEQ ID NO:86), CRD3 (SEQ ID NO:87), and Framework 4 (SEQ ID NO:88); both 29 and 44: all sequences (SEQ ID NO:89), Framework 1 (SEQ ID NO:90), CDR1 (SEQ ID NO:91), Framework 2 (SEQ ID NO:92), CDR2 (SEQ ID NO:93), Framework 3 (SEQ ID NO:94), CRD3 (SEQ ID NO:95), and Framework 4 (SEQ ID NO:96); A1=B4=F9: all sequences (SEQ ID NO:97), Framework 1 (SEQ ID NO:98), CDR1 (SEQ ID NO:99), Framework 2 (SEQ ID NO:100), CDR2 (SEQ ID NO:101), Framework 3 (SEQ ID NO:102), CRD3 (SEQ ID NO:103), and Framework 4 (SEQ ID NO:104); A5=C6: all sequences (SEQ ID NO:105), Framework 1 (SEQ ID NO:106), CDR1 (SEQ ID NO:107), Framework 2 (SEQ ID NO:108), CDR2 (SEQ ID NO:109), Framework 3 (SEQ ID NO:110), CRD3 (SEQ ID NO:111), and Framework 4 (SEQ ID NO:112); D4=E6: all sequences (SEQ ID NO:113), Framework 1 (SEQ ID NO:114), CDR1 (SEQ ID NO:115), Framework 2 (SEQ ID NO:116), CDR2 (SEQ ID NO:117), Framework 3 (SEQ ID NO:118), CRD3 (SEQ ID NO:119), and Framework 4 (SEQ ID NO:120); and C6D4: all sequences (SEQ ID NO:121), Framework 1 (SEQ ID NO:122), CDR1 (SEQ ID NO:123), Framework 2 (SEQ ID NO:124), CDR2 (SEQ ID NO:125), Framework 3 (SEQ ID NO:126), CRD3 (SEQ ID NO:127), and Framework 4 (SEQ ID NO:128).

[0085] FIG. 2 illustrates light chain amino acid sequences for clones used in the construction of the composite antibody C6D4. B2B2 35-20: all sequences (SEQ ID NO:129), Framework 1 (SEQ ID NO:130), CDR1 (SEQ ID NO:131), Framework 2 (SEQ ID NO:132), CDR2 (SEQ ID NO:133), Framework 3 (SEQ ID NO:134), CRD3 (SEQ ID NO:135), and Framework 4 (SEQ ID NO:136); B2B2 35-26: all sequences (SEQ ID NO:137), Framework 1 (SEQ ID NO:138), CDR1 (SEQ ID NO:139), Framework 2 (SEQ ID NO:140), CDR2 (SEQ ID NO:141), Framework 3 (SEQ ID NO:142), CRD3 (SEQ ID NO:143), and Framework 4 (SEQ ID NO:144); B15B11vk34-26: all sequences (SEQ ID NO:145), Framework 1 (SEQ ID NO:146), CDR1 (SEQ ID NO:147), Framework 2 (SEQ ID NO:148), CDR2 (SEQ ID NO:149), Framework 3 (SEQ ID NO:150), CRD3 (SEQ ID NO:151), and Framework 4 (SEQ ID NO:152); B15B11vk33-24: all sequences (SEQ ID NO:153), Framework 1 (SEQ ID NO:154), CDR1 (SEQ ID NO:155), Framework 2 (SEQ ID NO:156), CDR2 (SEQ ID NO:157), Framework 3 (SEQ ID NO:158), CRD3 (SEQ ID NO:159), and Framework 4 (SEQ ID NO:160);

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B15B11vk35-26: all sequences (SEQ ID NO:161), Framework 1 (SEQ ID NO:162), CDR1 (SEQ ID NO:163), Framework 2 (SEQ ID NO:164), CDR2 (SEQ ID NO:165), Framework 3 (SEQ ID NO:166), CRD3 (SEQ ID NO:167), and Framework 4 (SEQ ID NO:168); B13C12134-25: all sequences (SEQ ID NO:169), Framework 1 (SEQ ID NO:170), CDR1 (SEQ ID NO:171), Framework 2 (SEQ ID NO:172), CDR2 (SEQ ID NO:173), Framework 3 (SEQ ID NO:174), CRD3 (SEQ ID NO:175), and Framework 4 (SEQ ID NO:176); B13C12133-26: all sequences (SEQ ID NO:177), Framework 1 (SEQ ID NO:178), CDR1 (SEQ ID NO:179), Framework 2 (SEQ ID NO:180), CDR2 (SEQ ID NO:181), Framework 3 (SEQ ID NO:182), CRD3 (SEQ ID NO:183), and Framework 4 (SEQ ID NO:184); B13C4 35-20: all sequences (SEQ ID NO:185), Framework 1 (SEQ ID NO:186), CDR1 (SEQ ID NO:187), Framework 2 (SEQ ID NO:188), CDR2 (SEQ ID NO:189), Framework 3 (SEQ ID NO:190), CRD3 (SEQ ID NO:191), and Framework 4 (SEQ ID NO:192); B15B11vk35-20: all sequences (SEQ ID NO:193), Framework 1 (SEQ ID NO:194), CDR1 (SEQ ID NO:195), Framework 2 (SEQ ID NO:196), CDR2 (SEQ ID NO:197), Framework 3 (SEQ ID NO:198), CRD3 (SEQ ID NO:199), and Framework 4 (SEQ ID NO:200); B13C12335-25: all sequences (SEQ ID NO:201), Framework 1 (SEQ ID NO:202), CDR1 (SEQ ID NO:203), Framework 2 (SEQ ID NO:204), CDR2 (SEQ ID NO:205), Framework 3 (SEQ ID NO:206), CRD3 (SEQ ID NO:207), and Framework 4 (SEQ ID NO:208); B13C1233520: all sequences (SEQ ID NO:209), Framework 1 (SEQ ID NO:210), CDR1 (SEQ ID NO:211), Framework 2 (SEQ ID NO:212), CDR2 (SEQ ID NO:213), Framework 3 (SEQ ID NO:214), CRD3 (SEQ ID NO:215), and Framework 4 (SEQ ID NO:216); RSDLVK-1: all sequences (SEQ ID NO:217), Framework 1 (SEQ ID NO:218), CDR1 (SEQ ID NO:219), Framework 2 (SEQ ID NO:220), CDR2 (SEQ ID NO:221), Framework 3 (SEQ ID NO:222), CRD3 (SEQ ID NO:223), and Framework 4 (SEQ ID NO:224); RSDLVK-6: all sequences (SEQ ID NO:225), Framework 1 (SEQ ID NO:226), CDR1 (SEQ ID NO:227), Framework 2 (SEQ ID NO:228), CDR2 (SEQ ID NO:229), Framework 3 (SEQ ID NO:230), CRD3 (SEQ ID NO:231), and Framework 4 (SEQ ID NO:232); RSDLVK-10: all sequences (SEQ ID NO:233), Framework 1 (SEQ ID NO:234), CDR1 (SEQ ID NO:235), Framework 2 (SEQ ID NO:236), CDR2 (SEQ ID NO:237), Framework 3 (SEQ ID NO:238), CRD3 (SEQ ID NO:239), and Framework 4 (SEQ ID NO:240); RSDLVK-13: all sequences (SEQ ID NO:241), Framework 1 (SEQ ID NO:242), CDR1 (SEQ ID NO:243), Framework 2 (SEQ ID NO:244), CDR2 (SEQ ID NO:245), Framework 3 (SEQ ID NO:246), CRD3 (SEQ ID NO:247), and Framework 4 (SEQ ID

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NO:248); 29: all sequences (SEQ ID NO:249), Framework 1 (SEQ ID NO:250), CDR1 (SEQ ID NO:251), Framework 2 (SEQ ID NO:252), CDR2 (SEQ ID NO:253), Framework 3 (SEQ ID NO:254), CRD3 (SEQ ID NO:255), and Framework 4 (SEQ ID NO:256); 44: all sequences (SEQ ID NO:257), Framework 1 (SEQ ID NO:258), CDR1 (SEQ ID NO:259), Framework 2 (SEQ ID NO:260), CDR2 (SEQ ID NO:261), Framework 3 (SEQ ID NO:262), CRD3 (SEQ ID NO:263), and Framework 4 (SEQ ID NO:264); A1=B4=F9: all sequences (SEQ ID NO:265), Framework 1 (SEQ ID NO:266), CDR1 (SEQ ID NO:267), Framework 2 (SEQ ID NO:268), CDR2 (SEQ ID NO:269), Framework 3 (SEQ ID NO:270), CRD3 (SEQ ID NO:271), and Framework 4 (SEQ ID NO:272); A5=C6: all sequences (SEQ ID NO:273), Framework 1 (SEQ ID NO:274), CDR1 (SEQ ID NO:275), Framework 2 (SEQ ID NO:276), CDR2 (SEQ ID NO:277), Framework 3 (SEQ ID NO:278), CRD3 (SEQ ID NO:279), and Framework 4 (SEQ ID NO:280); D4=E6: all sequences (SEQ ID NO:281), Framework 1 (SEQ ID NO:282), CDR1 (SEQ ID NO:283), Framework 2 (SEQ ID NO:284), CDR2 (SEQ ID NO:285), Framework 3 (SEQ ID NO:286), CRD3 (SEQ ID NO:287), and Framework 4 (SEQ ID NO:288); and C6D4: all sequences (SEQ ID NO:289), Framework 1 (SEQ ID NO:290), CDR1 (SEQ ID NO:291), Framework 2 (SEQ ID NO:292), CDR2 (SEQ ID NO:293), Framework 3 (SEQ ID NO:294), CRD3 (SEQ ID NO:295), and Framework 4 (SEQ ID NO:296).

[0086] FIG. 3 is a plot of transforming growth factor-beta (TGF-β) binding inhibition percentages for different concentrations of the allosteric inhibitor B5 and the composite antibody C6D4.

[0087] FIG. 4 illustrates conservation of epitope among mammals, indicating the antibodies can be useful in multiple preclinical animal models and have broad utility, including in veterinary applications. Human αv (SEQ ID NO:591); Chimp αv (SEQ ID NO:592); Rhesus αv (SEQ ID NO:593); Cyno αv (SEQ ID NO:594); Cow αv (SEQ ID NO:595); Pig αv (SEQ ID NO:596); Horse αv (SEQ ID NO:597); Mouse αv (SEQ ID NO:598); Rat αv (SEQ ID NO:599); Armadillo αv (SEQ ID NO:600); Platypus αv (SEQ ID NO:601); Human β8 (SEQ ID NO:602); Chimp β8 (SEQ ID NO:603); Rhesus β8 (SEQ ID NO:604); Cyno β8 (SEQ ID NO:605); Cow β8 (SEQ ID NO:606); Pig β8(SEQ ID NO:607); Horse β8 (SEQ ID NO:608);

Mouse β8 (SEQ ID NO:609); Rat β8 (SEQ ID NO:610); Armadillo β8 (SEQ ID NO:611); and Platypus β8 (SEQ ID NO:612).

[0088] FIG. 5 illustrates integrin alphaV (SEQ ID NO:394) and beta8 (SEQ ID NO:395) sequences. The epitope for C6D4 is in bold underlined italics.

[0089] FIG. 6 illustrates cryoEM results, highlighting the interactions between C6D4 and the (SDL) loop of β8, the α1 and α2 helices of β8, and the head of αv.

[0090] FIG. 7 illustrates the residues of the SDL and β8 α1 and α2 helices and αv head of integrin αvβ8 that directly interact with C6D4 upon binding. The head sequence of integrin αv is FNLDVDSPAEYSGPEGSYFGFAVDFFVPSASSRMFLLVGAPKANTTQPGIVEGGQVLKC DWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWFGASVRSKQDKILACAPLYHWRTE MKQEREPVGTCFLQDGTKTVEYAPCRSQDIDADGQGFCQGGFSIDFTKADRVLLGGPGS FYWQGQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAIFDDSYLGYSVAVGDFNGD GIDDFVSGVPRAARTLGMVYIYDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYAD VFIGAPLFMDRGSDGKLQEVGQVSVSLQRASGDFQTTKLNGFEVFARFGSAIAPLGDLD QDGFNDIAIAAPYGGEDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSMPPSFGYSMKG ATDIDKNGYPDLIVGAFGVDRAILYRARP (SEQ ID NO:623). Sequences C6D4 Vh CDR1 (SEQ ID NO:613); C6D4 Vh CDR2 (SEQ ID NO:614); C6D4 Vh CDR3 (SEQ ID NO:615); C6D4 Vk CDR1 (SEQ ID NO:616); C6D4 Vk CDR2 (SEQ ID NO:617); C6D4 Vk CDR3 (SEQ ID NO:618); β8, α1 helix (SEQ ID NO:619); β8, SDL (SEQ ID NO:620); β8, α2 helix (SEQ ID NO:621) ; and αV, β-propeller domain blade W3 (SEQ ID NO:622).

[0091] FIG. 8 illustrates the overlapping of the C6D4 epitope with the ligand binding pocket of integrin αvβ8, in relation to the association of the integrin with latent TGF-β.

[0092] FIG. 9 is a plot of percent survival of mice injected with Lewis lung carcinoma (LLC) cells. The primary tumors were removed and the animals treated with C6D4 murine IgG2a or SV5 isotype control at a dosage of 7 mg/kg once per week. In this model, mice are euthanized after losing 20% body weight due to recurrence of the primary tumor or due to metastasis.

[0093] FIG 10 is a table of HepB surface antigen (HBSag) clearance from a chronic infection mouse model as a result of treatment with C6D4.

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[0094] FIG. 11A-B illustrate amino acid sequences for clones used in the construction of the engineered antibody 4F1F9, an antibody used for detection of αvβ8 in human tissues. FIG. 11A Sequences - 4F1 : all sequences (SEQ ID NO:624), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:628), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:634), Framework 3 (SEQ ID NO:637), CDR3 (SEQ ID NO:651), Framework 4 (SEQ ID NO:655), 6B9 : all sequences (SEQ ID NO:656), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:635), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:652), Framework 4 (SEQ ID NO:655), 6B9.1 : all sequences (SEQ ID NO:657), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:653), Framework 4 (SEQ ID NO:655), A1 : all sequences (SEQ ID NO:658), Framework 1 (SEQ ID NO:626), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:639), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A2 : all sequences (SEQ ID NO:659), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:640), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A8 : all sequences (SEQ ID NO:660), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:641), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A11 : all sequences (SEQ ID NO:661), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:630), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), B1 : all sequences (SEQ ID NO:662), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:642), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), B3 : all sequences (SEQ ID NO:663), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:643), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C4=F10 : all sequences (SEQ ID NO:664), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:644), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C7=D1 : all sequences (SEQ ID NO:665), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3

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(SEQ ID NO:644), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D3=F1 : all sequences (SEQ ID NO:666), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:645), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D10=E5 : all sequences (SEQ ID NO:667), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), G4 : all sequences (SEQ ID NO:668), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:647), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C4 : all sequences (SEQ ID NO:669), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:650), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D10 : all sequences (SEQ ID NO:670), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1A11 : all sequences (SEQ ID NO:671), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:650), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E1 : all sequences (SEQ ID NO:672), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1G3 : all sequences (SEQ ID NO:673), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:648), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E10 : all sequences (SEQ ID NO:674), Framework 1 (SEQ ID NO:627), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E9 : all sequences (SEQ ID NO:675), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1H12 : all sequences (SEQ ID NO:676), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:649), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), F9 : all

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sequences (SEQ ID NO:677), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), and Framework 4 (SEQ ID NO:655). FIG. 11B Sequences - 4F1 : all sequences (SEQ ID NO:678), Framework 1 (SEQ ID NO:692), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), 6B9 : all sequences (SEQ ID NO:679), Framework 1 (SEQ ID NO:699), CDR1 (SEQ ID NO:700), Framework 2 (SEQ ID NO:701), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:702), Framework 4 (SEQ ID NO:698), 6B9.1 : all sequences (SEQ ID NO:680), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A1 = A2 = C4 = C7 = D1 = D10 = E5 = F1 = F10 = G4 : all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A8 : all sequences (SEQ ID NO:682), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A11 : all sequences (SEQ ID NO:683), Framework 1 (SEQ ID NO:704), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), B1 : all sequences (SEQ ID NO:684), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), B3 : all sequences (SEQ ID NO:685), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), D10=E5 : all sequences (SEQ ID NO:686), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), C4 : all sequences (SEQ ID NO:687), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID

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NO:706), D10 : all sequences (SEQ ID NO:688), Framework 1 (SEQ ID NO:699), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:706), 4F1E1 = 1F1G3 = 4F1B5 = 4F1G11 = 4F1A9 = 4F1B9 = 4F1H9 = 4F1D10 = 4F1E9 = 4F1F10 = 4F1H11 = 4F1H12 : all sequences (SEQ ID NO:689), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), 4FA11 : all sequences (SEQ ID NO:690), Framework 1 (SEQ ID NO:705), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), F9 : all sequences (SEQ ID NO:691), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), and Framework 4 (SEQ ID NO:706).

[0095] FIG. 12 demonstrates how the C6D4 epitope overlaps directly with the ligand binding pocket of integrin αVβ8, preventing association of integrin αVβ8 with L-TGFβ and thus activation of L-TGFβ. Representative class averages of integrin complexes observed by negative staining electron microscopy.

[0096] FIG. 13 illustrates a model of how the complex is generated from the crystal structure of αVβ3 (PDB ID: 3IJE), with the β8 model based on β3 using CHIMERA and MODELLER (Yang *et al., J Struct Biol.* 2012 Sep;179(3):269-78). Refinement of the model to the cryo-electron microscopy map is done in rigid body in COOT (Emsley P, *et al., Acta Crystallographica Section D - Biological Crystallography.* 2010, 66:486-501), followed by complete refinement in PHENIX (Adams *et al., Acta Cryst.* 2010; D66:213-221).

[0097] FIG. 14 illustrates interaction of C6D4 Vk CDR1 (SEQ ID NO:616) with integrin αV (SEQ ID NO:622, positions 46-52 and 75-79): Model of the αVβ8/C6D4 Fab complex. Interacting residues are represented as sticks. The dashed lines represent inter-atom distances comprised between 2.5 and 4.0Å indicating potential interactions.

[0098] FIG. 15 illustrates interaction of C6D4 with the SDL region of integrin β8: Model of the αVβ8/C6D4 Fab complex. Interacting residues are represented as sticks. The dashed lines represent inter-atom distances comprised between 2.5 and 4.0Å indicating potential interactions.

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C6D4 Vh CDR1 (SEQ ID NO:707), C6D4 Vh CDR3 (SEQ ID NO:615), β8, SDL (SEQ ID NO:620), C6D4 Vk CDR1 (SEQ ID NO:616), C6D4 Vk CDR2 (SEQ ID NO:708), and C6D4 Vk CDR3 (SEQ ID NO:618).

[0099] FIG. 16 illustrates interaction of C6D4 Vk CDR2 (SEQ ID NO:617) with the α1 helix of integrin β8 (SEQ ID NO:619): Model of the αVβ8/C6D4 Fab complex. Interacting residues are represented as sticks. The dashed lines represent inter-atom distances comprised between 2.5 and 4.0Å indicating potential interactions.

[0100] FIG. 17 illustrates interaction of C6D4 Vk CDR1 (SEQ ID NO:613) with the α2 helix of integrin β8 (SEQ ID NO:621): Model of the αVβ8/C6D4 Fab complex. Interacting residues are represented as sticks. The dashed lines represent inter-atom distances comprised between 2.5 and 4.0Å indicating potential interactions.

[0101] FIG. 18 illustrates that C6D4 blocks the access of L-TGFβ to the ligand binding pocket of integrin β8 and C6D4 bound to integrin αVβ8 directly clashes with the position of the RGDLGRLKK loop of L-TGFβ (SEQ ID NO:712). The surface of the αVβ8/C6D4 Fab complex is shown. The surface is αVβ8, while the cartoon is C6D4. In sticks are superimposed the residues RGDLGRLKK (SEQ ID NO:712) from the integrin binding loop of L-TGFβ as found when bound to integrin αVβ6 (PDB 4UM9) ((4) Structural determinants of integrin β-subunit specificity for latent TGF-β. Dong X, *et al. Nat. Struct. Mol. Biol.* 2014 Dec;21(12):1091-6).

[0102] FIG. 19 shows that C6D4 is a potent inhibitor of binding of secreted αvβ8 to L-TGF-b3 peptide.

[0103] FIG. 20 shows that C6D4 is a potent inhibitor of cell αvβ8-mediated cell adhesion to L-TGF-b3 peptide.

[0104] FIG. 21 shows immunodetection of the integrin b8 subunit in formalin fixed paraffin embedded sections from patient infected with H. Pylori (A,B) or showing normal histology (C,D). The sections were stained with clone F9 in rabbit IgG format and detected using TSA signal amplification (Perkin Elmer). The brown precipitate indicates positive staining and the nuclei are counterstained with hematoxylin. The arrows indicate examples of positive crypts with stained crypt epithelial cells. The results show that the b8 integrin subunit is increased in expression in the stomachs of patients with H. Pylori.

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[0105] FIG. 22 shows quantification of Immunodetection of the integrin b8 subunit in formalin fixed paraffin embedded sections from patient infected with H. Pylori, showing normal histology or mild chronic inflammation. The sections were stained with clone F9 in rabbit IgG format and detected using TSA signal amplification (Perkin Elmer). The following scoring system was devised to capture the crypto-epithelial staining, 0=no stain, 1=just contrast+, 2=scattered, 3= diffuse and stromal staining, 0= no stain, 1=just contrast+, 2=scattered, 3=diffuse. Shown is a combined score and the n is shown. ANOVA with Sidak's multiple comparisons test. **p<0.01, * p<0.05

[0106] FIG. 23 shows binding assay of alkaline phosphatase (AP) αvβ3, αvβ6 and αvβ8 fusion proteins to CagL, the MAP RGD peptide derived from the TGFB3 sequence DDHGRGDLGRLK (SEQ ID NO:713), Fibronectin, Vitronectin or a MAP peptide derived from the TGFB2 sequence that corresponds to the RGD containing sequence of TGFB1 and TGFB3. All proteins are coated on ELISA plates at 5 ug/ml and input of AP receptors are normalized to AP activity. Results shown represent signal above BSA coated wells. The results show that αvβ8 (and αvβ6) binds to to CagL as well as to TGFb3 peptide, whereas αvβ3 binds to FN and VN, poorly to TGFB3 and not at all to CagL. αvβ3 and αvβ8 show no binding and αvβ6 shows very weak binding to the control TGFb2 peptide. Shown are S.E.M.

[0107] FIG. 24 shows binding assay of alkaline phosphatase (AP) αvβ8 fusion protein to CagL in the presence of C6D4, an allosteric inhibitor, B5, or a non-blocking antibody to the same epitope as B5, clone 68 which serves as a negative control. CagL is coated on ELISA plates at 5 ug/ml. Results shown represent signal above BSA coated wells. The results show that αvβ8 binding to to CagL is completely inhibited by C6D4 and are partially inhibited by B5.

[0108] FIG. 25 shows adhesion assay of Cho Lec cells stably expressing human ITGAV and ITGB8 to recombinant CagL protein at the indicated concentrations (gift of Eric. Sundberg, University of Maryland, MD). Binding is compared to wells coated with a multiple antigen presenting peptide containing the RGD peptide derived from the TGFB3 sequence DDHGRGDLGRLK (SEQ ID NO:713), which corresponds to aa 257-268 of human TGF-b3 (NP_003230). 50 x 10^3 cells were allowed to attach to the wells for 30 min at RT. Unbound cells were washed off with PBS. Results were presented as stained cells detected after staining with crystal violet (OD590). Results shown represent signal above the nominal binding of mock

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transfected Cho Lec cells to CagL or TGFB3 peptide coated wells (5 ug.ml). The results show that αvβ8 mediates cell adhesion to CagL as well as to TGFb3 peptide. Shown are S.E.M. Significance was determined by ANOVA and Sidak's multiple comparison test. ****=p<0.00001

[0109] FIG. 26 shows adhesion assay of Cho Lec cells stably expressing human ITGAV and ITGB8 to the TGF-b3 RGD MAP peptide (DDHGRGDLGRLK (SEQ ID NO:713)) (coating concentration 5 ug/ml). 50 x 10^3 cells were preincubated with cagL at the indicated concentrations of CagL vs PBS control for 15 min at RT and then the cells allowed to attach to the wells for 30 min at RT. Unbound cells were washed off with PBS. Results were presented as stained cells detected after staining with crystal violet (OD590). Results shown represent signal above the nominal binding of mock transfected Cho Lec cells to TGFB3 peptide coated wells (5 ug/ml). The results show that αvβ8 mediates cell adhesion to CagL is RGD dependent. Shown are S.E.M. N=3

[0110] FIG. 27 shows adhesion assay of modified Chinese Hamster Ovary Cells (Cho Lec) cells stably expressing human ITGAV and ITGB8 to recombinant CagL protein at 5 ug/ml coating concentration, 50 x 10^3 cells were mixed with the Mabs at the indicated concentrations and allowed to attach to the wells for 30 min at RT. B5 is a previously described allosteric inhibitor of αvβ8-binidng to TGF-B and L230 is a previously described anti-av blocking antibody. Unbound cells were washed off with PBS. Results are presented as stained cells detected after staining with crystal violet (OD590). Results shown represent % inhibition relative to the control binding defined by binding in presence of an isotype control antibody (anti-SV5) at the same concentration. Shown are S.E.M. Significance was determined by ANOVA and Sidak's multiple comparison test. ****=p<0.00001, ***p <0.001, *<0.05. The results show that C6D4 more efficiently blocks αvβ8 mediates cell adhesion to CagL than B5 or L230.

[0111] FIG. 28 shows a mouse model for evaluating lung metastasis using the LLC tumor cell line which does not express integrins αvβ6 or αvβ8. The LLC tumor cell line is syngenic to the host C57B/6 strain. The LLC.1 cell line has been passed though mice one time and regrown from lung metastasis. After two weeks, subcutaneously injected tumor ($1x10^6$) LLC.1 cells form large tumor nodules (~1cm). The tumors are removed surgically and when animals lose 20% body weight they are euthanized.

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[0112] FIGS. 29A and 29B show the effect of C6D4 on mouse survival using the the LLC tumor cell line model set forth in FIG. 28. Survival curves (FIG. 29A) represent mice euthanized for reasons of local recurrence or weight loss. FIG. 29B shows the survivial curve when animals removed for local recurrence are excluded. At autopsy, the animals with 20% weight loss all have metastatic implants in their lungs. Here, C6D4 antibodies have been injected for up to 90 days in surviving animals. This experiment was performed eleven times, each time providing similar results (data not shown). Additionally, post-mortem examination did not reveal any abnormal inflammatory response in the tissues examined.

[0113] FIGS. 30A-F show the effect of CD64 on tumor growth and tumor immune response using the LLC tumor cell line model set forth in FIG. 28. Here, resected LLC.1 primary tumors in mice that received two injections of isotype control (B5, which only reacts with human and not mouse b8) or C6D4 (which cross reacts with mouse and human), the primary tumor weights are recorded, dimensions are measured, and tumors are enzymatically disaggregated and immune cells isolated and counted. Flow cytometry was performed on the tumor infiltrating immune cells, and the tumor infiltrating immune cells are separated from tumor cells using Percoll gradient centrifugation. Shown here is one of three experiments each providing similar results. In each group n is equal to or greater than 10.

[0114] FIG. 31 shows a mouse model for evaluating metastatic disease using B16-F10 tumor cells. The B16-F10 highly metastatic tumor cell line is syngenic to the host C57B/6 strain. This line does not express integrins $\alpha v\beta 6$ or $\alpha v\beta 8$. The B16-F10 was transfected with murine itgb8 and after selection and sorting expresses surface $\alpha v\beta 8$ at high levels. When injected intravenously via the tail vein, visible lung metastases appear by 14 days.

[0115] FIGS. 32A-H are lung adenocarcinoma samples stained with anti-b8 (FIGS. 32E-H) or anti-PD-L1 (E1L3N, Cell signaling) FIG. 32A-D. Here, it was observed that beta 8 expression inversely correlated with PD-Ll expression.

[0116] FIG. 33A shows distribution of lung adenocarcinoma samples of FIG. 32 (n=29) with staining for either PD-L1 or beta 8. FIG. 33B shows in all cases that stained at least 30% for beta 8 or PD-L1 were grouped together and the staining proportions were correlated.

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[0117] FIGS. 34A-C shows the inhibition of B16 lung metastases as compared to an isotype sample. FIG. 34A are photographs of representative lungs in anterior and posterior views and visible lung metastases were counted and the total lung surface area involved with metastases was assessed. FIG. 34B shows the effect of C6D4 on total number of lung metastases. The B16-F10 highly metastatic tumor cell line is syngenic to the host C57B/6 strain and does not express integrins αvβ6 or αvβ8. The B16-F10 tumor cells were transfected with murine itgb8. After selection in G418 and two rounds of sorting a pool of high expressing αvβ8 cells was injected intravenously via the tail vein. After three injections (i.p.) of isotype control (SV5) or C6D4, both at 7 mg/kg at days 0, 7 and 14, the mice were euthanized at day 18. FIG. 34C shows the effect of C6D4 as measured by percentage of total lung surface area involved by metastatic melanoma.

[0118] FIGS. 35A-H show that C6D4 effects macrophage polarization to a proinflammatory phenotype. Increases in MHCII expression by tumor associated macrophages and dendritic cells is important in host immune responses to tumor antigens.

[0119] FIGS. 36A-C shows that C6D4 increases MHCII expression by tumor associated dendritic cells. Increases in MHCII by antigen presenting cells will increase antigen presentation.

[0120] FIGS. 37A-G are scatterplots showing integrin mediated differentiation of mouse Treg cells. Tumor associated CD4+ T regulatory cells play an important role in suppressing the host immune response and help tumors escape immune surveillance. The differentiation of Treg requires TGF-beta. It is thought that TGF-beta provided by mechanisms such as integrin αvβ8 mediated activation are important for Treg differentiation and function. Here, we immobilized the ectodomains of various integrins (2 mg/ml) on ELISA plates (co-coated with anti-CD3) and plate naïve murine splenic CD4+ cells with hIL-2 and retinoic acid. After 5 days the cells were fixed, permeabilized and stained with anti-CD4 and FoxP3. As a positive and negative control, cells were plated on wells with only anti-CD3 (no integrin) in the presence (+) or absence (-) of rTGF-b. The percentage of FoxP3 expressing cells are shown in each of the scatterplots (Q2).

[0121] FIGS. 38A-D shows structural representations of a C6D4 derivative (termed "RGD3" or "CD64-RGD3") that is cross-reactive to αvβ6 and αvβ8 but not αvβ1, αvβ3, or αvβ5. FIG.

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38A shows a close-up view of C6D4-RGD3 (gold) in complex with αvβ8 derived from cryoEM maps. Green is the av subunit and blue is the β8 subunit. Shown in red is the LTGF-B1 peptide derived from structures of Latent-TGFB1 in complex with the integrin αvβ6. (αvβ6 (SEQ ID NO:709), αIIbβ3 (SEQ ID NO:710 (GRGDSP) and SEQ ID NO:711 (AKQRGDV). FIG. 38B shows sequence alignments of hTGFβ1-3 and the position of the RGD domains in TGFβ1 (SEQ ID NO:714) and TGFβ3 (SEQ ID NO:715). TGFβ2 (SEQ ID NO:716) does not have an RGD sequence. FIG 38C shows the sequence of three mutant D4 Vk CDR1 loops containing portions of the hTGFB3 RGD sequence (in red) developed herein (C6D4 vk (SEQ ID NO:717); C6D4-RDG1 (SEQ ID NO:718); C6D4-RDG2 (SEQ ID NO:719); and C6D4-RDG3 (SEQ ID NO:720). FIG. 38D shows a zoomed image of the D4 loop (shown in gold) and the clash with the position of the bound RGD sequence of TGFβ1 in complex with integrin αvβ6.

[0122] FIG. 39 shows cell surface staining experiments of C6Vh expressed with either RGD1, RGD2 or RGD3 mutants (as set forth in FIG. 38) as rabbit IgG. Binding to human Cho cells expressing αvβ8 was expressed as a percentage of binding of C6D4.

[0123] FIG. 40 shows cell surface staining experiments of C6Vh expressed with either D4 Vk or RGD1, RGD2 or RGD3 mutants as rabbit IgG. Binding to Cho cells expressing human αvβ8 or SW480 cells expressing αvβ6 are shown. Relative binding is defined as staining compared to staining of non-transfected Cho or SW480 cells.

[0124] FIG. 41 shows binding experiments of C6Vh expressed with either D4 Vk or RGD1, RGD2 or RGD3 mutants as rabbit IgG, to various av-integrins. All integrins were coated on ELISA plates at 2 mg/ml, blocked with BSA, and antibodies were allowed to bind. Binding of C6D4 and C6D4-RGD3 were detected with anti-rabbit HRP. The results are shown relative to control wells coated with anti-av (clone 8B8) where av-integrins were detected with another av-antibody recognizing an non-overlapping epitope (L230-biotin), followed by SA-HRP.

[0125] FIG. 42 shows the effect of cations on the binding of C6D4 and C6D4-RGD3 to various receptors. Binding in EDTA containing buffer defines cation-dependence because EDTA binds to Ca^{++} and Mg^{++}. Magnesium cation buffers contains 1 mM Ca^{++} and 1 mM Mg^{++}. Here, the results are relative to anti-av, clone 11D12V2. All antibodies were coated on ELISA plates at 5 μg/ml. The αvβ8 or αvβ6 receptors (0.5 μg/ml) were bound for 1 hour and

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were then detected with biotinylated anti-av clone 8B8. The small amount of αvβ8 binding to C6D4-RGD3 in EDTA buffer (compared with no αvβ6 binding to C6D4-RGD3 in EDTA buffer) suggests that the binding to αvβ6 is more dependent on the RGD binding loop of Vk CDR1 than the binding to αvβ8.

[0126] FIGS. 43A and 43B show inhibition of αvβ8 adhesion and TGF-beta activation. Cho 3.2.8.1 cells transfected with b8 were used in adhesion assays to wells coated with branched GRGDLGRLK peptide (SEQ ID NO:721) (10 ug/ml). Cho-b8 cells were allowed to bind in adhesion assays (FIG. 43A) in the presence of C6D4, RGD3 or control Mab at various concentrations. Cho-b8 cells were allowed to attach to wells with TMLC TGF-β reporter cells in the presence of C6D4, RGD3 or control Mab at various concentrations (FIG. 43B). The values are shown as a proportion of control Mab (SV5) control. The results indicate that C6D4-RGD3 and C6D4 block αvβ8 function similarly.

[0127] FIGS. 44A-B show adhesion assays and FIGS. 44C-D show TGF-beta activation. Here, Cho3.2.8.1 cells were transfected with GARP and LTGFB1. GARP (LRRC32) is a cell surface scaffolding molecule present on the surface of Treg cells and binds LTGF-b to the cell surface. Upper panels (FIG. 44A and 44B) show adhesion assays of Cho cells expressing GARP/LTGFB adhering to immobilized αvβ8 (FIG. 44A) or αvβ6 (FIG. 44B) performed in the presence of anti-β8 (C6D4), 3G9 (anti-β6) or the bispecific antibody RGD3 (anti-β6 and anti-β8). In the lower panels (FIG. 44C and 44D), the TGF-beta reporters cells TMLC, were added to each well to determine the amount of TGF-β activation in response to αvβ8 (FIG. 44C) or αvβ6 (FIG. 44D) performed in the presence of anti-β8 (C6D4), 3G9 (anti-β6) or the bispecific antibody RGD3 (anti-β6 and anti-β8). The results are reported as relative luciferase activity to wells treated with isotype control antibody (SV5). Below each graph is the EC50 of each inhibitory antibody.

[0128] FIG. 45 shows binding assay of αvβ6 to TGFβ3 peptide. Mab 3G9 is a potent inhibitor of αvβ6-mediated TGF-b activation. C6D4-RGD3 shows cross-competition with 3G9 binding suggesting that they have overlapping binding footprints or allosterically influence each other's binding. However, these antibodies have different modes of action as 3G9 binding to αvβ6 is not cation-dependent while C6D4-RGD3 binding is cation dependent.

[0129] FIG. 46 illustrates heavy and light chain amino acid sequences for clones used in the construction of the composite humanized antibody C6D4. VH sequences - C6D4 : all sequences (SEQ ID NO:722), Framework 1 (SEQ ID NO:732), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:734), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:736), CDR3 (SEQ ID NO:737), Framework 4 (SEQ ID NO:738); HuC6D4 V1 : all sequences (SEQ ID NO:723), Framework 1 (SEQ ID NO:739), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:740), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:741), CDR3 (SEQ ID NO:737), Framework 4 (SEQ ID NO:738); Mutclone A3 : all sequences (SEQ ID NO:724), Framework 1 (SEQ ID NO:739), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:740), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:741), CDR3 (SEQ ID NO:737), Framework 4 (SEQ ID NO:738); Mutclone B7 : all sequences (SEQ ID NO:725), Framework 1 (SEQ ID NO:742), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:740), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:743), CDR3 (SEQ ID NO:744), Framework 4 (SEQ ID NO:738); Mutclone E5 : all sequences (SEQ ID NO:726), Framework 1 (SEQ ID NO:739), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:740), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:741), CDR3 (SEQ ID NO:744), and Framework 4 (SEQ ID NO:738). VK sequences - C6D4 : all sequences (SEQ ID NO:727), Framework 1 (SEQ ID NO:745), CDR1 (SEQ ID NO:746), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:749), CDR3 (SEQ ID NO:750), Framework 4 (SEQ ID NO:751); HuC6D4 V1 : all sequences (SEQ ID NO:728), Framework 1 (SEQ ID NO:752), CDR1 (SEQ ID NO:746), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:753), CDR3 (SEQ ID NO:750), Framework 4 (SEQ ID NO:754); Mutclone A3 : all sequences (SEQ ID NO:729), Framework 1 (SEQ ID NO:755), CDR1 (SEQ ID NO:756), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:753), CDR3 (SEQ ID NO:750), Framework 4 (SEQ ID NO:754); Mutclone B7 : all sequences (SEQ ID NO:730), Framework 1 (SEQ ID NO:757), CDR1 (SEQ ID NO:746), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:758), CDR3 (SEQ ID NO:750), Framework 4 (SEQ ID NO:754); Mutclone E5 : all sequences (SEQ ID NO:731), Framework 1 (SEQ ID NO:752), CDR1 (SEQ ID NO:756), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:753), CDR3 (SEQ ID NO:750), and Framework 4 (SEQ ID NO:754).

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[0130] FIG. 47 shows binding assay of humanized C6D4 or RDG3 to recombinant αvβ8. Humanized C6D4 or RGD3 (Frameworks and CH1 are human; hinge and CH2-3 are mouse) were immobilized on ELISA plates at the indicated concentrations. As a negative control, some wells were coated with anti-SV5 at the same concentrations. Non-specific binding sites were blocked with BSA. Recombinant αvβ8 ectodomain (0.5 ug/ml) was added to each well and after binding and washing in binding buffer (1 mM Ca and Mg), the bound αvβ8 was detected with biotinylated anti-αv (8b8) and detected with SA-HRP. Results are shown as specific binding (minus SV5 control).

[0131] FIG. 48 shows superposition of C6D4/αvβ8 cartoon model with wire map of C6D4/αvβ8 (FIG. 48A and 48C) compared to a superposition of the same C6D4/αvβ8 cartoon model with wire map of C6D4-RGD3/αvβ8 (FIG. 48B and D). The comparison of the two maps shows a different orientation of the CDR1 Vk loop of C6D4-RGD3 towards the beta8 subunit ligand binding site.

[0132] FIGS. 49A-C shows CryoEM maps of C6D4 and C6D4-RGD αvβ8 complexes having similar positioning. Here, C6D4 Fab-αvβ8 (FIG. 49A) is compared with RGD3-αvβ8 map (FIG. 49B), or in overlay (FIG. 49C), based on cryoEM derived density maps. The anti-αv 11D12V2 Fab was used to increase molecular mass of the complex and to assist in particle orientation.

[0133] FIG. 50 illustrates heavy chain amino acid sequences for clones used in the construction of the composite humanized antibodies C6D4 and C6D4-RGD3. Consensus sequences for the humanized version of C6D4 and C6D4-RGD3 are provided. VH sequences - HuC6D4V1: all (SEQ ID NO:395), Framework 1 (SEQ ID NO:396), CDR1 (SEQ ID NO:397), Framework 2 (SEQ ID NO:398), CDR2 (SEQ ID NO:399), Framework 3 (SEQ ID NO:400), CDR3 (SEQ ID NO:401), and Framework 4 (SEQ ID NO:402); HuC6D4A3: all (SEQ ID NO:403), Framework 1 (SEQ ID NO:404), CDR1 (SEQ ID NO:405), Framework 2 (SEQ ID NO:406), CDR2 (SEQ ID NO:407), Framework 3 (SEQ ID NO:408), CDR3 (SEQ ID NO:409), and Framework 4 (SEQ ID NO:410); HuC6D4B7: all (SEQ ID NO:411), Framework 1 (SEQ ID NO:412), CDR1 (SEQ ID NO:413), Framework 2 (SEQ ID NO:414), CDR2 (SEQ ID NO:415), Framework 3 (SEQ ID NO:416), CDR3 (SEQ ID NO:417), and Framework 4 (SEQ ID NO:418);

HuC6D4E5: all (SEQ ID NO:419), Framework 1 (SEQ ID NO:420), CDR1 (SEQ ID NO:421), Framework 2 (SEQ ID NO:422), CDR2 (SEQ ID NO:423), Framework 3 (SEQ ID NO:424), CDR3 (SEQ ID NO:425), and Framework 4 (SEQ ID NO:426); C6D4 : all sequences (SEQ ID NO:722), Framework 1 (SEQ ID NO:732), CDR1 (SEQ ID NO:733), Framework 2 (SEQ ID NO:734), CDR2 (SEQ ID NO:735), Framework 3 (SEQ ID NO:736), CDR3 (SEQ ID NO:737), and Framework 4 (SEQ ID NO:738); HuC6D4: all (SEQ ID NO:427), Framework 1 (SEQ ID NO:428), CDR1 (SEQ ID NO:429), Framework 2 (SEQ ID NO:430), CDR2 (SEQ ID NO:431), Framework 3 (SEQ ID NO:432), CDR3 (SEQ ID NO:433), and Framework 4 (SEQ ID NO:434); C6D4-RGD3: all (SEQ ID NO:435), Framework 1 (SEQ ID NO:436), CDR1 (SEQ ID NO:437), Framework 2 (SEQ ID NO:438), CDR2 (SEQ ID NO:439), Framework 3 (SEQ ID NO:440), CDR3 (SEQ ID NO:441), and Framework 4 (SEQ ID NO:442); HuC6D4-RGD3: all (SEQ ID NO:443), Framework 1 (SEQ ID NO:444), CDR1 (SEQ ID NO:445), Framework 2 (SEQ ID NO:446), CDR2 (SEQ ID NO:447), Framework 3 (SEQ ID NO:448), CDR3 (SEQ ID NO:449), and Framework 4 (SEQ ID NO:450); and Consensus VH: Framework 1 (SEQ ID NO:558), CDR1 (SEQ ID NO:563), Framework 2 (SEQ ID NO:559), CDR2 (SEQ ID NO:563), Framework 3 (SEQ ID NO:560), CDR3 (SEQ ID NO:564), and Framework 4 (SEQ ID NO:561).

[0134] FIG. 51 illustrates light chain amino acid sequences for clones used in the construction of the composite humanized antibodies C6D4 and C6D4-RGD3. Consensus sequences for the humanized version of C6D4 and C6D4-RGD3 are provided. VL sequences - HuC6D4V1: all (SEQ ID NO:451), Framework 1 (SEQ ID NO:452), CDR1 (SEQ ID NO:453), Framework 2 (SEQ ID NO:454), CDR2 (SEQ ID NO:455), Framework 3 (SEQ ID NO:456), CDR3 (SEQ ID NO:457), and Framework 4 (SEQ ID NO:458); HuC6D4A3: all (SEQ ID NO:459), Framework 1 (SEQ ID NO:460), CDR1 (SEQ ID NO:461), Framework 2 (SEQ ID NO:462), CDR2 (SEQ ID NO:463), Framework 3 (SEQ ID NO:464), CDR3 (SEQ ID NO:465), and Framework 4 (SEQ ID NO:466); HuC6D4B7: all (SEQ ID NO:467), Framework 1 (SEQ ID NO:468), CDR1 (SEQ ID NO:469), Framework 2 (SEQ ID NO:470), CDR2 (SEQ ID NO:471), Framework 3 (SEQ ID NO:472), CDR3 (SEQ ID NO:473), and Framework 4 (SEQ ID NO:474); HuC6D4E5: all (SEQ ID NO:475), Framework 1 (SEQ ID NO:476), CDR1 (SEQ ID NO:478), Framework 2 (SEQ ID NO:479), CDR2 (SEQ ID NO:480), Framework 3 (SEQ ID NO:481), CDR3 (SEQ ID NO:482), and Framework 4 (SEQ ID NO:483); C6D4 : all sequences (SEQ ID NO:727), Framework 1

(SEQ ID NO:745), CDR1 (SEQ ID NO:746), Framework 2 (SEQ ID NO:747), CDR2 (SEQ ID NO:748), Framework 3 (SEQ ID NO:749), CDR3 (SEQ ID NO:750), and Framework 4 (SEQ ID NO:751); HuC6D4: all sequences (SEQ ID NO:484), Framework 1 (SEQ ID NO:485), CDR1 (SEQ ID NO:486), Framework 2 (SEQ ID NO:487), CDR2 (SEQ ID NO:488), Framework 3 (SEQ ID NO:489), CDR3 (SEQ ID NO:490), and Framework 4 (SEQ ID NO:491); C6D4-RGD3: all (SEQ ID NO:492), Framework 1 (SEQ ID NO:493), CDR1 (SEQ ID NO:494), Framework 2 (SEQ ID NO:495), CDR2 (SEQ ID NO:496), Framework 3 (SEQ ID NO:497), CDR3 (SEQ ID NO:498), and Framework 4 (SEQ ID NO:499); HuC6D4-RGD3: all (SEQ ID NO:500), Framework 1 (SEQ ID NO:501), CDR1 (SEQ ID NO:502), Framework 2 (SEQ ID NO:503), CDR2 (SEQ ID NO:504), Framework 3 (SEQ ID NO:505), CDR3 (SEQ ID NO:506), and Framework 4 (SEQ ID NO:507); and Consensus VL: Framework 1 (SEQ ID NO:565), CDR1 (SEQ ID NO:569), Framework 2 (SEQ ID NO:566), CDR2 (SEQ ID NO:570), Framework 3 (SEQ ID NO:567), CDR3 (SEQ ID NO:571), and Framework 4 (SEQ ID NO:568). RDG3 loop (SEQ ID NO:721).

[0135] FIG. 52 illustrates heavy chain amino acid sequences for clones used in the construction of the composite antibody F9. Sequences - 4F1 : all sequences (SEQ ID NO:624), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:628), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:634), Framework 3 (SEQ ID NO:637), CDR3 (SEQ ID NO:651), Framework 4 (SEQ ID NO:655), 6B9 : all sequences (SEQ ID NO:656), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:635), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:652), Framework 4 (SEQ ID NO:655), 6B9.1 : all sequences (SEQ ID NO:657), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:653), Framework 4 (SEQ ID NO:655), A1 : all sequences (SEQ ID NO:658), Framework 1 (SEQ ID NO:626), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:639), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A2 : all sequences (SEQ ID NO:659), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:640), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A8 : all sequences (SEQ ID NO:660), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:641),

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CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), A11 : all sequences (SEQ ID NO:661), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:630), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), B1 : all sequences (SEQ ID NO:662), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:642), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), B3 : all sequences (SEQ ID NO:663), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:643), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C4=F10 : all sequences (SEQ ID NO:664), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:644), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C7=D1 : all sequences (SEQ ID NO:665), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:644), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D3=F1 : all sequences (SEQ ID NO:666), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:645), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D10=E5 : all sequences (SEQ ID NO:667), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), E8 : all sequences (SEQ ID NO:667), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), F2 : all sequences (SEQ ID NO:667), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), G4 : all sequences (SEQ ID NO:668), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:647), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), C4 : all sequences (SEQ ID NO:669), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:650), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), D10 : all sequences (SEQ ID NO:670), Framework 1 (SEQ ID

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NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:633), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:646), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1A11 : all sequences (SEQ ID NO:671), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:650), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E1 : all sequences (SEQ ID NO:672), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1G3 : all sequences (SEQ ID NO:673), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:648), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E10 : all sequences (SEQ ID NO:674), Framework 1 (SEQ ID NO:627), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1E9 : all sequences (SEQ ID NO:675), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:629), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), 4F1H12 : all sequences (SEQ ID NO:676), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:649), CDR3 (SEQ ID NO:654), Framework 4 (SEQ ID NO:655), F9 : all sequences (SEQ ID NO:677), Framework 1 (SEQ ID NO:625), CDR1 (SEQ ID NO:631), Framework 2 (SEQ ID NO:632), CDR2 (SEQ ID NO:636), Framework 3 (SEQ ID NO:638), CDR3 (SEQ ID NO:654), and Framework 4 (SEQ ID NO:655).

[0136] FIG. 53 illustrates light chain amino acid sequences for clones used in the construction of the composite antibody F9. VL Sequences - 4F1 : all sequences (SEQ ID NO:678), Framework 1 (SEQ ID NO:692), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), 6B9 : all sequences (SEQ ID NO:679), Framework 1 (SEQ ID NO:699), CDR1 (SEQ ID NO:700), Framework 2 (SEQ ID NO:701), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:702), Framework 4 (SEQ ID NO:698), 6B9.1 : all sequences (SEQ ID NO:680), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3

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(SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A1: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A2: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A8 : all sequences (SEQ ID NO:682), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), A11 : all sequences (SEQ ID NO:683), Framework 1 (SEQ ID NO:704), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), B1 : all sequences (SEQ ID NO:684), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), B3 : all sequences (SEQ ID NO:685), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), C4=F10: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), C7=D1: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), D3=F1: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), D10=E5 : all sequences (SEQ ID NO:686), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), E8: all sequences (SEQ ID NO:686), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:755), CDR3 (SEQ ID

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NO:697), Framework 4 (SEQ ID NO:698), F2: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), G4: all sequences (SEQ ID NO:681), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), C4 : all sequences (SEQ ID NO:687), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:706), D10 : all sequences (SEQ ID NO:688), Framework 1 (SEQ ID NO:699), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:706), 4F1E1 = 1F1G3 = 4F1B5 = 4F1G11 = 4F1A9 = 4F1B9 = 4F1H9 = 4F1D10 = 4F1E9 = 4F1F10 = 4F1H11 = 4F1H12 : all sequences (SEQ ID NO:689), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), 4FA11 : all sequences (SEQ ID NO:690), Framework 1 (SEQ ID NO:705), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), Framework 4 (SEQ ID NO:698), F9 : all sequences (SEQ ID NO:691), Framework 1 (SEQ ID NO:703), CDR1 (SEQ ID NO:693), Framework 2 (SEQ ID NO:694), CDR2 (SEQ ID NO:695), Framework 3 (SEQ ID NO:696), CDR3 (SEQ ID NO:697), and Framework 4 (SEQ ID NO:706).

[0137] FIG. 54A-54D are graphs showing percentage of cells staining positive for various cell surface markers. Mice were injected with Lewis lung carcinoma (LLC) cells and SV5 (isotype control) or C6D4 at a dosage of 7 mg/kg once per week.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0138] The inventors have discovered certain antibodies that bind to human integrin αvβ8 and cause at least partial reduction in ligand binding function. Based on that discovery, they have developed detailed structural models to aid in the discovery of antibodies that bind to integrin

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αvβ8 at particular epitopes that optimally block the ligand binding site of integrin αvβ8. Some of the antibodies identified bind to both the αv-integrin subunit head domain and the β8-integrin subunit head domain to effectively cover the ligand binding site of the integrin αvβ8 without engaging to the ligand binding site itself (i.e. acting as a ligand-mimetic).

[0139] Further, the inventors have discovered that blocking ligand binding to integrin αvβ8 is effective in inhibiting cancer (including but not limited to metastatic cancer) and also is effective in treating viral infections. Without intending to limit the scope of the described invention, it is believed that integrin αvβ8 plays a role in blocking regulatory T cells (Tregs) function and/or development and thus that the antibodies described herein stimulate immunity to tumor cells and viruses. Accordingly, antibodies and methods of their use, among other aspects, are provided herein.

[0140] The inventors have also identified introduced an "RGDL" sequence (SEQ ID NO:756) into a CDR of the anti-αvβ8 antibody and have shown that such an introduction renders the antibody able to bind αvβ6 while maintaining substantially the same binding activity for αvβ8.

II. Antibodies

[0141] Provided herein are antibodies that bind human (and in some embodiments other mammalian, *e.g.*, such as mouse, guinea pig, pig, and rabbit) integrin αvβ8. In some embodiments, the antibodies are isolated, are chimeric (comprising at least some heterologous amino acid sequence), are labeled or covalently linked to another molecule such a cytotoxic agent or a combination thereof. In some embodiments, the antibodies specifically bind human integrin αvβ8 and block binding of a ligand to human integrin αvβ8. Exemplary ligands can include, for example, TGFβ and LAP. In some embodiments, the antibodies bind in a cation-dependent manner or have enhanced binding in the presence of cations.

[0142] In some embodiments the epitope bound by the antibodies described herein on human integrin αvβ8 comprise amino acids in (1) the specificity determining loop (SDL) of the integrin β8 protein (e.g., TVSPYISIHPERIHNQC**S**D**Y**N**L**DCMPPH (SEQ ID NO:620)), (2) in the α1 (e.g., SASM**H**NNIEKLNSVGNDLSRKMAFFS (SEQ ID NO:619)) or α2 (e.g., NITEFEKAV**HR** (SEQ ID NO:621)) helices of the β8 integrin protein, (3) the head of the αv

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protein (e.g., DA**D**GQ (SEQ ID NO:757); SF**Y**WQ (SEQ ID NO:758); FD**D**SY (SEQ ID NO:759)) or other portions of KQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAPCRSQDI**DADG**QGFCQGG FSIDFTKADRVLLGGPGSF**Y**WQGQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAIFD (SEQ ID NO:760) or (4) a combination thereof (e.g., 1 and 2, 2 and 3, 1 and 3, or 1, 2, and 3) as they occur in the native human integrin αvβ8 protein, including for example to all of the listed portions of human integrin αvβ8. In some embodiments, the antibody binds to one or more or all amino acid in the SDL selected from: D175 (e.g., in NL**D**CM (SEQ ID NO:761)), L174 (e.g., in YN**L**DC (SEQ ID NO:762)), or S170, D171, or Y172 (e.g., in QC**SDY**NL (SEQ ID NO:763)), or combinations thereof, wherein the numbering is based on the human integrin β8 protein (SEQ ID NO:394). *See, e.g.*, FIG. 7. In some embodiments, the antibody binds to the amino acid H118 (e.g., in SM**H**NN) (SEQ ID NO:764) in the α1 helix of the β8 integrin protein), wherein the numbering is based on the human integrin β8 protein (SEQ ID NO:394). In some embodiments, the antibody binds to the amino acid H200 or R201 (e.g., in AV**HR**Q) in the α2 helix of the β8 integrin protein, or combinations thereof, wherein the numbering is based on the human integrin β8 protein (SEQ ID NO:394). In some embodiments, the antibody binds to one or more or all amino acid (underlined) in the head of the αv protein selected from: D148, A149, D150, G151, or Y178 (e.g., in SF**Y**WQ (SEQ ID NO:758)) or combinations thereof, wherein the numbering is based on the human integrin αv protein (SEQ ID NO:393). In some embodiments, the antibody binds to each of the above indicated (underlined) amino acids described in this paragraph. As can be seen from FIGS. 12-18, interaction with the above-described domains of integrin αvβ8 is beneficial.

[0143] As noted above, in some embodiments, the antibodies specifically bind human integrin αvβ8 and block binding of a ligand to human integrin αvβ8. The ability of an antibody to block αvβ8 integrin binding of a ligand can be determined by inhibition of binding of a soluble form of αvβ8 or a full-length form of αvβ8 expressed on the surface of cells to immobilized latent-TGF-beta or a portion thereof containing the sequence RGDL *See, e.g.*, Ozawa, A, *et al. J Biol Chem.* 291(22):11551-65 (2016).

[0144] In some embodiments, the antibodies comprise one or more CDR (or all of the heavy chain CDRs of a clone, or all of the light chain CDRs of a clone) as follows:

Heavy Chains	Clone name	CDR1 Vh (SEQ ID:)	CDR2 Vh (SEQ ID:)	CDR3 Vh (SEQ ID:)
Heavy	B2B2	TFTDYSMH (313)	RINTETGEPTFADDFGG (314)	YYYGRDS (315)
Heavy	B13C4	TFTDYSMH (316)	WIKTETGEPTYADDFKG (317)	YYYGRDS (318)
Heavy	B13H3	TFTDYSMH (319)	WIKTETDEPTYADDFKE (320)	YYYGRDS (321)
Heavy	B15B11	TFTDYSMH (322)	RINTETGEPTFADDFRG (323)	YYYGRDS (324)
Heavy	B13C12	TFTDYSIH (325)	WIKTETGEPTYADDFNG (326)	YYYGRDS (327)
Heavy	A1	TFTDYSMH (328)	RINTETGEPTFADDFRG (329)	YYYGRDT (330)
Heavy	C6	TFTDYSMH (331)	RINTETGEPTFADDFRG (332)	FYYGRDS (333)

Light Chains	Clone name	CDR1 Vk	CDR2 Vk	CDR3 Vk
Light	B2B2	KASQDINSYLS (334)	RANRLVD (335)	LQYDEFPPLT (336)
Light	B13C4	KSSQSLLNSRTRKNYLA (337)	WASTRES (338)	KQSYNLLT (339)
Light	B13H3	KSSQSLLNSRIRKNYLA (340)	WASTRES (341)	KQSYNLLT (342)
Light	B15B11.1	SASSSVSYMH (343)	DTSNLAS (344)	QQWSSNPLT (345)
Light	B15B11.2	SASSSVSYMH (346)	DTSNLAS (347)	QQWSSNPPT (348)
Light	B15B11.3	KSSQSLLNSRTRKNYLA (349)	WASTRES (350)	KQSYNLLT (351)
Light	B13C12.1	SASSSVSYMH (352)	DTSKLAS (353)	QQWSSNPFT (354)
Light	B13C12.2	SASSSVSYMH (355)	GTSNLAS (356)	QQWSSNPPT (357)
Light	B13C12.3	KSSQSLLHSRTRKNYLA (358)	WASTRES (359)	KQSYNLLT (360)
Light	D4	KSSQSLLNSRTRKNYLA (361)	WASTRES (362)	KQSYNLLS (363)

[0145] In some embodiments, the antibodies comprise one or more CDR (or all of the heavy chain CDRs of a clone, or all of the light chain CDRs of a clone) as follows:

Heavy Chains	Clone name	CDR1 Vh (SEQ ID:)	CDR2 Vh (SEQ ID:)	CDR3 Vh (SEQ ID
Heavy	HuC6D4V1	DYSMH (397)	RINTETGEPTFADDFRG (399)	FYYGRDS (401)
Heavy	HuC6D4A3	DYSMH (405)	RINTETGEPTFADDFRG (407)	FYYGRDS (409)
Heavy	HuC6D4B7	DYSMH (413)	RINTETGEPTFADDFRG (415)	FYYGRDT (417)
Heavy	HuC6D4E5	DYSMH (421)	RINTETGEPTFADDFRG (423)	FYYGRDT (425)
Heavy	HuC6D4	DYSMH (429)	RINTETGEPTFADDFRG (431)	FYYGRDT (433)
Heavy	C6D4-RGD3	DYSMH (437)	RINTETGEPTFADDFRG (439)	FYYGRDS (441)
Heavy	HuC6D4-RGD3	DYSMH (445)	RINTETGEPTFADDFRG (447)	FYYGRDT (449)

Light Chains	Clone name	CDR1 Vk (SEQ ID:)	CDR2 Vk (SEQ ID:)	CDR3 Vk (SEQ ID:
Light	HuC6D4V1	KSSQSLLNSRTRKNYLA (529)	WASTRES (530)	KQSYNLLS (531)
Light	HuC6D4A3	KSSQSLLNSRSRKNYLA (532)	WASTRES (533)	KQSYNLIS (534)
Light	HuC6D4B7	KSSQSLLNSRTRKNYLA (535)	WASTRES (536)	KQSSNLIS (537)
Light	HuC6D4E5	KSSQSLLNSRSRKNYLA (538)	WASTRES (539)	KQSYNLLS (540)

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Light	HuC6D4	KSSQSLLNSRSRKNYLA (541)	WASTRES (542)	KQSYNLLS (543)
Light	C6D4-RGD3	KSSQSLLGRGDLGRLKKNALA (544)	WASTRES (545)	KQSYNLLS (546)
Light	HuC6D4--RGD3	KSSQSLLGRGDLGRLKKNALA (547)	WASTRES (548)	KQSYNLLS (549)

[0146] In some embodiments, an antibody described herein comprises heavy and light chain CDRs as paired in the following table:

Combinations (H+L	Clone name	CDR1 (SEQ ID:)	CDR2 (SEQ ID:)	CDR3 (SEQ ID:)
H	B2B2	TFTDYSMH (313)	RINTETGEPTFADDFGG (314)	YYYGRDS (315)
L	B2B2	KASQDINSYLS (334)	RANRLVD (335)	LQYDEFPPLT (33
H	B13H3	TFTDYSMH (319)	WIKTETDEPTYADDFKE (320)	YYYGRDS (321)
L	B13H3	KSSQSLLNSRIRKNYLA (340)	WASTRES (341)	KQSYNLLT (342)
H	B13C4	TFTDYSMH (316)	WIKTETGEPTYADDFKG (317(	YYYGRDS (318
L	B13C4	KSSQSLLNSRTRKNYLA (337)	WASTRES (338)	KQSYNLLT (339)
H	B15B11	TFTDYSMH (322)	RINTETGEPTFADDFRG (323)	YYYGRDS (324)
H	B15B11.1	SASSSVSYMH (343)	DTSNLAS (344)	QQWSSNPLT (345
H	B15B11	TFTDYSMH (322)	RINTETGEPTFADDFRG (323)	YYYGRDS (324)
L	B15B11.2	SASSSVSYMH (346)	DTSNLAS (347)	QQWSSNPPT (348
H	B15B11	TFTDYSMH (322)	RINTETGEPTFADDFRG (323)	YYYGRDS (324)
L	B15B11.3	KSSQSLLNSRTRKNYLA (358)	WASTRES (359)	KQSYNLLT (360)
H	B13C12	TFTDYSIH (325)	WIKTETGEPTYADDFNG (326)	YYYGRDS (327)
L	B13C12.1	SASSSVSYMH (352)	DTSKLAS (353)	QQWSSNPFT (354
H	B13C12	TFTDYSIH (325)	WIKTETGEPTYADDFNG (326)	YYYGRDS (327)
L	B13C12.2	SASSSVSYMH (355)	GTSNLAS (356)	QQWSSNPPT (357
H	B13C12	TFTDYSIH (325)	WIKTETGEPTYADDFNG (326)	YYYGRDS (327)
L	B13C12.3	KSSQSLLHSRTRKNYLA (358)	WASTRES (359)	KQSYNLLT (360)
H	RSDLVH-3	TFTDYSIH (367)	WIKTETGEPTYADDFNG (368)	YYYGRDS (369)
L	RSDLVK-10	KSSQSLLNSRTRKNYLA (373)	WASTRES (374)	KQSYNLLT (375)
H	RSDLVH-1	TFTDYSIH (364)	WIKTETGEPTYADDFKG (365)	YYYGRDS (366)
L	RSDLVK-10	KSSQSLLNSRTRKNYLA (373)	WASTRES (374)	KQSYNLLT (375)
H	RSDLVH-3	TFTDYSIH (367)	WIKTETGEPTYADDFNG (368)	YYYGRDS (369)

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L	RSDLVK-13	KSSQSLLHSRTRKNYLA (376)	WASTRES (377)	KQSYNLLT (378)
H	RSDLVH-16	TFTDYSMH (370)	RINTETGEPTFADDFRG (37	YYYGRDS (372)
L	RSDLVK-10	KSSQSLLNSRTRKNYLA (373)	WASTRES (374)	KQSYNLLT (375)
H	C6H	TFTDYSMH (766)	RINTETGEPTFADDFRG (767)	FYYGRDS (768)
L	C6K	KSSQSLLNSRTRKNYLA (382)	WASTRES (383)	KQSYNLLT (384)
H	D4H	TFTDYSMH (379)	RINTETGEPTFADDFRG (380)	YYYGRDS (381)
L	D4K	KSSQSLLNSRTRKNYLA (361)	WASTRES (362)	KQSYNLLS (363)
H	C6H	TFTDYSMH (766)	RINTETGEPTFADDFRG (767)	FYYGRDS (768)
L	D4K	KSSQSLLNSRTRKNYLA (361)	WASTRES (362)	KQSYNLLS (363)

[0147] In some embodiments, an antibody described herein comprises heavy and light chain CDRs as paired in the following table:

Combinations (H+L)	Clone name	CDR1 (SEQ ID:)	CDR2 (SEQ ID:)	CDR3 (SEQ ID
H	HuC6D4V1	DYSMH (397)	RINTETGEPTFADDFRG (398)	FYYGRDS (399
L	HuC6D4V1	KSSQSLLNSRTRKNYLA (529)	WASTRES (530)	KQSYNLLS (531)
H	HuC6D4A3	DYSMH (405)	RINTETGEPTFADDFRG (407)	FYYGRDS (409)
L	HuC6D4A3	KSSQSLLNSRSRKNYLA (532)	WASTRES (533)	KQSYNLIS (534)
H	HuC6D4B7	DYSMH (413)	RINTETGEPTFADDFRG (415)	FYYGRDT (417)
L	HuC6D4B7	KSSQSLLNSRTRKNYLA (535)	WASTRES (536)	KQSSNLIS (537)
H	HuC6D4E5	DYSMH (421)	RINTETGEPTFADDFRG (423)	FYYGRDT (425)
L	HuC6D4E5	KSSQSLLNSRSRKNYLA (538)	WASTRES (539)	KQSYNLLS (540)
H	HuC6D4	DYSMH (429)	RINTETGEPTFADDFRG (431)	FYYGRDT (433)
L	HuC6D4	KSSQSLLNSRSRKNYLA (541)	WASTRES (542)	KQSYNLLS (543)
H	C6D4-RGD3	DYSMH (437)	RINTETGEPTFADDFRG (439)	FYYGRDS (441)
L	C6D4-RGD3	KSSQSLLGRGDLGRLKKNALA (544)	WASTRES (545)	KQSYNLLS (546)
H	HuC6D4-RGD3	DYSMH (445)	RINTETGEPTFADDFRG (447)	FYYGRDT (449)
L	HuC6D4-RGD3	KSSQSLLGRGDLGRLKKNALA (547)	WASTRES (548)	KQSYNLLS (549)

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H	C6D4	DYSMH (123)	RINTETGEPTFADDFRG (125)	FYYGRDS (127)
L	C6D4	KSSQSLLNSRSRKNYLA (291)	WASTRES (293)	KQSYNLLS (295)
H	C6RGD2	DYSMH (769)	RINTETGEPTFADDFRG (770)	FYYGRDS (771)
L	C6RGD2	KSSQSLLNSGRGDLGNALA (772)	WASTRES (773)	KQSYNLIS (774)
H	C6RGD3-1	DYSMH (775)	RINTETGEPTFADDFRG (776)	FYYGRDT (777)
L	C6RGD3-1	KSSQSLLGRGDLGRLKKQKDHNALA (778)	WASTRES (779)	KQSSNLIS (780)
H	C6RGD3-2	DYSMH (781)	RINTETGEPTFADDFRG (782)	FYYGRDY (783)
L	C6RGD3-2	KSSQSLLGRGDLGRLKKQKDNALA (784)	WASTRES (785)	KQSYNLLS (786)
H	C6RGD3-3	DYSMH (787)	RINTETGEPTFADDFRG (788)	FYYGRDT (789)
L	C6RGD3-3	KSSQSLLGRGDLGRLKKQKNALA (790)	WASTRES (791)	KQSYNLLS (792)
H	C6RGD3-4	DYSMH (793)	RINTETGEPTFADDFRG (794)	FYYGRDS (795)
L	C6RGD3-4	KSSQSLLGRGDLGRLKKQNALA (796)	WASTRES (797)	KQSYNLLS (798)
H	C6RGD3	DYSMH (799)	RINTETGEPTFADDFRG (800)	FYYGRDT (801
L	C6RGD3	KSSQSLLGRGDLGRLKKNALA (802)	WASTRES (803)	KQSYNLLS (804)
H	C6RGD3-6	DYSMH (805)	RINTETGEPTFADDFRG (806)	FYYGRDS (807
L	C6RGD3-6	KSSQSLLGRGDLGRLKNALA (808)	WASTRES (809)	KQSYNLLS (810)
H	C6RDG3-7	DYSMH (811)	RINTETGEPTFADDFRG (812)	FYYGRDS (813)
L	C6RGD3-7	KSSQSLLGRGDLGRLNALA (814)	WASTRES (815)	KQSYNLIS (816)
H	C6RGD3-8	DYSMH (817)	RINTETGEPTFADDFRG (818)	FYYGRDT (819)
L	C6RGD3-8	KSSQSLLGRGDLGRNALA (820)	WASTRES (821)	KQSSNLIS (822)
H	C6RGD1	DYSMH (823)	RINTETGEPTFADDFRG (824)	FYYGRDY (825)
L	C6RGD1	KSSQSLLGRGDLGNALA (826)	WASTRES (827)	KQSYNLLS (828)
H	C6RGD3-9	DYSMH (829)	RINTETGEPTFADDFRG (830)	FYYGRDT (831)
L	C6RGD3-9	KSSQSLLGRGDLGRLKKQKDHH (832)	WASTRES (833)	KQSYNLLS (834)
H	C6RGD3-10	DYSMH (835)	RINTETGEPTFADDFRG (836)	FYYGRDS (837)
L	C6RGD3-10	KSSQSLLGRGDLGRLKKQKDH (838)	WASTRES (839)	KQSYNLLS (840)
H	C6RGD3-11	DYSMH (841)	RINTETGEPTFADDFRG (842)	FYYGRDT (843)
L	C6RGD3-11	KSSQSLLGRGDLGRLKKQKD (844	WASTRES (845)	KQSYNLLS (846)

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H	C6RGD3-12	DYSMH (847)	RINTETGEPTFADDFRG (848)	FYYGRDT (849)
L	C6RGD3-12	KSSQSLLGRGDLGRLKKQK (850)	WASTRES (851)	KQSSNLIS (852)
H	C6RGD3-13	DYSMH (853)	RINTETGEPTFADDFRG (854)	FYYGRDY (855)
L	C6RGD3-13	KSSQSLLGRGDLGRLKKQ (856)	WASTRES (857)	KQSYNLLS (858)
H	C6RGD3-14	DYSMH (859)	RINTETGEPTFADDFRG (860)	FYYGRDT (861)
L	C6RGD3-14	KSSQSLLGRGDLGRLKK (862)	WASTRES (863)	KQSYNLLS (864)
H	C6RGD3-15	DYSMH (865)	RINTETGEPTFADDFRG (866)	FYYGRDS (867)
L	C6RGD3-15	KSSQSLLGRGDLGRLK (868)	WASTRES (869)	KQSYNLLS (870)
H	C6RGD3-16	DYSMH (871)	RINTETGEPTFADDFRG (872)	FYYGRDT (873)
L	C6RGD3-16	KSSQSLLGRGDLGRL (874)	WASTRES (875)	KQSYNLLS (876)

[0148] In some embodiments, an antibody as described herein comprises one, two, three or all four of the framework sequences as provided here:

Frameworks	Fr 1 (SEQ ID NO:)	Fr2 (SEQ ID NO:)
H	(Q)IQL(L)(Q)SGPELKKPGETVKISCKASGY (385)	WVKQAPGKGLKW(V)A (386)
	E M E	M
	Where (X) can be specified AA	
L	(D)IVM(T)QSPSSLAV(S)AGE(K)VT(M)SC (389)	WYQQKPGQSP(R)LLIY (390)
	E S P N V	K
	Where (X) can be specified AA all alternatives listed under	

Frameworks	Fr3 (SEQ ID NO:)	Fr4 (SEQ ID NO:)
H	RFA(V)SLETSASTAYLQINNLKNEDTATYFCAI (387(	WGQGTT(L)TVSS (388
	F	V
L	GVPDRFTGSGSGTDFTLTISSVQAEDLAVY(Y)C (391)	FGAGT(K)LE(L)K (392)
	F	R I

[0149] In some embodiments, an antibody as described herein comprises one, two, three or all four of the framework sequences as provided here:

Frameworks	Fr 1 (SEQ ID NO:)	Fr2 (SEQ ID NO:)
H	QIQLVQSG(P)(E)(L)KKPG(E)(T)VKISCKASGYTFT (550)	WV(K)QAPG(K)GL(K)WVA (551)
	A K V A S	R Q E
	Where (X) can be specified AA	

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L	(D)IVMTQ(S)P(S)(S)L(A)VS(A)GE(K)VTMSC (554)	WYQQKPGQSPRLLIY (555)
	E T A T S P R	A
	V I	

Frameworks Fr3 (SEQ ID NO:)

H	RF(A)V(S)L(E)TS(A)STAYL(Q)I(N)(N)L(K)(N)(E)DTA(T)YFCAI (552)	
	T T D T E R S R S D V	
	S T	
	Where (X) can be specified AA all alternatives listed under	
L	(G)VP(D)RF(T)GSGSGT(D)FTLTISSVQ(A)ED(L)AVYYC (556)	
	D A S E S F	
Frameworks	Fr4 (SEQ ID NO:)	
H	WGQGT(T)LTVSS (553)	
	A	
L	FG(A)GT(K)LE(L)KR (557)	
	Q V I	

[0150] In some embodiments, an antibody as described herein comprises one, two, three or all four of the framework sequences as provided here:

Frameworks Fr 1 (SEQ ID NO:) Fr2 (SEQ ID NO:)

H	QIQL(V)QSG(P)(E)(L)KKPG(E)(T)VKISCKASGYTFT (550)	WV(K)QAPG(K)GL(K)W(V)(A) (877)
	L A K V A S	R Q E M G
	Where (X) can be specified AA	
L	(D)IVM(T)Q(S)P(S)(S)L(A)VS(A)GE(K)VTMSC (880)	WYQQKPGQ(S)PRLLIY (881)
	E S T A T S P R	A
	V I	

Frameworks Fr3 (SEQ ID NO:)

H	RF(A)(V)(S)L(E)TS(A)(S)TA(Y)L(Q)I(N)(N)L(K)(N)(E)DTA(T)YFCAI (878)	
	T F T D T T N E R S R S D V S I K	
	T	
	Where (X) can be specified AA all alternatives listed under	
L	(G)VP(D)RF(T)GSGSGT(D)FTLTISSVQ(A)ED(L)AVYYC (882)	
	D A S E S F D	
Frameworks	Fr4 (SEQ ID NO:)	
H	WGQGT(T)LTVSS (879)	
	A	
L	FG(A)GT(K)LE(I)KR (883)	
	Q V L	

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[0151] In some embodiments, the antibodies comprise the CDR1, CDR2, and CDR3 heavy chain sequences as provided herein, including but not limited to, e.g.,

SEQ ID NO:3, SEQ ID NO:5, and SEQ ID NO:7;
SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15;
SEQ ID NO:19, SEQ ID NO:21, and SEQ ID NO:23;
SEQ ID NO:27, SEQ ID NO:29, and SEQ ID NO:31;
SEQ ID NO:35, SEQ ID NO:37, and SEQ ID NO:39;
SEQ ID NO:43, SEQ ID NO:45, and SEQ ID NO:47;
SEQ ID NO:51, SEQ ID NO:53, and SEQ ID NO:55;
SEQ ID NO:59, SEQ ID NO:61, and SEQ ID NO:63;
SEQ ID NO:67, SEQ ID NO:69, and SEQ ID NO:71;
SEQ ID NO:75, SEQ ID NO:77, and SEQ ID NO:79;
SEQ ID NO:83, SEQ ID NO:85, and SEQ ID NO:87;
SEQ ID NO:91, SEQ ID NO:93, and SEQ ID NO:95;
SEQ ID NO:99, SEQ ID NO:101, and SEQ ID NO:103;
SEQ ID NO:107, SEQ ID NO:109, and SEQ ID NO:111;
SEQ ID NO:115, SEQ ID NO:117, and SEQ ID NO:119;
SEQ ID NO:123, SEQ ID NO:125, and SEQ ID NO:127;
SEQ ID NO:291, SEQ ID NO:293, and SEQ ID NO:295;
SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:315;
SEQ ID NO:316, SEQ ID NO:317, and SEQ ID NO:318;
SEQ ID NO:319, SEQ ID NO:320, and SEQ ID NO:321;
SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324;
SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327;
SEQ ID NO:328, SEQ ID NO:329, and SEQ ID NO:330;
SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333;
SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369;
SEQ ID NO:364, SEQ ID NO:365, and SEQ ID NO:366;
SEQ ID NO:370, SEQ ID NO:371, and SEQ ID NO:372;
SEQ ID NO:379, SEQ ID NO:380, and SEQ ID NO:381;
SEQ ID NO:397, SEQ ID NO:399, and SEQ ID NO:401;

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SEQ ID NO:405, SEQ ID NO:407, and SEQ ID NO:409;
SEQ ID NO:413, SEQ ID NO:415, and SEQ ID NO:417;
SEQ ID NO:421, SEQ ID NO:423, and SEQ ID NO:425; or
SEQ ID NO:429, SEQ ID NO:431, and SEQ ID NO:433.

[0152] In some embodiments, the antibodies comprise the heavy chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above.

[0153] In some embodiments, the antibodies comprise the light chain CDR1, CDR2, and CDR3 sequences as provided herein, including but not limited to, e.g.,

SEQ ID NO:131, SEQ ID NO:133, and SEQ ID NO:135;
SEQ ID NO:139, SEQ ID NO:141, and SEQ ID NO:143 ;
SEQ ID NO:147, SEQ ID NO:149, and SEQ ID NO:151 ;
SEQ ID NO:155, SEQ ID NO:157, and SEQ ID NO:159 ;
SEQ ID NO:163, SEQ ID NO:165, and SEQ ID NO:167 ;
SEQ ID NO:171, SEQ ID NO:173, and SEQ ID NO:175 ;
SEQ ID NO:179, SEQ ID NO:181, and SEQ ID NO:183 ;
SEQ ID NO:187, SEQ ID NO:189, and SEQ ID NO:191 ;
SEQ ID NO:195, SEQ ID NO:197, and SEQ ID NO:199 ;
SEQ ID NO:203, SEQ ID NO:205, and SEQ ID NO:207 ;
SEQ ID NO:211, SEQ ID NO:213, and SEQ ID NO:215 ;
SEQ ID NO:219, SEQ ID NO:221, and SEQ ID NO:223 ;
SEQ ID NO:227, SEQ ID NO:229, and SEQ ID NO:231 ;
SEQ ID NO:243, SEQ ID NO:245, and SEQ ID NO:247 ;
SEQ ID NO:251, SEQ ID NO:253, and SEQ ID NO:255 ;
SEQ ID NO:259, SEQ ID NO:261, and SEQ ID NO:263 ;
SEQ ID NO:267, SEQ ID NO:269, and SEQ ID NO:271 ;
SEQ ID NO:275, SEQ ID NO:277, and SEQ ID NO:279 ;
SEQ ID NO:283, SEQ ID NO:285, and SEQ ID NO:287 ;
SEQ ID NO:291, SEQ ID NO:293, and SEQ ID NO:295;
SEQ ID NO:307, SEQ ID NO:309, and SEQ ID NO:311;

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SEQ ID NO:334, SEQ ID NO:335, and SEQ ID NO:336;
SEQ ID NO:337, SEQ ID NO:338, and SEQ ID NO:339;
SEQ ID NO:340, SEQ ID NO:341, and SEQ ID NO:342;
SEQ ID NO:343, SEQ ID NO:344, and SEQ ID NO:345;
SEQ ID NO:346, SEQ ID NO:347, and SEQ ID NO:348;
SEQ ID NO:349, SEQ ID NO:350, and SEQ ID NO:351;
SEQ ID NO:352, SEQ ID NO:353, and SEQ ID NO:354;
SEQ ID NO:355, SEQ ID NO:356, and SEQ ID NO:357;
SEQ ID NO:358, SEQ ID NO:359, and SEQ ID NO:360;
SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363;
SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375;
SEQ ID NO:376, SEQ ID NO:377, and SEQ ID NO:378;
SEQ ID NO:382, SEQ ID NO:383, and SEQ ID NO:384;
SEQ ID NO:453, SEQ ID NO:455, and SEQ ID NO:457;
SEQ ID NO:461, SEQ ID NO:463, and SEQ ID NO:465;
SEQ ID NO:469, SEQ ID NO:471, and SEQ ID NO:473;
SEQ ID NO:478, SEQ ID NO:480, and SEQ ID NO:482; or
SEQ ID NO:486, SEQ ID NO:488, and SEQ ID NO:490.

[0154] In some embodiments, the antibodies comprise the light chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above. In some embodiments, the light chain CDR1 sequence is 12-18 amino acids long, , e.g., 14-17, e.g., 12, 13, 14, 15, 16, 17, or 18 amino acids long.

[0155] In some embodiments, the antibodies comprise the heavy and light chain CDR1, CDR2, and CDR3 sequences as provided herein, including but not limited to, e.g.,

heavy chain CDRs SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:315; and light chain CDRs SEQ ID NO:334, SEQ ID NO:335, and SEQ ID NO:336; or

heavy chain CDRs SEQ ID NO:319, SEQ ID NO:320, and SEQ ID NO:321; and light chain CDRs SEQ ID NO:340, SEQ ID NO:341, and SEQ ID NO:342; or

heavy chain CDRs SEQ ID NO:316, SEQ ID NO:317, and SEQ ID NO:318; and light chain CDRs SEQ ID NO:337, SEQ ID NO:338, and SEQ ID NO:339; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:343, SEQ ID NO:344, and SEQ ID NO:345; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:346, SEQ ID NO:347, and SEQ ID NO:348; or

heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:349, SEQ ID NO:350, and SEQ ID NO:351; or

heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:352, SEQ ID NO:353, and SEQ ID NO:354; or

heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:355, SEQ ID NO:356, and SEQ ID NO:357; or

heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:358, SEQ ID NO:359, and SEQ ID NO:360; or

heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:364, SEQ ID NO:365, and SEQ ID NO:366; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:376, SEQ ID NO:377, and SEQ ID NO:378; or

heavy chain CDRs SEQ ID NO:370, SEQ ID NO:371, and SEQ ID NO:372; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:382, SEQ ID NO:383, and SEQ ID NO:384; or

heavy chain CDRs SEQ ID NO:379, SEQ ID NO:380, and SEQ ID NO:381; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:508, SEQ ID NO:509, and SEQ ID NO:510; and light chain CDRs SEQ ID NO:529, SEQ ID NO:530, and SEQ ID NO:531; or

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heavy chain CDRs SEQ ID NO:511, SEQ ID NO:512, and SEQ ID NO:513; and light chain CDRs SEQ ID NO:532, SEQ ID NO:533, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:514, SEQ ID NO:515, and SEQ ID NO:516; and light chain CDRs SEQ ID NO:535, SEQ ID NO:536, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:517, SEQ ID NO:518, and SEQ ID NO:519; and light chain CDRs SEQ ID NO:538, SEQ ID NO:539, and SEQ ID NO:540; or

heavy chain CDRs SEQ ID NO:520, SEQ ID NO:521, and SEQ ID NO:522; and light chain CDRs SEQ ID NO:541, SEQ ID NO:542, and SEQ ID NO:543; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:544, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528; and light chain CDRs SEQ ID NO:547, SEQ ID NO:548, and SEQ ID NO:549.

[0156] In some embodiments, the antibodies comprise the heavy and light chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above.

[0157] In some embodiments, any antibody described herein can comprise a light chain CDR1 comprising a RGD sequence, e.g., as provided in the following table:

CDR_{L1}	Vk
KSSQSLLNSRSRKNYLA (SEQ ID NO:572)	D4
KSSQSLLNSGRGDLGNALA (SEQ ID NO:574)	RGD2
KSSQSLLGRGDLGRLKKQKDHNALA (SEQ ID NO:576)	RGD3-1
KSSQSLLGRGDLGRLKKQKDNALA (SEQ ID NO:577)	RGD3-2
KSSQSLLGRGDLGRLKKQKNALA (SEQ ID NO:578)	RGD3-3
KSSQSLLGRGDLGRLKKQNALA(SEQ ID NO:579)	RGD3-4
KSSQSLLGRGDLGRLKKNALA (SEQ ID NO:575)	RGD3
KSSQSLLGRGDLGRLKNALA (SEQ ID NO:580)	RGD3-6
KSSQSLLGRGDLGRLNALA(SEQ ID NO:581)	RGD3-7
KSSQSLLGRGDLGRNALA (SEQ ID NO:582)	RGD3-8
KSSQSLLGRGDLGNALA (SEQ ID NO:573)	RGD1
KSSQSLLGRGDLGRLKKQKDHH (SEQ ID NO:583)	RGD3-9
KSSQSLLGRGDLGRLKKQKDH (SEQ ID NO:584)	RGD3-10
KSSQSLLGRGDLGRLKKQKD (SEQ ID NO:585)	RGD3-11
KSSQSLLGRGDLGRLKKQK (SEQ ID NO:586)	RGD3-12
KSSQSLLGRGDLGRLKKQ (SEQ ID NO:587)	RGD3-13
KSSQSLLGRGDLGRLKK (SEQ ID NO:588)	RGD3-14
KSSQSLLGRGDLGRLK (SEQ ID NO:589)	RGD3-15

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KSSQSLLGRGDLGRL (SEQ ID NO:590)	RGD3-16

[0158] In some embodiments, any of the antibodies described herein can comprise as CDR1 one of the CDRs selected from SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, and SEQ ID NO:590.

[0159] In some embodiments, the antibody can comprise heavy and light chain CDR1, CDR2, and CDR3 sequences as provided below, including but not limited to, e.g.,

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:572, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:573, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:574, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:575, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:576, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:577, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:578, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:579, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:580, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:581, SEQ ID NO:545, and SEQ ID NO:546; or

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heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:582, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:583, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:584, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:585, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:586, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:587, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:589, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:590, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:572, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:573, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:574, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:575, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:576, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:577, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:578, SEQ ID NO:545, and SEQ ID NO:534; or

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heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:579, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:580, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:581, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:582, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:583, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:584, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:585, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:586, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:587, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:588, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:589, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:590, SEQ ID NO:545, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:572, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:573, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:574, SEQ ID NO:545, and SEQ ID NO:537; or

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heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:575, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:576, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:577, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:578, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:579, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:580, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:581, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:582, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:583, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:584, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:585, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:586, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:587, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:588, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:589, SEQ ID NO:545, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:590, SEQ ID NO:545, and SEQ ID NO:537.

[0160] In some embodiments, the antibodies comprise the heavy and light chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above.

[0161] In some embodiments, any of the antibodies disclosed herein can comprise one of the heavy chain variable regions selected from SEQ ID NO:1, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:33, SEQ ID NO:41, SEQ ID NO:49, SEQ ID NO:57, SEQ ID NO:65, SEQ ID NO:73, SEQ ID NO:81, SEQ ID NO:89, SEQ ID NO:97, SEQ ID NO:105, SEQ ID NO:113, SEQ ID NO:121, or SEQ ID NO:297, or SEQ ID NO:395, SEQ ID NO:403, SEQ ID NO:411, SEQ ID NO:419, SEQ ID NO:427, SEQ ID NO:435, or SEQ ID NO:443.

[0162] In some embodiments, any of the antibodies disclosed herein can comprise one of the light chain variable regions selected from SEQ ID NO:129, SEQ ID NO:137, SEQ ID NO:145, SEQ ID NO:153, SEQ ID NO:161, SEQ ID NO:169, SEQ ID NO:177, SEQ ID NO:185, SEQ ID NO:193, SEQ ID NO:201, SEQ ID NO:209, SEQ ID NO:217, SEQ ID NO:225, SEQ ID NO:233, SEQ ID NO:241, SEQ ID NO:249, SEQ ID NO:257, SEQ ID NO:265, SEQ ID NO:273, SEQ ID NO:281, SEQ ID NO:289, SEQ ID NO:305, or SEQ ID NO:451, SEQ ID NO:459, SEQ ID NO:467, SEQ ID NO:475, SEQ ID NO:484, SEQ ID NO:492, or SEQ ID NO:500.

[0163] In some embodiments, the antibodies disclosed here can comprise one or more or all of the light chain variable regions (CDRs or framework regions) selected from SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, or SEQ ID NO:571.

[0164] In some embodiments, any of the antibodies disclosed herein can comprise one or more or all of the heavy chain variable regions (CDRs or framework regions) selected from SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, or SEQ ID NO:564.

[0165] Heavy chain variable regions can be paired with light chain regions as desired, including or not limited to for variable regions comprising the paired CDRs as set forth above.

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[0166] In addition, as noted above, the inventors have discovered that an RGDL sequence (SEQ ID NO:756) can be inserted into a light chain CDR1 sequence in an αvβ8-binding antibody to obtain an antibody that has six CDRs in total and that binds both αvβ8 and αvβ6. The antibodies at least partially block ligand binding function. See, *e.g.*, FIGS. 38A-D. Thus in some embodiments, antibodies are provided that bind to αvβ8 and αvβ6 and comprise an RGDL sequence (SEQ ID NO:756) in the light chain CDR1 sequence. For instance, in some embodiments the light chain CDR1 is between 20-22 amino acids (e.g., 21 amino acids) an optionally comprises KSSQSLLGRGDLGRLKK (SEQ ID NO:765) or a sequence containing 1, 2, or 3 conservative amino acid substitutions.

[0167] Additionally, the inventors have discovered that an RGDL sequence (SEQ ID NO:756) can be inserted into a light chain CDR1 sequence in an αvβ8-binding antibody to obtain an antibody that has six CDRs and that binds αvβ8, αvβ6 and αvβ3 (*i.e.*, is tri-specific). See, Example 12.

[0168] In some embodiments, any antibody described herein can comprise a light chain CDR1 sequence selected from, but not limited to, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, and SEQ ID NO:590. In some embodiments, any of the light chain CDR1 sequences set forth in this paragraph can be combined with any light chain CDR2, light chain CDR3, heavy chain CDR1, heavy chain CDR2 and heavy chain CDR3, set forth herein.

[0169] In some embodiments, antibodies comprising the light chain CDR1 sequences described in the preceding paragraph can contain 1, 2, or 3 conservative amino acid substitutions in the CDR1 sequence compared to those listed above (*i.e.*, SEQ ID NO:572-590).

[0170] In some embodiments, the antibodies can comprise the heavy chain CDR1, CDR2, and CDR3 sequences as provided herein, including but not limited to, e.g.,

SEQ ID NO:437, SEQ ID NO:439, and SEQ ID NO:441; or
SEQ ID NO:445, SEQ ID NO:447, and SEQ ID NO:449.

[0171] In some embodiments, the antibodies can comprise the heavy chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above.

[0172] In some embodiments, the antibodies can comprise the light chain CDR1, CDR2, and CDR3 sequences as provided herein, including but not limited to, e.g.,

SEQ ID NO:494, SEQ ID NO:496, and SEQ ID NO:498; or
SEQ ID NO:502, SEQ ID NO:504, and SEQ ID NO:506.

[0173] In some embodiments, the antibodies can comprise the light chain CDR1, CDR2, and CDR3 sequences described above but contain 1, 2, or 3 conservative amino acid substitutions in one, two or more CDR sequences compared to those listed above.

[0174] Heavy chain variable regions can be paired with light chain regions as desired, including or not limited to for variable regions comprising the paired CDRs as set forth above.

[0175] For preparation and use of suitable antibodies as described herein, *e.g.*, recombinant, monoclonal, or polyclonal antibodies, many techniques known in the art can be used (*see*, *e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4: 72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. (1985); Coligan, *Current Protocols in Immunology* (1991); Harlow & Lane, *Antibodies, A Laboratory Manual* (1988); and Goding, *Monoclonal Antibodies: Principles and Practice* (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, *e.g.*, the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (*see, e.g.*, Kuby, *Immunology* (3rd ed. 1997)). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Patent 4,946,778, U.S. Patent No. 4,816,567) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, can be used to express humanized or human antibodies (*see, e.g.*, U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks *et al.*, *Bio/Technology* 10:779-783 (1992); Lonberg *et al.*, *Nature*

368:856-859 (1994); Morrison, *Nature* 368:812-13 (1994); Fishwild *et al.*, *Nature Biotechnology* 14:845-51 (1996); Neuberger, *Nature Biotechnology* 14:826 (1996); and Lonberg & Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990); Marks *et al.*, *Biotechnology* 10:779-783 (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (*see, e.g.*, WO 93/08829, Traunecker *et al.*, *EMBO J.* 10:3655-3659 (1991); and Suresh *et al.*, *Methods in Enzymology* 121:210 (1986)). Antibodies can also be heteroconjugates, *e.g.*, two covalently joined antibodies, or immunotoxins (*see, e.g.*, U.S. Patent No. 4,676,980 , WO 91/00360; WO 92/200373; and EP 03089).

[0176] Antibodies can be produced using any number of expression systems, including prokaryotic and eukaryotic expression systems. In some embodiments, the expression system is a mammalian cell expression, such as a hybridoma, or a CHO cell expression system. Many such systems are widely available from commercial suppliers. In embodiments in which an antibody comprises both a V_H and V_L region, the V_H and V_L regions may be expressed using a single vector, *e.g.*, in a di-cistronic expression unit, or under the control of different promoters. In other embodiments, the V_H and V_L region may be expressed using separate vectors. A V_H or V_L region as described herein may optionally comprise a methionine at the N-terminus.

[0177] An antibody as described herein can also be produced in various formats, including as a Fab, a Fab', a $F(ab')_2$, a scFv, or a dAB. The antibody fragments can be obtained by a variety of methods, including, digestion of an intact antibody with an enzyme, such as pepsin (to generate $(Fab')_2$ fragments) or papain (to generate Fab fragments); or *de novo* synthesis. Antibody fragments can also be synthesized using recombinant DNA methodology. In some embodiments, an anti-β8 antibody comprises $F(ab')_2$ fragments that specifically bind β8. An antibody of the invention can also include a human constant region. See, *e.g.*, Fundamental Immunology (Paul ed., 4d ed. 1999); Bird, *et al.*, *Science* 242:423 (1988); and Huston, *et al.*, *Proc. Natl. Acad. Sci. USA* 85:5879 (1988).

[0178] Methods for humanizing or primatizing non-human antibodies are also known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to

as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (*see, e.g.*, Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-327 (1988); Verhoeyen *et al.*, *Science* 239:1534-1536 (1988) and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0179] In some cases, the antibody or antibody fragment can be conjugated to another molecule, *e.g.*, polyethylene glycol (PEGylation) or serum albumin, to provide an extended half-life *in vivo*. Examples of PEGylation of antibody fragments are provided in Knight *et al. Platelets* 15:409, 2004 (for abciximab); Pedley *et al.*, *Br. J. Cancer* 70:1126, 1994 (for an anti-CEA antibody); Chapman *et al.*, *Nature Biotech.* 17:780, 1999; and Humphreys, *et al.*, *Protein Eng. Des.* 20: 227,2007). The antibody or antibody fragment can also be labeled, or conjugated to a therapeutic agent as described below.

[0180] The specificity of antibody binding can be defined in terms of the comparative dissociation constants (Kd) of the antibody for the target (*e.g.*, β8) as compared to the dissociation constant with respect to the antibody and other materials in the environment or unrelated molecules in general. Typically, the Kd for the antibody with respect to the unrelated material will be at least 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, 200-fold or higher than Kd with respect to the target.

[0181] The desired affinity for an antibody, *e.g.*, high (pM to low nM), medium (low nM to 100nM), or low (about 100nM or higher), may differ depending upon whether it is being used as a diagnostic or therapeutic. For example, an antibody with medium affinity may be more successful in localizing to desired tissue as compared to one with a high affinity. Thus, antibodies having different affinities can be used for diagnostic and therapeutic applications.

[0182] A targeting moiety will typically bind with a Kd of less than about 1000 nM, *e.g.*, less than 250, 100, 50, 20 or lower nM. In some embodiments, the Kd of the affinity agent is less

than 15, 10, 5, or 1 nM. In some embodiments, the Kd is 1-100 nM, 0.1-50 nM, 0.1-10 nM, or 1-20 nM. The value of the dissociation constant (Kd) can be determined by well-known methods, and can be computed even for complex mixtures by methods as disclosed, *e.g.*, in Caceci *et al.*, Byte (1984) 9:340-362.

[0183] Affinity of an antibody, or any targeting agent, for a target can be determined according to methods known in the art, *e.g.*, as reviewed in Ernst *et al.* Determination of Equilibrium Dissociation Constants, Therapeutic Monoclonal Antibodies (Wiley & Sons ed. 2009).

[0184] Quantitative ELISA, and similar array-based affinity methods can be used. ELISA (Enzyme linked immunosorbent signaling assay) is an antibody-based method. In some cases, an antibody specific for target of interest is affixed to a substrate, and contacted with a sample suspected of containing the target. The surface is then washed to remove unbound substances. Target binding can be detected in a variety of ways, *e.g.*, using a second step with a labeled antibody, direct labeling of the target, or labeling of the primary antibody with a label that is detectable upon antigen binding. In some cases, the antigen is affixed to the substrate (*e.g.*, using a substrate with high affinity for proteins, or a Strepavidin-biotin interaction) and detected using a labeled antibody (or other targeting moiety). Several permutations of the original ELISA methods have been developed and are known in the art (see Lequin (2005) *Clin. Chem.* 51:2415-18 for a review).

[0185] The Kd, Kon, and Koff can also be determined using surface plasmon resonance (SPR), *e.g.*, as measured by using a Biacore T100 system or using kinetic exclusion assays (e.g., KinExA®). SPR techniques are reviewed, *e.g.*, in Hahnfeld *et al.* Determination of Kinetic Data Using SPR Biosensors, Molecular Diagnosis of Infectious Diseases (2004). In a typical SPR experiment, one interactant (target or targeting agent) is immobilized on an SPR-active, gold-coated glass slide in a flow cell, and a sample containing the other interactant is introduced to flow across the surface. When light of a given frequency is shined on the surface, the changes to the optical reflectivity of the gold indicate binding, and the kinetics of binding. Kinetic exclusion assays is the preferred method to determine affinity unless indicated otherwise. This technique is described in, e.g. Darling *et al.*, *Assay and Drug Development Technologies* Vol. 2, number 6 647-657 (2004).

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[0186] Binding affinity can also be determined by anchoring a biotinylated interactant to a streptavidin (SA) sensor chip. The other interactant is then contacted with the chip and detected, *e.g.*, as described in Abdessamad *et al.* (2002) *Nuc. Acids Res.* 30:e45.

[0187] Also provided are polynucleotides encoding the antibodies described herein ,or binding fragments thereof comprising at least heavy chain or light chain CDRs or both, *e.g.*, polynucleotides, expression cassettes (e.g., a promoter linked to a coding sequence), or expression vectors encoding heavy or light chain variable regions or segments comprising the complementary determining regions as described herein. In some embodiments, the polynucleotide sequence is optimized for expression, e.g., optimized for mammalian expression or optimized for expression in a particular cell type.

III. Methods of treatment

[0188] The anti-αvβ8 antibodies described herein (including αvβ8 binding fragments thereof, labeled antibodies, immunoconjugates, pharmaceutical compositions, etc.) as well as antibodies that bind both αvβ8 and αvβ6 as described herein or binding fragments thereof can be used to detect, treat, ameliorate, or prevent chronic obstructive pulmonary disease (COPD) and asthma, inflammatory bowel disease, inflammatory brain autoimmune disease, multiple sclerosis, a demylinating disease (*e.g.*, transverse myelitis, Devic's disease, Guillain-Barré syndrome), neuroinflammation, kidney disease, or glioma, arthritis, fibrotic disorders, such as airway fibrosis, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, post-infectious lung fibrosis, diffuse alveolar damage, collagen-vascular disease associated lung fibrosis, drug-induced lung fibrosis, silicosis, asbestos-related lung fibrosis, respiratory bronchiolitis, respiratory bronchiolitis interstitial lung disease, desquamative interstitial fibrosis, cryptogenic organizing pneumonia, chronic hypersensitivity pneumonia, drug-related lung or hepatic fibrosis, renal fibrosis, and liver fibrosis (*e.g.*, induced by alcohol, drug use, steatohepatitis, viral infection (*e.g.*, hepatitis B or C), choleostasis, etc., and cancer, including but not limited to adenocarcinoma, squamous carcinoma, breast carcinoma, and cancer growth and metastasis. Accordingly, the antibodies and pharmaceutical compositions described herein can be administered to a human having or suspected of having one of the above-listed diseases in an appropriate dosage to ameliorate or treat one of the disease or at least one symptom thereof.

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[0189] Without intending to limit the scope of the invention, in some embodiments it is believed that antibodies described herein function in part by triggering an increase in MHCII expression in antigen presenting cells. *See, e.g.*, FIG. 36A-F.

[0190] Moreover, the anti-αvβ8 antibodies described herein (including αvβ8 binding fragments thereof, labeled antibodies, immunoconjugates, pharmaceutical compositions, etc.) can be used to treat, ameliorate, or prevent viral infections (e.g., by stimulating an immune response). Other antibodies that specifically bind to αvβ8 and that block binding of one or more αvβ8 ligand, for example such as described in WO2011/103490 or WO2015/026004 can also be used to treat, ameliorate, or prevent viral infections. Exemplary viral infections include but are not limited to hepatitis A, B (HBV), and C (HCV), herpes simplex virus (e.g., HSVI, HSVII), HIV, and influenza infections, all of which are enhanced by Treg-mediated immune suppression (Keynan, Y, *et al.*, *Clin Infect Dis.* 2008 Apr 1;46(7):1046-52.

[0191] Also provided are pharmaceutical compositions comprising the present anti-αvβ8 antibodies or antigen-binding molecules as well as antibodies that bind both αvβ8 and αvβ6 as described herein or binding fragments thereof, either of which can be formulated together with a pharmaceutically acceptable carrier. The compositions can additionally contain other therapeutic agents that are suitable for treating or preventing a given disorder. Pharmaceutically carriers can enhance or stabilize the composition, or to facilitate preparation of the composition. Pharmaceutically acceptable carriers include solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[0192] A pharmaceutical composition as described herein can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, or administered proximal to the site of the target. The pharmaceutically acceptable carrier should be suitable for intravenous, intramuscular, subcutaneous, parenteral, intranasal, inhalational, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, i.e., antibody, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

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[0193] The antibodies, alone or in combination with other suitable components, can be made into aerosol formulations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0194] In some embodiments, the composition is sterile and fluid. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

[0195] Pharmaceutical compositions of the invention can be prepared in accordance with methods well known and routinely practiced in the art. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention. Applicable methods for formulating the antibodies and determining appropriate dosing and scheduling can be found, for example, in *Remington: The Science and Practice of Pharmacy*, 21st Ed., University of the Sciences in Philadelphia, Eds., Lippincott Williams & Wilkins (2005); and in *Martindale: The Complete Drug Reference*, Sweetman, 2005, London: Pharmaceutical Press., and in Martindale, *Martindale: The Extra Pharmacopoeia*, 31st Edition., 1996, Amer Pharmaceutical Assn, and Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically, a therapeutically effective dose or efficacious dose of the anti-αvβ8 antibody is employed in the pharmaceutical compositions of the invention. The anti-αvβ8 antibodies are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the desired response (e.g., a therapeutic response). In determining a therapeutically or prophylactically effective dose, a low dose can be administered and then incrementally increased until a desired response is achieved with minimal

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or no undesired side effects. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0196] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

[0197] In some embodiments, the pharmacological compositions comprise a mixture of the anti-αvβ8 antibody or antigen binding molecule (e.g. that blocks ligand binding or blocks activation by ligand binding) and a second pharmacological agent. Without intending to limit the invention, it is noted that the inventors have found that thymic stromal lymphopoietin (TSLP) is an inducer of viral clearance in a mouse model of acute and chronic HBV and thus is useful to combine TSLP with an antbody as described herein for anti-viral treatments. Moreover, the inventors have found that OX40 agonists are effective in stimulating an immune response to HBV in combination with an antbody as described herein.

[0198] As an alternative to mixing the anti-αvβ8 antibody and second pharmacological agent in a pharmacological composition, the anti-αvβ8 antibody and second pharmacological agent can be separately administered to the human in need thereof within a time frame (e.g., within 3, 2, o 1 day or within 24, 13, 6, or 3 hours of each other).

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IV. Diagnostic compositions and applications

[0199] Integrin αvβ8 is expressed on fibroblasts, stellate cells, chondrocytes, activated macrophages and subsets of T and B-cells. Integrin αvβ8 is increased in expression in fibroblasts in COPD and pulmonary fibrosis, and can be used as a surrogate marker for increased fibroblast cell mass. Thus the presently disclosed antibodies can be broadly applicable to bioimaging strategies to detect fibroinflammatory processes. The presently described therapeutic and diagnostic antibodies can be applied to: inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), asthma, arthritis, a hepatic fibroinflammatory disorder, alcohol induced liver injury, non-alcoholic steatohepatitis (NASH), viral hepatitis, and primary biliary cirrhosis (PBC), graft rejection after liver transplantation, autoimmune hepatitis, an autoimmune disorder, lupus erythematosus, scleroderma, dermatomyositis, bullous pemphigoid, pemphigus vulgaris, a pulmonary fibrotic disorder, an inflammatory brain autoimmune disease, multiple sclerosis, a demyelinating disease, neuroinflammation, kidney disease, glomerulonephritis, hepatocellular carcinoma (HCC), adenocarcinoma, squamous carcinoma, glioma, melanoma, prostate, ovarian, uterine and breast carcinoma.

The inventors have found that β8 and PD-L1 expression inversely correlate. Thus, anti-αvβ8 antibodies described herein can be used as a marker for PD-L1 expression and optionally for selecting invenniduals most likely to benefit from anti-αvβ8 treatment.

[0200] Anti-αvβ8 antibodies described herein (including αvβ8 binding fragments thereof, affinity matured variants, or scFvs) can be used for diagnosis, either *in vivo* or *in vitro* (*e.g.*, using a biological sample obtained from an individual). In addition to the above-described antibodies, antibodies having the following CDRs can be used for diagnosis and prognosis: heavy chain CDRs SEQ ID NO:299, SEQ ID NO:301, and SEQ ID NO:303; and light chain CDRs SEQ ID NO:307, SEQ ID NO:309, and SEQ ID NO:311. In some embodiments, the antibodies have a heavy chain variable region comprising SEQ ID NO:297 and a light chain variable region of SEQ ID NO:305. Alternatively, any antibodies having heavy chain CDRs or a heavy chain variable region as set forth in FIG. 53 and light chain CDRs or a light chain variable region from a corresponding sequence as set forth in FIG. 54 can be used. The antibodies are particularly useful in detecting αvβ8 in samples that have been fixed, for example in formalin-

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fixed samples, including for example formalin-fixed paraffin-embedded (FFPE) biological (e.g., tissue or cell) samples.

[0201] When used for detection or diagnosis, the antibody is typically conjugated or otherwise associated with a detectable label. The association can be direct *e.g.*, a covalent bond, or indirect, *e.g.*, using a secondary binding agent, chelator, or linker.

[0202] A labeled antibody can be provided to an individual to determine the applicability of an intended therapy. For example, a labeled antibody may be used to detect the integrin β8 density within a diseased area. For therapies intended to target TGFβ or αvβ8 activity (to reduce TGFβ or αvβ8 activity), the density of β8 is typically high relative to non-diseased tissue. A labeled antibody can also indicate that the diseased area is accessible for therapy. Patients can thus be selected for therapy based on imaging results. Anatomical characterization, such as determining the precise boundaries of a cancer, can be accomplished using standard imaging techniques (*e.g.*, CT scanning, MRI, PET scanning, etc.). Such *in vivo* methods can be carried out using any of the presently disclosed antibodies.

[0203] Any of the presently disclosed antibodies can also be used for *in vitro* diagnostic or monitoring methods, *e.g.*, using cells or tissue from a patient sample. In some embodiments, labeled F9 (or a β8 binding fragment or affinity-matured variant) is used, as it can bind fixed cells as well as non-fixed cells.

[0204] In some embodiments, the diagnostic antibody is a single-chain variable fragment (scFv). Intact antibodies (*e.g.*, IgG) can be used for radioimmunotherapy or targeted delivery of therapeutic agents because they exhibit high uptake and retention. In some cases, the persistence in circulation of intact mAbs can result in high background (Olafsen *et al.* (2012) *Tumour Biol.* 33:669-77; Cai *et al.* (2007) *J Nucl Med.* 48:304-10). ScFvs, typically with a molecular mass of ~ 25kD, are rapidly excreted by the kidneys, but are monovalent and can have lower affinity. The issues of monovalency can be overcome with advanced antibody engineering (as shown herein), where affinities can be improved to the low nM to pM range. Such antibodies have short enough half-lives to be useful as imaging agents and have suitable binding characteristics for tissue targeting (Cortez-Retamozo *et al.* (2004) *Cancer Res.* 64:2853-7). As shown herein, we have created a very high affinity scFV antibody derivatives of 4F1, 6B9 , called F9, that can

be converted to humanized scFV platforms. These improved antibodies are not function blocking, and thus can be used in combination with a therapeutic agent that targets β8.

[0205] A diagnostic agent comprising an antibody described herein can include any diagnostic agent known in the art, as provided, for example, in the following references: Armstrong *et al.*, *Diagnostic Imaging*, 5th Ed., Blackwell Publishing (2004); Torchilin, V. P., Ed., *Targeted Delivery of Imaging Agents*, CRC Press (1995); Vallabhajosula, S., *Molecular Imaging: Radiopharmaceuticals for PET and SPECT*, Springer (2009). The terms "detectable agent," "detectable moiety," "label," "imaging agent," and like terms are used synonymously herein. A diagnostic agent can be detected by a variety of ways, including as an agent providing and/or enhancing a detectable signal. Detectable signals include, but are not limited to, gamma-emitting, radioactive, echogenic, optical, fluorescent, absorptive, magnetic, or tomography signals. Techniques for imaging the diagnostic agent can include, but are not limited to, single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), optical imaging, positron emission tomography (PET), computed tomography (CT), x-ray imaging, gamma ray imaging, and the like. PET is particularly sensitive and quantitative, and thus valuable for characterizing fibrotic processes *in vivo* (Olafsen *et al.* (2012) *Tumour Biol.* 33:669-77; Cai *et al.* (2007) *J Nucl Med.* 48:304-10). This is useful beyond a companion diagnostic and would be generally useful to diagnose, clinically stage and follow fibrotic patients during any treatment regimen.

[0206] A radioisotope can be incorporated into the diagnostic agents described herein and can include radionuclides that emit gamma rays, positrons, beta and alpha particles, and X-rays. Suitable radionuclides include but are not limited to ^{225}Ac, ^{72}As, ^{211}At, ^{11}B, ^{128}Ba, ^{212}Bi, ^{75}Br, ^{77}Br, ^{14}C, ^{109}Cd, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{18}F, ^{67}Ga, ^{68}Ga, ^{3}H, ^{166}Ho, ^{123}I, ^{124}I, ^{125}I, ^{130}I, ^{131}I, ^{111}In, ^{177}Lu, ^{13}N, ^{15}O, ^{32}P, ^{33}P, ^{212}Pb, ^{103}Pd, ^{186}Re, ^{188}Re, ^{47}Sc, ^{153}Sm, ^{89}Sr, ^{99m}Tc, ^{88}Y and ^{90}Y. In certain embodiments, radioactive agents can include ^{111}In-DTPA, ^{99m}Tc(CO)$_3$-DTPA, ^{99m}Tc(CO)$_3$-ENPy2, $^{62/64/67}$Cu-TETA, ^{99m}Tc(CO)$_3$-IDA, and ^{99m}Tc(CO)$_3$triamines (cyclic or linear). In other embodiments, the agents can include DOTA and its various analogs with ^{111}In, ^{177}Lu, ^{153}Sm, $^{88/90}$Y, $^{62/64/67}$Cu, or $^{67/68}$Ga. In some embodiments, a nanoparticle can be labeled by incorporation of lipids attached to chelates, such as DTPA-lipid, as provided in the following references: Phillips *et al.*, *Wiley Interdisciplinary Reviews: Nanomedicine and*

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Nanobiotechnology, 1(1): 69-83 (2008); Torchilin, V.P. & Weissig, V., Eds. *Liposomes 2nd Ed.*: Oxford Univ. Press (2003); Elbayoumi, T.A. & Torchilin, V.P., *Eur. J. Nucl. Med. Mol. Imaging* 33:1196–1205 (2006); Mougin-Degraef, M. *et al.*, *Int'l J. Pharmaceutics* 344:110-117 (2007).

[0207] In some embodiments, a diagnostic agent can include chelators that bind, *e.g.*, to metal ions to be used for a variety of diagnostic imaging techniques. Exemplary chelators include but are not limited to ethylenediaminetetraacetic acid (EDTA), [4-(1,4,8, 11-tetraazacyclotetradec-1-yl) methyl] benzoic acid (CPTA), Cyclohexanediaminetetraacetic acid (CDTA), ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA), diethylenetriaminepentaacetic acid (DTPA), citric acid, hydroxyethyl ethylenediamine triacetic acid (HEDTA), iminodiacetic acid (IDA), triethylene tetraamine hexaacetic acid (TTHA), 1,4,7, 10-tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid) (DOTP), 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), N^1,N^1-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (ENPy2) and derivatives thereof.

[0208] In some embodiments, the diagnostic agent can be associated with a secondary binding ligand or to an enzyme (an enzyme tag) that will generate a colored product upon contact with a chromogenic substrate. Examples of suitable enzymes include urease, alkaline phosphatase, (horseradish) hydrogen peroxidase and glucose oxidase. Secondary binding ligands include, *e.g.*, biotin and avidin or streptavidin compounds as known in the art.

[0209] In some embodiments, the diagnostic agents can include optical agents such as fluorescent agents, phosphorescent agents, chemiluminescent agents, and the like. Numerous agents (*e.g.*, dyes, probes, labels, or indicators) are known in the art and can be used in the present invention. (*See, e.g.*, Invitrogen, The Handbook—A Guide to Fluorescent Probes and Labeling Technologies, Tenth Edition (2005)). Fluorescent agents can include a variety of organic and/or inorganic small molecules or a variety of fluorescent proteins and derivatives thereof. For example, fluorescent agents can include but are not limited to cyanines, phthalocyanines, porphyrins, indocyanines, rhodamines, phenoxazines, phenylxanthenes, phenothiazines, phenoselenazines, fluoresceins, benzoporphyrins, squaraines, dipyrrolo pyrimidones, tetracenes, quinolines, pyrazines, corrins, croconiums, acridones, phenanthridines, rhodamines, acridines, anthraquinones, chalcogenopyrylium analogues, chlorins, naphthalocyanines, methine dyes, indolenium dyes, azo compounds, azulenes, azaazulenes,

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triphenyl methane dyes, indoles, benzoindoles, indocarbocyanines, benzoindocarbocyanines, and BODIPY™ derivatives.

EXAMPLES

[0210] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1. Construction of composite antibody C6D4

[0211] ITGB-8 knockout mice were immunized with recombinant Human Integrin alpha V beta 8 (αvβ8) protein. Approximately 5000 hybridomas were generated and screened for their ability to bind to αvβ8 in an enzyme-linked immunosorbent assay (ELISA). Results were confirmed by cell staining, and function blocking was determined with the use of a transforming growth factor-beta (TGF-β) bioassay. Blocking antibodies were screened against a recombinant form of αvβ8 engineered to lack the specificity determining loop (SDL) of the β8 head domain. Antibodies not binding this engineered αvβ8 were then selected.

[0212] Variable (V) genes from eight hybridomas were next isolated, sequenced, and found to comprise seven V_H and eleven V_K genes that were unique but related. FIG. 1 and FIG. 2 provide sequence information for the products of these V_H and V_K genes. Sequence information is using the Kabat numbering scheme. Each V gene was amplified under mutagenic conditions, and a single-chain variable fragment (scFV) library was constructed by mixing the amplified cDNA and using splice overlap. The library served as an amplification template using primers designed to complement rabbit IgG expressing dual V_H and V_L vectors. Eleven distinct V_H genes and sixteen distinct V_K genes were identified after sequencing >100 random clones and transfected in 165 different combinations into 293 cells. The eight pairs that produced the best binders were determined by cell staining and FACS analysis, and by measuring binding affinity for CHO cells expressing αvβ8. The eight pairs each comprised a V_H domain selected from RSDLVH-1, RSDLVH-3, and RSDLVH-16; and a V_K domain selected from RSDLVK-1, RSDLVK-6, RSDLVK-10, and RSDLVK-13; the sequences of which are shown in FIG. 1 and FIG. 2 .

[0213] These eight rabbit IgG V_H/V_K pairs were then used to create a new mutagenic scFV yeast display library that was inserted into a yeast expression library vector. Two high-affinity binders from this selection and affinity maturation step were identified and designated clone 29 and clone 44. Random mutation mutagenic libraries were next made from genes of clones 29

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and 44, and from these libraries the higher-affinity binding clones C6 and D4 were selected and determined (FIG. 1 and FIG. 2). Mutations in the complementarity-determining regions (CDRs) of C6 V_H and D4 V_K were identified, and the two chains were combined to create the composite antibody C6D4 (FIG. 1 and FIG. 2).

Example 2. Characterization of C6D4 binding affinity

[0214] A Kinetic Exclusion Assay (KINEXA ®) was used to measure the binding affinity of C6D4. The affinity as a murine IgG2a was measured as 832 pM. As a recombinant IgG, C6D4 was found to result in substantially complete blockage of αvβ8-mediated TGF-β activation. This result implies blockage that is better than with B5, an allosteric inhibitor of αvβ8-mediated TGF-β activation. (Minagawa, et al, *Sci Trans Med.* 2014 Jun 18;6(241):241ra79)

[0215] C6D4 was also shown to block adhesion of cells to immobilized latent TGF-β. A peptide with the sequence DDHGRGDLGRLK (SEQ ID NO:713), which corresponds to aa 257-268 of human TGF-β3 (NP_003230) was synthesized on an 8 lysine core (Multiple antigen presenting peptide, BioSyn) and used at 1 ug/ml to coat a 96 well ELISA plate. A truncated secreted form of αvβ8 which was fused in frame to alkaline phosphatase (Gline SE, *et al. J Biol Chem.* 2004 Dec 24; 279(52):54567-72) was added with Mab at the indicated concentrations. The results (FIG. 19) show the superiority of C6D4 over B5 and the improvement of C6D4 compared to Clone 13C12. The table gives the IC50 values in μg/ml.

[0216] Further, a peptide with the sequence DDHGRGDLGRLK (SEQ ID NO:713), which corresponds to aa 257-268 of human TGF-β3 (NP_003230) was synthesized on an 8 lysine core (Multiple antigen presenting peptide, BioSyn) and used at 0.51 ug/ml to coat a 96 well ELISA plate. CHO lec cells stably transfected with αvβ8 were allowed to bind to the peptide coated wells for 30 min at RT. Unbound cells were washed off with PBS. The Mab C6D4 was added at the indicated concentrations. Results were presented as stained cells detected after staining with crystal violet (OD590). The results (FIG. 20) show that C6D4 almost completely blocks cell adhesion to the peptide.

Example 3. Characterization of C6D4 binding structure

[0217] The current understanding of integrin structure is faced with the hurdle of having to reconcile two polar opposite views of integrin conformation. One camp proposes that integrins are always bent. The other believes that integrins must undergo a significant conformational "switchblade" change from a bent conformation to an extended conformation upon activation, opening the "headpieces" of the integrins to be fully functional. This model of integrin extension proposes one of the largest tertiary and quaternary structural rearrangements in biology.

[0218] Proof of such conformational extremes has been hampered by compromises and shortcomings associated with techniques routinely used in structural biology. Traditional crystallography produces crystal structures with atomic resolution but is reliant on the conformations and conditions under which crystals can be formed. In the case of integrins, only compact, closed conformations have been seen by crystallography. Alternatively, size exclusion chromatography (SEC) of integrins under activating conditions have demonstrated large shifts in size consistent with integrin extension. Such changes in conformation have been directly visualized using negative stain electron microscopy (EM) studies but at low resolution. Thus, the atomic details of the integrin ligand binding and the integrin activation mechanism remains unresolved.

[0219] Single-particle cryo-electron microscopy (cryoEM) can be used to determine the structure of biological macromolecules without crystals, thus offering an alternative that circumvents the obstacles of crystalizing integrins in the extended form. Recent hardware and software developments demonstrate that single-particle cryoEM has the power to provide atomic-level structural understanding of molecules that are traditionally challenging to study. Because single-particle cryoEM does not require the formation of crystals, and allows examination in the native functional conformations unaffected by crystal packing forces or high-salt crystallization buffers, this method is uniquely suited to understanding structures of proteins or integrin-ligand or integrin-Fab complexes that are difficult to crystallize. Here, we have used single particle cryoEM to address some of the biggest mysteries in structural biology, the structural mechanisms of integrin activation and conversely the mechanism of action of integrin inhibitors.

[0220] Previously published crystal structures of the latent TGF-β arginine-glycyine-aspartic acid (RGD) peptide of αvβ6 show the positioning of the TGF-β RGD in the αvβ6 binding pocket,

as well as the positioning of the R of the TGF-β RGD proximate to the αv head. Cryo-electron microscopy of the new composite antibody C6D4 structure have now produced a ~4-5-angstrom-resolution structure of the C6D4 Fab binding to αvβ8. To generate the structures of αvβ8 in complex with C6D4, purified recombinant αvβ8 and C6D4 Fab complexes were isolated by size exclusion chromatography and then plunge frozen on grids in liquid nitrogen. Images of ~61,000 individual particle images captured by electron microscopy were selected to produce a 3D electron density map which was used to build model of αvβ8 in complex with C6D4 Fab using existing Protein Data Bank (PDB) entries for the integrin αvβ3, αIIbβ3, and Fabs with similar CDRs.

[0221] FIGS. 13A and 13B presents cryoEM results showing binding of the C6D4 Fab to the integrin αvβ8 at the head domain. FIGS. 13A and 13B illustrate this binding between C6D4 and αvβ8 in closer detail. From the C6D4 antibody footprint of FIG. 6, it can be seen that C6D4 binds primarily to the SDL loop of β8, making additional contacts with other secondary structures on the β8 α1 and α2 helices and on the head of αv. Together, these components of the binding configuration result in the almost complete occlusion of the ligand binding pocket. The residues of the β8 α1 and α2 helices and αv head that directly interact with C6D4 are further detailed in FIG. 7.

[0222] The elucidated structure shows that the CDR1 domain of the D4 V_L binds close to the contact site for the R of RGD in the previously published αvβ6-RGD crystal structure. Because the αv subunit is shared by both αvβ6 and αvβ8, this finding suggests that the CDR1 loop of D4 V_L is optimally positioned to sterically inhibit the binding of the R of RGD of latent TGF-β to αvβ8. On the other side of the SDL is a hydrophobic binding pocket having an L that immediately follows the RGD, forming an RGDL peptide. This hydrophobic pocket has been shown to be essential as a secondary binding site for the binding of the latent TGF-β RGD peptide to αvβ6. *See, e.g.*, Shi M, *et al.*, *Nature* 474(7351):343-9 (2011). The L or RGDL has also been shown to be essential for the binding of the latent TGF-β RGD peptide to αvβ8. (See, *e.g.*, Ozawa, A, *et al. J Biol Chem.* 291(22):11551-65 (2016). The CDR3 loop of C6 V_H has now been shown to bind in such a way as to substantially cover the hydrophobic binding pocket located on the β8 subunit head domain. Additionally, C6D4 was found to interact extensively with the SDL of β8. FIG. 8 illustrates the overlapping of the C6D4 epitope with the ligand

binding pocket of integrin αvβ8, showing how it can prevent the association of the integrin with latent TGF-β, and thus the activation of latent TGF-β. Importantly, all contact residues with C6D4 are believed to be conserved in αvβ8 across all mammalian species. This is in contrast to the allosteric inhibitor B5, which only reacts significantly against human αvβ8.

Example 4. Modeling of C6D4 effects on lung cancer survival

[0223] Syngeneic models for the study of lung cancer are very limited. The Lewis lung carcinoma (LLC) model is the only reproducible syngeneic lung cancer model currently widely in use. LLC is a cell line established from the lung of a C57BL mouse bearing a primary Lewis lung carcinoma. This line is highly tumorigenic and is used to model pulmonary metastasis that results after resection of the primary tumor. In this way the model mimics the clinical scenario closely. It is a useful model for evaluating the efficacy of chemotherapeutic agents *in vivo*. An advantage of the LLC model is that tumor cells are immunologically compatible, unlike the immunodeficient strains used in most other xenograft models. The LLC model was used as a preclinical model to evaluate vinorelbine prior to its use in clinical trials. The LLC cell line is injected subcutaneously into the subcutis of C57B6 mice, and within two weeks primary tumors reproducibly reach sizes of 10 mm. After resection of the primary tumor, lung metastasis appears in 2-4 weeks. The primary endpoints in this model are weight loss and lung metastasis number.

[0224] FIG. 9 presents result indicating that C6D4 increases survival in the LLC model. Mice received intraperitoneal injections of either C6D4 murine IgG2a or SV5 isotype control (7mg/kg) at the time of primary tumor removal (day 0), and then once every week until weight loss exceeded 20%. The positive results indicate the first demonstration of an anti-β8 antibody inhibiting lung cancer metastasis. The fact that C6D4 inhibits lung cancer metastasis in this model indicates its potential as a treatment to prevent lung cancer metastasis. Because the mechanism of this antibody in cancer likely involves inhibiting the function or development of immunosuppressive Treg cells, C6D4 can have broad applications to any number of cancers where Treg cells play an immunosuppressive role.

[0225] FIG. 28 provides a schematic of the LLC model used herein to evaluate lung metastasis. The LLC tumor cell line is syngeneic to the host C57B/6 strain. This cell line does not express the integrins αvβ6 or αvβ8. The LLC.1 cell line has been passed though mice one

time and regrown from lung metastasis. After two weeks, subcutaneously injected tumor ($1x10^6$) LLC.1 cells form large tumor nodules (~1cm). The tumors are removed surgically and when animals lose 20% of their body weight they are euthanized.

[0226] The LLC model lung metastasis experiment described in the preceding paragraph was repeated eleven (11) times and the results in each of the eleven experiments were found to be similar (data not shown). FIGS. 29A and 29B present data from the eleventh experiment indicating that C6D4 increases survival in the LLC model. In each instance, mice received intraperitoneal injections of either C6D4 murine IgG2a or SV5 isotype control (7mg/kg) at the time of primary tumor removal (day 0), and then once every week until weight loss exceeded 20%. The results indicate the anti-β8 antibody (C6D4) inhibits lung cancer metastasis. Survival curves in FIG. 29A represent mice euthanized for reasons of local recurrence or weight loss. In FIG. 29B, the animals removed for local recurrence are excluded. At autopsy, the animals with 20% weight loss all have metastatic implants in their lungs. The C6D4 antibodies were injected for up to 90 days in surviving animals. Interestingly, post-mortem examination did not reveal any abnormal inflammatory response in the tissues examined. The fact that C6D4 inhibits lung cancer metastasis in this model indicates its potential as a treatment to prevent lung cancer metastasis. Because the mechanism of this antibody in cancer likely involves inhibiting the function or development of immunosuppressive Treg cells, C6D4 can have broad applications to any number of cancers where Treg cells play an immunosuppressive role.

[0227] The effect of C6D4 was also evaluated with respect to tumor growth and tumor immune response. From the resected LLC.1 primary tumors in mice that received two injections of isotype control (B5, which only cross reacts with human and not mouse b8) or C6D4 (which cross-reacts with mouse and human), the primary tumor weights were recorded and dimensions measured. The tumors were enzymatically disaggregated and immune cells isolated and counted. Flow cytometry was performed and tumor infiltrating immune cells separated from tumor cells using Percoll gradient centrifugation. FIGS. 30A-F is one of three experiments with similar results (remaining data not shown). In each experiment, n was greater than, or equal to, 10 in each test group.

Example 5. C6D4 effects on metastatic disease using a melanoma disease model

[0228] A model for the study of metastasis was tested herein that utilized the B16-F10 tumor cell line. The B16-F10 highly metastatic tumor cell line is syngenic to the host C57B/6 strain. This line does not express the integrins αvβ6 or αvβ8. The B16-F10 cell line was transfected with murine ITGb8 and after selection in G418 and two rounds of sorting, a pool of high expressing αvβ8 cells were identified. When injected intravenously via the tail vein, visible lung metastases appeared within 14 days. A schematic of the metastatic disease melanoma model described in this paragraph is provided in FIG. 31. After three injections (i.p.) of isotype control (SV5) or C6D4, both at 7 mg/kg, at days 0, 7 and 14, the mice were euthanized at day 18. FIG. 34A shows photographs of representative lungs in anterior and posterior views; visible lung metastases were counted and the total lung surface area involved with metastases was assessed. FIG. 34B shows the total number of metastases and FIG. 34C shows the percentage of total lung surface area involved in metastatic melanoma.

Example 6. Modeling of C6D4 effects on hepatitis B infection and disease outcome

[0229] Because the hepatitis B virus (HBV) does not infect mice, research has typically focused on using transgenic and knockout mouse models to study HBV immunity. In this model, viral antigens in the liver are exposed to an immune system that is not immunologically tolerant, and that has not been previously exposed to HBV. The goal is to mimic the immunologic events that would normally occur during primary HBV infection. In addition, this model permits manipulation of the immune system that is exposed to the virus, to be able to identify and dissect the cells, cytokines, and chemokines contributing to chronic hepatitis or disease resolution.

[0230] To generate the model, the resident (tolerized) immune system of the HBV-transgenic mice is ablated by backcrossing to immune-deficient strains (Mombaerts *et al.* (1992) *Nature* 360:225 and Mombaerts *et al.* (1992) *Cell* 68:869). This breeding strategy generates animals expressing high levels of viral antigen (HBV-Env) or virus (HBV-replication) in the liver, in the absence of a tolerant immune system (Baron *et al.* (2002) *Immunity* 16:583). Into these mice, HBV-naive syngeneic splenocytes (the equivalent of a whole spleen) are transferred from wild-type mice to reconstitute the immune system, mimic the point of primary infection, and test the importance of cellular and soluble mediators in HBV pathogenesis. Careful monitoring of

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immune responses and pathologic outcomes has revealed the utility of this model in mimicking or modifying acute and chronic HBV infection (Publicover *et al.* (2011) *J. Clin. Investigation* 2011:1154 and Publicover *et al.* (2013) *J. Clin. Investigation* 123:3728). In this way, the mouse model provides an experimental system to examine the reversibility of the altered immune priming that facilitates HBV persistence, and to test immune-modulatory therapeutics.

[0231] Results shown in FIG. 10 indictate that C6D4 induces HBV viral clearance in the chronic infection mouse model without causing hepatitis. In the figure, HepB surface anitigen (HBSag) is a surrogate for intact HBV. Clearance of HBSag is a marker of HBV clearance. ALT is the liver enzyme monitored to measure liver inflammation and damage. The normal range of ALT in mice is 15-40. It can be seen from the data that the C6D4 antibody promoted HBsAg clearance in three of four chronic HBV model mice.

Example 7. Construction and characterization of composite antibody 4F1F9

[0232] A yeast display scFV library was created using V-genes from hybridoma clones 6B9 and 4F1, a new clone 6B9.1 was selected from this library, then another yeast display scFV library was created using the V-gene of 6B9.1 and random mutagenesis, sixteen affinity-matured variant from this second library were characterized in terms of binding affinity and two clones C4 and D10 were transformed in to rabbit IgG format, both reacts weakly with human β8 in formalin-fixed paraffin-embedded tissue. A third mutagenic scFV library was then created from the variable regions of these two antibodies and inserted in a phage display vector and displayed as scFv on the phage surface (FIG. 11A-B). The induced phage library was screened against immobilized paraffin-embedded human αvβ8. Multiple rounds of selection were carried out, and fifteen phage clones were characterized in detail before the final clone F9 (FIG. 11A-B) was picked and transformed into IgG format for in vitro characterization.

[0233] Clone F9 in the IgG format was found to work efficiently in formalin-fixed paraffin-embedded tissues. The clone can be suitable for use as a companion diagnostic, for example to determine tumors expressing αvβ8 or infiltrated by immune cells expressing αvβ8 (i.e. dendritic cells, Treg cells), as a bioimaging reagent for measuring β8-specific tumor uptake and for informing C6D4 treatment decisions. The F9 antibody can also be used to detect αvβ8 in fluid or tissue lysate samples using ELISA.

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Example 8. Methods to inhibit and/or treat *H. Pylori* pathogenicity

[0234] The bacterium *Helicobacter pylori* (*H. pylori*) infects the stomachs of approximately half of the world's population and is associated with peptic ulcer disease, gastric carcinoma and gastric lymphoma (MALToma). The pathogenicity of *Helicobacter pylori* is linked to a type IV secretion system and the cytotoxicity-associated gene pathogenicity island cagPAI. The cagPAI proteins are transcribed from a 40kb stretch of *H. pylori* DNA encoding ~31 genes of which one, cagL, contains an RGDL integrin binding motif. This RGDL motif is thought to act as a receptor for integrins so that the *H. pylori* pilus can interact with gastric epithelial cells and then penetrate the cell membrane and the oncogenic toxin cagA can be injected into the cell (see Kwok, et al, *Nature*, , 2007449, 862-866, and Barden, et al, *Journal of Molecular Biology*, 2015, 427 (6) Part B, 1304-1315). We have used the anti-β8 clone F9 to stain human stomach biopsies and have found that the integrin αvβ8 is expressed by gastric crypt epithelial cells and this expression is increased in patients with chronic active gastritis due to H. pylori infection (see FIG. 21 and 22). The ectodomain of integrins αvβ6 and αvβ8, but not other RGD-binding integrins (αvβ1, αvβ3, αvβ5 and α5β1) have been shown to preferentially bind to CagL via an RGDL dependent mechanism (see Barden, et al, *Gastroenterology*, 2010, 138(3). Previously, it was thought that the α5β1 integrin was the main CagL receptor on gastric epithelial cells (see Kwok, et al, *Nature*, 2007, 449 (7164):862-6. We have found that the integrins αvβ6 and αvβ8 bind with similar efficiency to CagL while the αvβ3 integrin does not bind to CagL (See FIG. 23). The αvβ8-mediated binding to CagL can be efficiently blocked by C6D4 (See FIG. 24). The αvβ8 integrin also mediates strong cell adhesion to CagL (see Fig. 25) and CagL can compete for αvβ8-mediated cell adhesion to the TGF-β3 RGD peptide, indicating that αvβ8 binds to the RGD site of CagL (See FIG. 26). C6D4 can efficiently block cell adhesion to CagL (See FIG. 27).

[0235] Blocking αvβ8-mediated binding of CagL with C6D4 or its derivatives (i.e. IgA, monomeric or dimeric) can be used as a method to inhibit *H. Pylori* pathogenicity (i.e. peptic ulcer disease, gastric carcinoma or MALToma) by blocking entry of the oncogenic toxin CagA. In addition, C6D4 could provide protection against *H. Pylori* itself or from its indirect oncogenic and toxic effects by inhibiting Treg function and increasing more effective immunity against *H. Pylori*, gastric carcinoma, and MALToma. Such effects can be predicted by findings in murine models where *H. Pylori* immune escape has been shown to be mediated by dendritic

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cell-induced Treg skewing and Th17 suppression (see Kao, et al, *Gastroenterology*, 2010 138(3):1046-54). Because the integrin αvβ8-mediated TGF-β activation has been shown to be required for Treg development and function (see Worthington, et al, *Immunity*, 2015, Volume 42, Issue 5, pp. 903–915), inhibiting αvβ8-mediated TGF-β activation using C6D4 or its derivatives will protect against the oncogenic effects of *H. Pylori* infection by enhancing immunity to *H. Pylori* itself while simultaneously increasing anti-tumoral immunity. Another possible mechanism by which blocking αvβ8-mediated TGF-β activation with C6D4 or its derivatives could block Treg function is by inhibiting migration of Tregs to the *H. Pylori* infected gastric mucosa. The chemokine CCL20 is a potent chemokine for Tregs and dendritic cells, which are required for Treg differentiation, and αvβ8-mediated TGF-β activation provides a major contribution to CCL20 production and function (see Cook, et al, *Gut* (2014), 63(10):1550-9; Brand, et al, *J Biol Chem*, 2015, 290(23):14717-28, Hashimoto, et al, *J Immunol* 195(3):1182-90.). Therefore, treating patients with C6D4 or another anti-αvβ8 antibody alone, in combination with antibodies to other CagL binding integrins (α5β1, Act-1, or αvβ6, 3G9) or in combination with standard *H. Pylori* therapy (i.e. bismuth salts, proton pump inhibitors, macrolides, amoxicillin, metronidazole) would treat not only the pathogenic mechanism of *H. Pylori* but would enhance immunity to more efficiently eliminate *H. Pylori*, while at the same time protecting and/or treating the malignant complications of chronic *H. pylori* infection.

Example 9. Construction of composite humanized antibody C6D4

[0236] FIG. 46, FIG. 50, and FIG. 51, show sequence alignment of various C6D4 humanized clones. FIGS. 50 and 51 also provide heavy chain and light chain amino acid consensus sequences for the humanized C6D4 related clones. The C6D4 antibody humanization focused on the V domain framework region of both the heavy and light chain. The humanization process was performed to include three criteria:

(1) The humanized version of antibody(HuC6D4) should have similar or improved affinity and specificity for αvβ8 as the murine version C6D4;

(2) The final amino acid in the HuC6D4 antibody framework region should be as close as possible to the translated antibody framework region of the human germline version that was selected as the target gene family (VH1/VK3);

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(3) Production levels of the final humanized version (HuC6D4) in IgG or other format should be scalable for industry application.

[0237] We designed a potential humanized lead version of the murine C6D4 based on the chosen germline of human antibody(VH1/VK3), and the humanization algorithm developed at UCSF, and other published information for antibody human drug development, with main consideration on IgG general structure, VH-VL interface, IgG folding packing, surface accessibility, vernier zone impact, humanization hotspots and other risk factors.

[0238] These designed lead versions were synthesized and expressed as scFV using yeast display. The measured Kd showed an approximate 2-fold decrease from the parent murine C6D4 scFv.

[0239] Next, a random mutation based yeast scFv display library was created using the humanized lead version as the starting point, and FACS sorting performed to pick the best binders to αvβ from the displayed yeast library. Three mutant candidates (C6D4-RGD1, C6D4-RGD2 and C6D4-RGD3) were chosen for further testing in IgG format (*See, for example* FIG. 38C and FIG. 39).

Example 10. Characterization of humanized C6D4 and CD64-RGD3 binding affinity

[0240] Shown in FIG. 39 is cell surface staining experiments of C6Vh expressed with either RGD1, RGD2, or RGD3 mutants (as disclosed in Example 8) as rabbit IgG. Binding to human Cho cells expressing αvβ8 was expressed as a percentage of binding of C6D4. The results show that RGD3 mutant has substantially higher relative binding to αvβ8 as compared to wildtype C6D4, RGD1 mutant or RDG2 mutant.

[0241] FIG. 40 shows cell surface staining experiments of C6Vh expressed with either D4 Vk or RGD1, RGD2 or RGD3 mutants (as disclosed in Example 8) as rabbit IgG. Binding to Cho cells expressing human αvβ8 or SW480 cells expressing αvβ6 are shown. Relative binding is defined as staining compared to staining of non-transfected Cho or SW480 cells. The results show that the C6D4-RGD3 mutant has substantially higher relative binding to αvβ6 as compared to wildtype C6D4, RGD1 mutant, or RDG2 mutant.

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[0242] Shown in FIG. 41 is a binding experiment of C6Vh expressed with either D4 Vk or RGD1, RGD2 or RGD3 mutants (as disclosed in Example 8) as rabbit IgG to various av-integrins. The integrins αvβ1, αvβ3, αvβ5, αvβ6 and αvβ8 were purchased from R&D systems. All integrins were coated on ELISA plates at 2 mg/ml, blocked with BSA, and antibodies were allowed to bind. Binding of C6D4 and RGD3 was detected with anti-rabbit HRP. The results shown are relative to control wells coated with anti-av (clone 8B8) where av-integrins were detected with another av-antibody recognizing an non-overlapping epitope (L230-biotin), followed by SA-HRP. The results show that RGD3 mutant has substantially higher binding to αvβ6, while C6D4 has higher relative binding to αvβ8.

[0243] C6D4 and C6D4-RGD3 were also shown to bind avidly to αvβ8. Humanized C6D4 or C6D4-RGD3 (Frameworks and CH1 are human; hinge and CH2-3 are mouse) were immobilized on ELISA plates at the indicated concentrations. As a negative control, some wells were coated with anti-SV5 at the same concentrations. Non-specific binding sites were blocked with BSA. Recombinant αvβ8 ectodomain (0.5 ug/ml) was added to each well and after binding and washing in binding buffer (1 mM Ca^{++} and Mg^{++}), the bound αvβ8 was detected with biotinylated anti-αv (8b8) and detected with SA-HRP. The results of this experiment are shown as specific binding (minus SV5 control)(FIG. 47). The results show that C6D4 and C6D4-RGD3 outperform murine C6D4 and C6D4-RGD3 antibodies by avidly binding αvβ8.

Example 11. Characterization of humanized C6D4-RGD3 binding structure

[0244] As set forth in Example 3, modeling and CryoEM maps can be used to provide structural information with respect to antibody binding. FIG. 48 presents a map of RGD3 binding to the ligand pocket of αvβ8. The map is derived from C6D4 in complex with αvβ8 and is compared to C6D4-RGD3 in complex with αvβ8. The density map when compared with the headpiece of αvβ6 in complex with LTGFβ1 shows the similarity of the position of the RGD residues of LTGFB1 with the RGD residues of C6D4-RGD3. Magenta wire represent s RGD3+αvβ8 density map, Black represents C6D4+αvβ8 density map; Gold represents C6D4 Fab; Green represents the αv subunit; Blue represents the β8 subunit.

[0245] FIG. 49 is a cryoEM map showing the CDR Vk1 loop of C6D4-RGD3 occupies the ligand binding pocket of αvβ8. Here, models of C6D4 Fab-αvβ8 (FIG. 49A) are compared with

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RGD3-αvβ8 map (FIG. 49B) or in overlay (FIG. 49C) based on cryoEM derived density maps. The anti-αv 11D12V2 Fab was used to increase molecular mass of the complex and to assist in particle orientation. The results show that the C6D4 and C6D4-RGD3 complexes possess highly similar positioning.

Example 12. Characterization of D4-RGD3 mutants having various loop length of the RGD and flanking sequence of Pro-TGF-beta 3

[0246] There is an amphipathic alpha-helix following the R-G-D sequence of Latent-TGF-beta1 and Latent-TGF-beta3. Of the 3 engineered versions (RGD1, RGD2, RGD3) of D4 only RGD3 contained the amphipathic helix. Therefore, we engineered various loops containing portions of the RGD and flanking sequences of Pro-TGF–beta 3 to determine if loop length altered affinity, specificity or production of each clone. Because the Vh was not altered, we cloned all new constructs into the CDRL1 region of the C6D4 murine IgG expression vector and transfected the various new D4-RGD3-mutants into 293 cells. After 10 days, protein expression was compared using an murine IgG ELISA (shown as relative expression levels in the Table provided below). Integrins αvβ1, αvβ3, αvβ5, αvβ6 or αvβ8 (R&D systems) were coated on Immulon 4HBX ELISA plates (Thermo Scientific) for 1 hour at room temperature followed by blocking with a 5% bovine serum albumin solution (Sigma-Aldrich) overnight at 4°C. Supernatants with various RGD3 mutant antibodies were applied at 1/10 dilutions onto the wells for 1 hour at room temperature. Antibodies bound to the integrins were detected with an anti-mouse IgG-HRP antibody (GE Healthcare) and revealed with TMB substrate (Pierce). Binding was quantified by intensity as 0-4 (0 representing no apparent binding; 4 representing robust binding) and results normalized to expression. As can be seen from the data provided in the table below, different CDR_{L1} swaps into Vk D4 show distinct binding specificities. As a result, we identified several mutants having bi-specific (*e.g.,* RGD3-2 and RGD3-3) or tri-specific (*e.g.,* RGD3-7 and RGD3-8) binding specificities.

Inserted Vk CDR_{L1} domain swap into D4	Murine IgG H+L Vector		IgG ELISA	Binding to recombinant human integrins				
CDR_{L1}	Vh	Vk	Expression Level	αvβ1	αvβ3	αvβ5	αvβ6	αvβ8
KSSQSLLNSRSRKNYLA (SEQ ID NO: 572)	C6	D4	4	0	0	0	0	4

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KSSQSLLNSGRGDLGNALA (SEQ ID NO: 574)	C6	RGD2	4	0	0	0	0	2
KSSQSLLGRGDLGRLKKQKDHNALA (SEQ ID NO: 576)	C6	RGD3-1	3	0	0	0	4	1
KSSQSLLGRGDLGRLKKQKDNALA (SEQ ID NO: 577)	C6	RGD3-2	3	0	0	0	4	4
KSSQSLLGRGDLGRLKKQKNALA (SEQ ID NO: 578)	C6	RGD3-3	3	0	0	0	4	4
KSSQSLLGRGDLGRLKKQNALA (SEQ ID NO: 579)	C6	RGD3-4	3	0	0	0	4	4
KSSQSLLGRGDLGRLKKNALA (SEQ ID NO: 575)	C6	RGD3	3	0	0	0	4	4
KSSQSLLGRGDLGRLKNALA (SEQ ID NO: 580)	C6	RGD3-6	3	0	0	0	4	4
KSSQSLLGRGDLGRLNALA (SEQ ID NO: 581)	C6	RGD3-7	3	0	4	0	2	2
KSSQSLLGRGDLGRNALA (SEQ ID NO: 582)	C6	RGD3-8	3	0	3	0	3	3
KSSQSLLGRGDLGNALA (SEQ ID NO: 573)	C6	RGD1	2	0	0	0	0	1
KSSQSLLGRGDLGRLKKQKDHH (SEQ ID NO: 583)	C6	RGD3-9	1	0	0	0	3	0
KSSQSLLGRGDLGRLKKQKDH (SEQ ID NO: 584)	C6	RGD3-10	2	0	0	0	1	0
KSSQSLLGRGDLGRLKKQKD (SEQ ID NO: 585)	C6	RGD3-11	2	0	0	0	2	1
KSSQSLLGRGDLGRLKKQK (SEQ ID NO: 586)	C6	RGD3-12	2	0	1	0	2	0
KSSQSLLGRGDLGRLKKQ (SEQ ID NO: 587)	C6	RGD3-13	2	0	0	0	2	0
KSSQSLLGRGDLGRLKK (SEQ ID NO: 588)	C6	RGD3-14	3	0	0	0	1	1
KSSQSLLGRGDLGRLK (SEQ ID NO: 589)	C6	RGD3-15	3	0	0	0	0	0
KSSQSLLGRGDLGRL (SEQ ID NO: 590)	C6	RGD3-16	3	0	0	0	0	0

Example 13. C6D4 induces Th1 bias and increases CD8 IFN-γ producing cells

[0247] Seventeen C57B/7 mice were injected with 10^6 Lewis lung carcinoma (LLC) tumor cells and 8 were injected IP with anti-SV5 (isotype control) or 9 mice with C6D4 (both groups at 7 mg/kg). Mab injections were repeated at day 7 and tumors were harvested at day 11. Tumor infiltrating lymphoid cells were isolated from tumors by enzyme digestion and Percoll gradient centrifugation and stained for CD45, TCRb, CD4, CD8 and surface capture assay for IFNg. Live CD45+ cells were gated and B220, Ly6g, CD11c, CD11b negative, TCRb positive cells were segregated in CD4, CD8, IFN-g positive subsets. The results from this experiment are shown in FIG. 54A-54D. Shown are percentages. * $p<0.05$, ** $p<0.01$.

[0248] <deleted>

[0249] Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only and are not meant to be limiting in any way. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

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Informal Sequence Listing

SEQ ID NO:1 B13C4 15-8 EVQLQQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWMG WIKTETGEPTYADDFKG RFAFSLETSATTAYLQINNLKNEDTAKYFCAI YYYGRDS WGQGTTLTVSS

SEQ ID NO:2 VH Framework 1 EVQLQQSGPELKKPGETVKISCKASGY

SEQ ID NO:3 VH CDR1 TFTDYSMH

SEQ ID NO:4 VH Framework 2 WVKQAPGKGLKWMG

SEQ ID NO:5 VH CDR2 WIKTETGEPTYADDFKG

SEQ ID NO:6 VH Framework 3 RFAFSLETSATTAYLQINNLKNEDTAKYFCAI

SEQ ID NO:7 VH CDR 3 YYYGRDS

SEQ ID NO:8 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:9 B13C4 15-10 QIQLLQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWMG WIKTETGEPTYADDFKG RFAFSLETSATTAYLQINNLKNEDTAKYFCAI YYYGRDS WGQGTTLTVSS

SEQ ID NO:10 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY

SEQ ID NO:11 VH CDR1 TFTDYSMH

SEQ ID NO:12 VH Framework 2 WVKQAPGKGLKWMG

SEQ ID NO:13 VH CDR2 WIKTETGEPTYADDFKG

SEQ ID NO:14 VH Framework 3 RFAFSLETSATTAYLQINNLKNEDTAKYFCAI

SEQ ID NO:15 VH CDR 3 YYYGRDS

SEQ ID NO:16 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:17
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SEQ ID NO:18 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY

SEQ ID NO:19 VH CDR1 TFTDYSMH

SEQ ID NO:20 VH Framework 2 WVKQAPGKGLKWMG

SEQ ID NO:21 VH CDR2 WIKTETDEPTYADDFKE

SEQ ID NO:22 VH Framework 3 RFAFSLETSASTANLQIINLKNEDTATYFCAI

SEQ ID NO:23 VH CDR 3 YYYGRDS

SEQ ID NO:24 VH Framework 4 WGQGTTLTVSSSEQ

SEQ ID NO:25
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SEQ ID NO:26 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY

SEQ ID NO:27 VH CDR1 TFTDYSIH

SEQ ID NO:28 VH Framework 2 WVKQAPGKGLKWMG

SEQ ID NO:29 VH CDR2 WIKTETGEPTYADDFNG

SEQ ID NO:30 VH Framework 3 RFAFSLETSASTAYLQINNLKNEDTATYFCAI

SEQ ID NO:31 VH CDR 3 YYYGRDS

SEQ ID NO:32 VH Framework 4 WGQGTTLTVSS

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SEQ ID NO:33
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SEQ ID NO:35 VH CDR1 TFTDYSMH

SEQ ID NO:36 VH Framework 2 WVKQAPGKGLKWVA

SEQ ID NO:37 VH CDR2 RINTETGEPTFADDFRG

SEQ ID NO:38 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI

SEQ ID NO:39 VH CDR 3 YYYGRDS

SEQ ID NO:40 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:41
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SEQ ID NO:42 VH Framework 1 QIQLLQSGPELKKPGETVKISCLASGY

SEQ ID NO:43 VH CDR1 TFTDYSMH

SEQ ID NO:44 VH Framework 2 WVKQAPGKGLKWVA

SEQ ID NO:45 VH CDR2 RINTETGEPTFADDFGG

SEQ ID NO:46 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI

SEQ ID NO:47 VH CDR 3 YYYGRDS

SEQ ID NO:48 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:49
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RFTISRDNAKNTLYLQMSSLKSEDTAMYYCAS ACYRYGAFFDY WGQGTTLTVSS

SEQ ID NO:50 VH Framework 1 EVQLVESGGGLVQPGGSLKLSCAASGF

SEQ ID NO:51 VH CDR1 TFSSFGMS

SEQ ID NO:52 VH Framework 2 WVRQTPDKRLELVA

SEQ ID NO:53 VH CDR2 TINSNGGSTYYPDNMKG

SEQ ID NO:54 VH Framework 3 RFTISRDNAKNTLYLQMSSLKSEDTAMYYCAS

SEQ ID NO:55 VH CDR 3 ACYRYGAFFDY

SEQ ID NO:56 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:57
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SEQ ID NO:59 VH CDR1 TFTDYSIH

SEQ ID NO:60 VH Framework 2 WVKQAPGKGLKWMG

SEQ ID NO:61 VH CDR2 WIKTETGEPTYADDFKG

SEQ ID NO:62 VH Framework 3 RFAFSLETSASTAYLQINNLKNEDTATYFCAI

SEQ ID NO:63 VH CDR 3 YYYGRDS

SEQ ID NO:64 VH Framework 4 WGQGTTVTVSS

SEQ ID NO:65
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RFAFSLETSASTAYLQINNLKNEDTATYFCAI YYYGRDS WGQGTTVTVSS

SEQ ID NO:66 VH Framework 1 EVQLLESGPELKKPGETVKISCKASGY
SEQ ID NO:67 VH CDR1 TFTDYSIH
SEQ ID NO:68 VH Framework 2 WVKQAPGKGLKWMG
SEQ ID NO:69 VH CDR2 WIKTETGEPTYADDFKG
SEQ ID NO:70 VH Framework 3 RFAFSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:71 VH CDR 3 YYYGRDS
SEQ ID NO:72 VH Framework 4 WGQGTTVTVSS

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SEQ ID NO:75 VH CDR1 TFTDYSIH
SEQ ID NO:76 VH Framework 2 WVKQAPGKGLKWMG
SEQ ID NO:77 VH CDR2 WIKTETGEPTYADDFNG
SEQ ID NO:78 VH Framework 3 RFAFSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:79 VH CDR 3 YYYGRDS
SEQ ID NO:80 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:81
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SEQ ID NO:82 VH Framework 1 QIQLQQSGPELKKPGETVKISCKASGY
SEQ ID NO:83 VH CDR1 TFTDYSMH
SEQ ID NO84 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:85 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:86 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:87 VH CDR 3 YYYGRDS
SEQ ID NO:88 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:89
29_and_44 QIQLLQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG RFAVSLETSASTAYLQINNLKNEDTATYFCAI YYYGRDS WGQGTTLTVSS
SEQ ID NO:90 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY
SEQ ID NO:91 VH CDR1 TFTDYSMH
SEQ ID NO:92 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:93 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:94 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:95 VH CDR 3 YYYGRDS
SEQ ID NO:96 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:97
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SEQ ID NO:99 VH CDR1 TFTDYSMH
SEQ ID NO:100 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:101 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO: 102 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI

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SEQ ID NO:103 VH CDR 3 YYYGRDT
SEQ ID NO:104 VH Framework 4 WGQGTTLSVSS

SEQ ID NO:105
A5=C6 QIQLLQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG
RFAVSLETSASTAYLQINNLKNEDTATYFCAI FYYGRDS WGQGTALTVSS
SEQ ID NO:106 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY
SEQ ID NO:107 VH CDR1 TFTDYSMH
SEQ ID NO:108 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:109 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:110 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:111 VH CDR 3 FYYGRDS
SEQ ID NO:112 VH Framework 4 WGQGTALTVSS

SEQ ID NO:113
D4=E6 QIQLLQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG
RFAVSLETSASTAYLQINNLKNEDTATYFCAI YYYGRDS WGQGTTLTVSS
SEQ ID NO:114 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY
SEQ ID NO:115 VH CDR1 TFTDYSMH
SEQ ID NO:116 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:117 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:118 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:119 VH CDR 3 YYYGRDS
SEQ ID NO:120 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:121
C6D4 QIQLLQSGPELKKPGETVKISCKASGY TFTDYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG
RFAVSLETSASTAYLQINNLKNEDTATYFCAI FYYGRDS WGQGTTLTVSS
SEQ ID NO:122 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGY
SEQ ID NO:123 VH CDR1 TFTDYSMH
SEQ ID NO:124 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:125 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:126 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:127 VH CDR 3 FYYGRDS
SEQ ID NO:128 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:129
B2B2 35-20 DIVMSQSPSSMYASLGERVTITC KASQDINSYLS WFQQKPGKSPKTLIY RANRLVD
GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC LQYDEFPPLT FGAGTKLELKA
SEQ ID NO:130 VL Framework 1 DIVMSQSPSSMYASLGERVTITC
SEQ ID NO:131 VL CDR1 KASQDINSYLS
SEQ ID NO:132 VL Framework 2 WFQQKPGKSPKTLIY
SEQ ID NO:133 VL CDR2 RANRLVD
SEQ ID NO:134 VL Framework 3 GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC
SEQ ID NO:135 VL CDR 3 LQYDEFPPLT
SEQ ID NO:136 VL Framework 4 FGAGTKLELKA

SEQ ID NO:137
B2B2 35-26 QIVLTQSPSSMYASLGERVTITC KASQDINSYLS WFQQKPGKSPKTLIY RANRLVD
GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC LQYDEFPPLT FGAGTKLELKA

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SEQ ID NO:138 VL Framework 1 QIVLTQSPSSMYASLGERVTITC
SEQ ID NO:139 VL CDR1 KASQDINSYLS
SEQ ID NO:140 VL Framework 2 WFQQKPGKSPKTLIY
SEQ ID NO:141 VL CDR2 RANRLVD
SEQ ID NO:142 VL Framework 3 GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC
SEQ ID NO:143 VL CDR 3 LQYDEFPPLT
SEQ ID NO:144 VL Framework 4 FGAGTKLELKA

SEQ ID NO:145
B15B11vk34-26 QIVLTQSPAIMSASPGEKVTMTC SASSSVSYMH WYQQKPGTSPKLWIY DTSNLAS GVPARFSGSGSGTSYSLTISSMEAEDAATYYC QQWSSNPLT FGSGTKLEIKA
SEQ ID NO:146 VL Framework 1 QIVLTQSPAIMSASPGEKVTMTC
SEQ ID NO:147 VL CDR1 SASSSVSYMH
SEQ ID NO:148 VL Framework 2 WYQQKPGTSPKLWIY
SEQ ID NO:149 VL CDR2 DTSNLAS
SEQ ID NO:150 VL Framework 3 GVPARFSGSGSGTSYSLTISSMEAEDAATYYC
SEQ ID NO:151 VL CDR 3 QQWSSNPLT
SEQ ID NO:152 VL Framework 4 FGSGTKLEIKA

SEQ ID NO:153
B15B11vk33-24 EIVLTQSPAIMSASPGEKVTMTC SASSSVSYMH WYQQKPGSSPKLWIY DTSNLAS GVPARFSGSGSGTSYSLTISSMEAEDAATYYC QQWSSNPLT FGDGTRLEIKA
SEQ ID NO:154 VL Framework 1 EIVLTQSPAIMSASPGEKVTMTC
SEQ ID NO:155 VL CDR1 SASSSVSYMH
SEQ ID NO:156 VL Framework 2 WYQQKPGSSPKLWIY
SEQ ID NO:157 VL CDR2 DTSNLAS
SEQ ID NO:158 VL Framework 3 GVPARFSGSGSGTSYSLTISSMEAEDAATYYC
SEQ ID NO:159 VL CDR 3 QQWSSNPLT
SEQ ID NO:160 VL Framework 4 FGDGTRLEIKA

SEQ ID NO:161
B15B11vk35-26 QIVLTQSPAIMSASPGEKVTMTC SASSSVSYMH WYQQKSGTSPKLWIY DTSNLAS GVPARFSGSGSGTSYSLTISSMEAEDAATYYC QQWSSNPPT FGAGTKLELKA
SEQ ID NO:162 VL Framework 1 QIVLTQSPAIMSASPGEKVTMTC
SEQ ID NO:163 VL CDR1 SASSSVSYMH
SEQ ID NO:164 VL Framework 2 WYQQKSGTSPKLWIY
SEQ ID NO:165 VL CDR2 DTSNLAS
SEQ ID NO:166 VL Framework 3 GVPARFSGSGSGTSYSLTISSMEAEDAATYYC
SEQ ID NO:167 VL CDR 3 QQWSSNPPT
SEQ ID NO:168 VL Framework 4 FGAGTKLELKA

SEQ ID NO:169
B13C12134-25 DIKMTQSPAIMSASPGEKVTMTC SASSSVSYMH WYQQKSGTSPKRWIY DTSKLAS GVPARFSGSGSGTSYSLTISSMEAEDAATYYC QQWSSNPFT FGSGTKLEIKA
SEQ ID NO:170 VL Framework 1 DIKMTQSPAIMSASPGEKVTMTC
SEQ ID NO:171 VL CDR1 SASSSVSYMH
SEQ ID NO:172 VL Framework 2 WYQQKSGTSPKRWIY
SEQ ID NO:173 VL CDR2 DTSKLAS
SEQ ID NO:174 VL Framework 3 GVPARFSGSGSGTSYSLTISSMEAEDAATYYC

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SEQ ID NO:175 VL CDR 3 QQWSSNPFT
SEQ ID NO:176 VL Framework 4 FGSGTKLEIKA

SEQ ID NO:177
B13C12133-26 QMVLTHSPAIMSASPGEKVTMTC SASSSVSYMH WYQQKPGSSPKPWIY GTSNLAS GVPARFSGSGSGTSYSLTISRMEAEDAATYYC QQWSSNPPT FGDGTRLEIKA
SEQ ID NO:178 VL Framework 1 QMVLTHSPAIMSASPGEKVTMTC
SEQ ID NO:179 VL CDR1 SASSSVSYMH
SEQ ID NO:180 VL Framework 2 WYQQKPGSSPKPWIY
SEQ ID NO:181 VL CDR2 GTSNLAS
SEQ ID NO:182 VL Framework 3 GVPARFSGSGSGTSYSLTISRMEAEDAATYYC
SEQ ID NO:183 VL CDR 3 QQWSSNPPT
SEQ ID NO:184 VL Framework 4 FGDGTRLEIKA

SEQ ID NO:185
B13C4 35-20 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:186 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:187 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:188 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:189 VL CDR2 WASTRES
SEQ ID NO:190 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:191 VL CDR 3 KQSYNLLT
SEQ ID NO:192 VL Framework 4 FGAGTKLELKA

SEQ ID NO:193
B15B11vk35-20 DIVMSQSPSSLAVSAGENVTVSC KSSQSLLNSRTRKNYLA WYQQKPGQSPKLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYFC KQSYNLLT FGAGTKLELKA
SEQ ID NO:194 VL Framework 1 DIVMSQSPSSLAVSAGENVTVSC
SEQ ID NO:195 VL CDR1 DIVMSQSPSSLAVSAGENVTVSC
SEQ ID NO:196 VL Framework 2 WYQQKPGQSPKLLIY
SEQ ID NO:197 VL CDR2 WASTRES
SEQ ID NO:198 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYFC
SEQ ID NO:199 VL CDR 3 KQSYNLLT
SEQ ID NO:200 VL Framework 4 FGAGTKLELKA

SEQ ID NO:201
B13C12335-25 DIKMTQSPSSLAVSPGEKVTMSC KSSQSLLHSRTRKNYLA WYQQKPGQSPKLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:202 VL Framework 1 DIKMTQSPSSLAVSPGEKVTMSC
SEQ ID NO:203 VL CDR1 KSSQSLLHSRTRKNYLA
SEQ ID NO:204 VL Framework 2 WYQQKPGQSPKLLIY
SEQ ID NO:205 VL CDR2 WASTRES
SEQ ID NO:206 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:207 VL CDR 3 KQSYNLLT
SEQ ID NO:208 VL Framework 4 FGAGTKLELKA

SEQ ID NO:209
B13C1233520 DIVMSQSPSSLAVSPGEKVTMSC KSSQSLLHSRTRKNYLA WYQQKPGQSPKLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA

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SEQ ID NO:210 VL Framework 1 DIVMSQSPSSLAVSPGEKVTMSC
SEQ ID NO:211 VL CDR1 KSSQSLLHSRTRKNYLA
SEQ ID NO:212 VL Framework 2 WYQQKPGQSPKLLIY
SEQ ID NO:213 VL CDR2 WASTRES
SEQ ID NO:214 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:215 VL CDR 3 KQSYNLLT
SEQ ID NO:216 VL Framework 4 FGAGTKLELKA

SEQ ID NO:217
RSDLVK-1 DIVMTQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKR
SEQ ID NO:218 VL Framework 1 DIVMTQSPSSLAVSAGEKVTMSC
SEQ ID NO:219 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:220 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:221 VL CDR2 WASTRES
SEQ ID NO:222 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:223 VL CDR 3 KQSYNLLT
SEQ ID NO:224 VL Framework 4 FGAGTKLELKR

SEQ ID NO:225
RSDLVK-6 DIVMTQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTRLEIKR
SEQ ID NO:226 VL Framework 1 DIVMTQSPSSLAVSAGEKVTMSC
SEQ ID NO:227 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:228 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:229 VL CDR2 WASTRES
SEQ ID NO:230 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:231 VL CDR 3 KQSYNLLT
SEQ ID NO:232 VL Framework 4 FGAGTRLEIKR

SEQ ID NO:233
RSDLVK-10 DIVMTQSPSSLAVSAGENVTVSC KSSQSLLNSRTRKNYLA WYQQKPGQSPKLLIY WASTRES GVPDRFTGSGSGTGFTLTISSVQAEDLAVYFC KQSYNLLT FGAGTRLEIKR
SEQ ID NO:234 VL Framework 1 DIVMTQSPSSLAVSAGENVTVSC
SEQ ID NO:235 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:236 VL Framework 2 WYQQKPGQSPKLLIY
SEQ ID NO:237 VL CDR2 WASTRES
SEQ ID NO:238 VL Framework 3 GVPDRFTGSGSGTGFTLTISSVQAEDLAVYFC
SEQ ID NO:239 VL CDR 3 KQSYNLLT
SEQ ID NO:240 VL Framework 4 FGAGTRLEIKR

SEQ ID NO:241
RSDLVK-13 DIVMSQSPSSLAVSPGEKVTMSC KSSQSLLHSRTRKNYLA WYQQKPGQSPKLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKR
SEQ ID NO:242 VL Framework 1 DIVMSQSPSSLAVSPGEKVTMSC
SEQ ID NO:243 VL CDR1 KSSQSLLHSRTRKNYLA
SEQ ID NO:244 VL Framework 2 WYQQKPGQSPKLLIY
SEQ ID NO:245 VL CDR2 WASTRES
SEQ ID NO:246 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC

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SEQ ID NO:247 VL CDR 3 KQSYNLLT
SEQ ID NO:248 VL Framework 4 FGAGTKLELKR

SEQ ID NO:249
29 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:250 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:251 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:252 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:253 VL CDR2 WASTRES
SEQ ID NO:254 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:255 VL CDR 3 KQSYNLLT
SEQ ID NO:256 VL Framework 4 FGAGTKLELKA

SEQ ID NO:257
44 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:258 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:259 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:260 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:261 VL CDR2 WASTRES
SEQ ID NO:262 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC
SEQ ID NO:263 VL CDR 3 KQSYNLLT
SEQ ID NO:264 VL Framework 4 FGAGTKLELKA

SEQ ID NO:265
A1=B4=F9 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:266 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:267 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:268 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:269 VL CDR2 WASTRES
SEQ ID NO:270 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:271 VL CDR 3 KQSYNLLT
SEQ ID NO:272 VL Framework 4 FGAGTKLELKA

SEQ ID NO:273
A5=C6 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLT FGAGTKLELKA
SEQ ID NO:274 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:275 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:276 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:277 VL CDR2 WASTRES
SEQ ID NO:278 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:279 VL CDR 3 KQSYNLLT
SEQ ID NO:280 VL Framework 4 FGAGTKLELKA

SEQ ID NO:281
D4=E6 DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQXPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC KQSYNLLS FGAGTKLELKA

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SEQ ID NO:282 VL Framework 1 DIVMSQSPSSLAVSAGEKVTMSC
SEQ ID NO:283 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:284 VL Framework 2 WYQQKPGQXPRLLIY
SEQ ID NO:285 VL CDR2 WASTRES
SEQ ID NO:286 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC
SEQ ID NO:287 VL CDR 3 KQSYNLLS
SEQ ID NO:288 VL Framework 4 FGAGTKLELKA

SEQ ID NO:289
C6D4 DIVMTQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLS FGAGTKLELKR
SEQ ID NO:290 VL Framework 1 DIVMTQSPSSLAVSAGEKVTMSC
SEQ ID NO:291 VL CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:292 VL Framework 2 WYQQKPGQSPRLLIY
SEQ ID NO:293 VL CDR2 WASTRES
SEQ ID NO:294 VL Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:295 VL CDR 3 KQSYNLLS
SEQ ID NO:296 VL Framework 4 FGAGTKLELKR

SEQ ID NO:297
F9 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIQ WVKQRPGQGLEWIG VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:298 VH Framework 1 QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:299 VH CDR1 AFTDYLIQ
SEQ ID NO:300 VH Framework 2 WVKQRPGQGLEWIG
SEQ ID NO:301 VH CDR2 VINPETGGTNYNAKFRG
SEQ ID NO:302 VH Framework 3 KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:303 VH CDR 3 EAGNYIYAMDY
SEQ ID NO:304 VH Framework 4 WGQGTSVTVSS

SEQ ID NO:305
F9 VL DIVMTQSPAFLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKR
SEQ ID NO:306 VL Framework 1 DIVMTQSPAFLSASVGETVTITC
SEQ ID NO:307 VL CDR1 RASVNIYSYLV
SEQ ID NO:308 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:309 VL CDR2 NAKTLAE
SEQ ID NO:310 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:311 VL CDR 3 QHHHGTPYT
SEQ ID NO:312 VL Framework 4 FGGGTKLEIKR

SEQ ID NO:313 B2B2 VH CDR1 TFTDYSMH
SEQ ID NO:314 B2B2 VH CDR2 RINTETGEPTFADDFGG
SEQ ID NO:315 B2B2 VH CDR3 YYYGRDS

SEQ ID NO:316 B13C4 VH CDR1 TFTDYSMH
SEQ ID NO:317 B13C4 VH CDR2 WIKTETGEPTYADDFKG
SEQ ID NO:318 B13C4 VH CDR3 YYYGRDS

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SEQ ID NO:319	B13H3VH CDR1 TFTDYSMH
SEQ ID NO:320	B13H3VH CDR2 WIKTETDEPTYADDFKE
SEQ ID NO:321	B13H3VH CDR3 YYYGRDS
SEQ ID NO:322	B15B11VH CDR1 TFTDYSMH
SEQ ID NO:323	B15B11VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:324	B15B11VH CDR3 YYYGRDS
SEQ ID NO:325	B13C12VH CDR1 TFTDYSIH
SEQ ID NO:326	B13C12VH CDR2 WIKTETGEPTYADDFNG
SEQ ID NO:327	B13C12VH CDR3 YYYGRDS
SEQ ID NO:328	A1 VH CDR1 TFTDYSMH
SEQ ID NO:329	A1 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:330	A1 VH CDR3 YYYGRDT
SEQ ID NO:331	C6 VH CDR1 TFTDYSMH
SEQ ID NO:332	C6 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:333	C6 VH CDR3 FYYGRDS
SEQ ID NO:334	B2B2 Vk CDR1 KASQDINSYLS
SEQ ID NO:335	B2B2Vk CDR2 RANRLVD
SEQ ID NO:336	B2B2Vk CDR3 LQYDEFPPLT
SEQ ID NO:337	B13C4 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:338	B13C4Vk CDR2 WASTRES
SEQ ID NO:339	B13C4Vk CDR3 KQSYNLLT
SEQ ID NO:340	B13H3 Vk CDR1 KSSQSLLNSRIRKNYLA
SEQ ID NO:341	B13H3Vk CDR2 WASTRES
SEQ ID NO:342	B13H3Vk CDR3 KQSYNLLT
SEQ ID NO:343	B15B11.1 Vk CDR1 SASSSVSYMH
SEQ ID NO:344	B15B11.1Vk CDR2 DTSNLAS
SEQ ID NO:345	B15B11.1Vk CDR3 QQWSSNPLT
SEQ ID NO:346	B15B11.2 Vk CDR1 SASSSVSYMH
SEQ ID NO:347	B15B11.2Vk CDR2 DTSNLAS
SEQ ID NO:348	B15B11.2Vk CDR3 QQWSSNPPT
SEQ ID NO:349	B15B11.3 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:350	B15B11.3Vk CDR2 WASTRES
SEQ ID NO:351	B15B11.3Vk CDR3 KQSYNLLT
SEQ ID NO:352	B13C12.1 Vk CDR1 SASSSVSYMH
SEQ ID NO:353	B13C12.1Vk CDR2 DTSKLAS

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SEQ ID NO:354 B13C12.1Vk CDR3 QQWSSNPFT

SEQ ID NO:355 B13C12.2 Vk CDR1 SASSSVSYMH
SEQ ID NO:356 B13C12.2Vk CDR2 GTSNLAS
SEQ ID NO:357 B13C12.2Vk CDR3 QQWSSNPPT

SEQ ID NO:358 B13C12.3 Vk CDR1 KSSQSLLHSRTRKNYLA
SEQ ID NO:359 B13C12.3 Vk CDR2 WASTRES
SEQ ID NO:360 B13C12.3 Vk CDR3 KQSYNLLT

SEQ ID NO:361 D4 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:362 D4Vk CDR2 WASTRES
SEQ ID NO:363 D4Vk CDR3 KQSYNLLS

SEQ ID NO:364 RSDLVH-1 VH CDR1 TFTDYSIH
SEQ ID NO:365 RSDLVH-1VH CDR2 WIKTETGEPTYADDFKG
SEQ ID NO:366 RSDLVH-1VH CDR3 YYYGRDS

SEQ ID NO:367 RSDLVH-3 VH CDR1 TFTDYSIH
SEQ ID NO:368 RSDLVH-3VH CDR2 WIKTETGEPTYADDFNG
SEQ ID NO:369 RSDLVH-3VH CDR3 YYYGRDS

SEQ ID NO:370 RSDLVH-16 VH CDR1 TFTDYSMH
SEQ ID NO:371 RSDLVH-16VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:372 RSDLVH-16VH CDR3 YYYGRDS

SEQ ID NO:373 RSDLVK-10 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:374 RSDLVK-10Vk CDR2 WASTRES
SEQ ID NO:375 RSDLVK-10Vk CDR3 KQSYNLLT

SEQ ID NO:376 RSDLVK-13 Vk CDR1 KSSQSLLHSRTRKNYLA
SEQ ID NO:377 RSDLVK-13Vk CDR2 WASTRES
SEQ ID NO:378 RSDLVK-13Vk CDR3 KQSYNLLT

SEQ ID NO:379 D4H VH CDR1 TFTDYSMH
SEQ ID NO:380 D4H VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:381 D4H VH CDR3 YYYGRDS

SEQ ID NO:382 C6k Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:383 C6k Vk CDR2 WASTRES
SEQ ID NO:384 C6k Vk CDR3 KQSYNLLT

SEQ ID NO:385 **heavy chain FR1** (Q/E)IQL(L/M)(Q/E)SGPELKKPGETVKISCKASGY
SEQ ID NO:386 **heavy chain FR2** WVKQAPGKGLKW(V/M)A
SEQ ID NO:387 **heavy chain FR3** RFA(V/F)SLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:388 **heavy chain FR4** WYQQKPGQSP(K/R)LLIY

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SEQ ID NO:389 **light chain FR1** (D/E)IVM(T/S)QSPSSLAV(/PS)AGE(K/N)VT(M/V)SC
SEQ ID NO:390 **light chain FR2** WYQQKPGQSP(K/R)LLIY
SEQ ID NO:391 **light chain FR3** GVPDRFTGSGSGTDFTLTISSVQAEDLAVY(Y/F)C
SEQ ID NO:392 **light chain FR4** FGAGT(R/K)LE(L/I)K

SEQ ID NO:393 Human αv

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1    FNLDVDSPAEYSGPEGSYFGFAVDFFVPSASSRMFLLVGAPKANTTQPGI 50
51   VEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWFGASVRS 100
101  KQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAPCRSQDIDAD 150
151  GQGFCQGGFSIDFTKADRVLLGGPGSFYWQGQLISDQVAEIVSKYDPNVY 200
201  SIKYNNQLATRTAQAIFDDSYLGYSVAVGDFNGDGIDDFVSGVPRAARTL 250
251  GMVYIYDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYADVFIGAPLF 300
301  MDRGSDGKLQEVGQVSVSLQRASGDFQTTKLNGFEVFARFGSAIAPLGDL 350
351  DQDGFNDIAIAAPYGGEDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSM 400
401  PPSFGYSMKGATDIDKNGYPDLIVGAFGVDRAILYRARPVITVNAGLEVY 450
451  PSILNQDNKTCSLPGTALKVSCFNVRFCLKADGKGVLPRKLNFQVELLLD 500
501  KLKQKGAIRRALFLYSRSPSHSKNMTISRGGLMQCEELIAYLRDESEFRD 550
551  KLTPITIFMEYRLDYRTAADTTGLQPILNQFTPANISRQAHILLDCGEDN 600
601  VCKPKLEVSVDSDQKKIYIGDDNPLTLIVKAQNQGEGAYEAELIVSIPLQ 650
651  ADFIGVVRNNEALARLSCAFKTENQTRQVVCDLGNPMKAGTQLLAGLRFS 700
701  VHQQSEMDTSVKFDLQIQSSNLFDKVSPVVSHKVDLAVLAAVEIRGVSSP 750
751  DHVFLPIPNWEHKENPETEEDVGPVVQHIYELRNNGPSSFSKAMLHLQWP 800
801  YKYNNNTLLYILHYDIDGPMNCTSDMEINPLRIKISSLQTTEKNDTVAGQ 850
851  GERDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQVGRLDRGKSAILYVK 900
901  SLLWTETFMNKENQNHSYSLKSSASFNVIEFPYKNLPIEDITNSTLVTTN 950
951  VTWGIQPAPMPVPVWVIILAVLAGLLLLAVLVFVMYRMGFFKRVRPPQEE 1000
1001 QEREQLQPHENGEGNSET                                1018
```

SEQ ID NO:394 Human β8

```
1   EDNRCASSNAASCARCLALGPECGWCVQEDFISGGSRSERCDIVSNLISK 50
51  GCSVDSIEYPSVHVIIPTENEINTQVTPGEVSIQLRPGAEANFMLKVHPL 100
101 KKYPVDLYYLVDVSASMHNNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYV 150
151 DKTVSPYISIHPERIHNQCSDYNLDCMPPHGYIHVLSLTENITEFEKAVH 200
201 RQKISGNIDTPEGGFDAMLQAAVCESHIGWRKEAKRLLLVMTDQTSHLAL 250
251 DSKLAGIVVPNDGNCHLKNNVYVKSTTMEHPSLGQLSEKLIDNNINVIFA 300
301 VQGKQFHWYKDLLPLLPGTIAGEIESKAANLNNLVVEAYQKLISEVKVQV 350
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351 ENQVQGIYFNITAICPDGSRKPGMEGCRNVTSNDEVLFNVTVTMKKCDVT 400
401 GGKNYAIIKPIGFNETAKIHIHRNCSCQCEDNRGPKGKCVDETFLDSKCF 450
451 QCDENKCHFDEDQFSSESCKSHKDQPVCSGRGVCVCGKCSCHKIKLGKVY 500
501 GKYCEKDDFSCPYHHGNLCAGHGECEAGRCQCFSGWEGDRCQCPSAAAQH 550
551 CVNSKGQVCSGRGTCVCGRCECTDPRSIGRFCEHCPTCYTACKENWNCMQ 600
601 CLHPHNLSQAILDQCKTSCALMEQQHYVDQTSECFSSPSYLRIFFIIFIV 650
651 TFLIGLLKVLIIRQVILQWNSNKIKSSSDYRVSASKKDKLILQSVCTRAV 700
701 TYRREKPEEIKMDISKLNAHETFRCNF 727
```

SEQ ID NO:395

HuC6D4V1 QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDS WGQGTTLTVSS

SEQ ID NO:396 VH Framework 1 QIQLVQSGAEVKKPGASVKISCKASGYTFT

SEQ ID NO:397 VH CDR1 DYSMH

SEQ ID NO:398 VH Framework 2 WVRQAPGQGLEWVA

SEQ ID NO:399 VH CDR2 RINTETGEPTFADDFRG

SEQ ID NO:400 VH Framework 3 RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI

SEQ ID NO:401 VH CDR 3 FYYGRDS

SEQ ID NO:402 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:403

HuC6D4A3 QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDS WGQGTTLTVSS

SEQ ID NO:404 VH Framework 1 QIQLVQSGAEVKKPGASVKISCKASGYTFT

SEQ ID NO:405 VH CDR1 DYSMH

SEQ ID NO:406 VH Framework 2 WVRQAPGQGLEWVA

SEQ ID NO:407 VH CDR2 RINTETGEPTFADDFRG

SEQ ID NO:408 VH Framework 3 RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI

SEQ ID NO:409 VH CDR 3 FYYGRDS

SEQ ID NO:410 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:411

HuC6D4B7 QIQLVQSGAKVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG RFSVTLDTSTSTAYLEITSLRSDDTAVYFCAI FYYGRDT WGQGTALTVSS

SEQ ID NO:412 VH Framework 1 QIQLVQSGAKVKKPGASVKISCKASGYTFT

SEQ ID NO:413 VH CDR1 DYSMH

SEQ ID NO:414 VH Framework 2 WVRQAPGQGLEWVA

SEQ ID NO:415 VH CDR2 RINTETGEPTFADDFRG

SEQ ID NO:416 VH Framework 3 RFSVTLDTSTSTAYLEITSLRSDDTAVYFCAI

SEQ ID NO:417 VH CDR 3 FYYGRDT

SEQ ID NO:418 VH Framework 4 WGQGTALTVSS

SEQ ID NO:419

HuC6D4E5 QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDT WGQGTTLTVSS

SEQ ID NO:420 VH Framework 1 QIQLVQSGAEVKKPGASVKISCKASGYTFT

SEQ ID NO:421 VH CDR1 DYSMH

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SEQ ID NO:422 VH Framework 2 WVRQAPGQGLEWVA
SEQ ID NO:423 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:424 VH Framework 3 RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:425 VH CDR 3 FYYGRDT
SEQ ID NO:426 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:427
HuC6D4 QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG
RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDT WGQGTTLTVSS
SEQ ID NO:428 VH Framework 1 QIQLVQSGAEVKKPGASVKISCKASGYTFT
SEQ ID NO:429 VH CDR1 DYSMH
SEQ ID NO:430 VH Framework 2 WVRQAPGQGLEWVA
SEQ ID NO:431 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:432 VH Framework 3 RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:433 VH CDR 3 FYYGRDT
SEQ ID NO:434 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:435
C6D4-RGD3 QIQLLQSGPELKKPGETVKISCKASGYTFT DYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG
RFAVSLETSASTAYLQINNLKNEDTATYFCAI FYYGRDS WGQGTTLTVSS
SEQ ID NO:436 VH Framework 1 QIQLLQSGPELKKPGETVKISCKASGYTFT
SEQ ID NO:437 VH CDR1 DYSMH
SEQ ID NO:438 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:439 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:440 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI
SEQ ID NO:441 VH CDR 3 FYYGRDS
SEQ ID NO:442 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:443
HuC6D4-RGD3 QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA RINTETGEPTFADDFRG
RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDT WGQGTTLTVSS
SEQ ID NO:444 VH Framework 1 QIQLVQSGAEVKKPGASVKISCKASGYTFT
SEQ ID NO:445 VH CDR1 DYSMH
SEQ ID NO:446 VH Framework 2 WVRQAPGQGLEWVA
SEQ ID NO:447 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:448 VH Framework 3 RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:449 VH CDR 3 FYYGRDT
SEQ ID NO:450 VH Framework 4 WGQGTTLTVSS

SEQ ID NO:451
HuC6D4V1 EIVMTQSPATLSVSPGERVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQAPRLLIY WASTRES
GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR
SEQ ID NO:452 Vk Framework 1 EIVMTQSPATLSVSPGERVTMSC
SEQ ID NO:453 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:454 Vk Framework 2 WYQQKPGQAPRLLIY
SEQ ID NO:455 Vk CDR2 WASTRES
SEQ ID NO:456 Vk Framework 3 GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC
SEQ ID NO:457 Vk CDR 3 KQSYNLLS
SEQ ID NO:458 Vk Framework 4 FGQGTVLEIKR

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SEQ ID NO:459
HuC6D4A3 EIVMTQSPATLSVSPGEIVTMSC KSSQSLLNSRSRKNYLA WYQQKPGQAPRLLIY WASTRES
GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLIS FGQGTVLEIKR

SEQ ID NO:460 Vk Framework 1 EIVMTQSPATLSVSPGEIVTMSC

SEQ ID NO:461 Vk CDR1 KSSQSLLNSRSRKNYLA

SEQ ID NO:462 Vk Framework 2 WYQQKPGQAPRLLIY

SEQ ID NO:463 Vk CDR2 WASTRES

SEQ ID NO:464 Vk Framework 3 GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC

SEQ ID NO:465 Vk CDR 3 KQSYNLIS

SEQ ID NO:466 Vk Framework 4 FGQGTVLEIKR

SEQ ID NO:467
HuC6D4B7 EIVMTQTPVTLSVSPGERVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQAPRLLIY WASTRES
DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSSNLIS FGQGTVLEIKR

SEQ ID NO:468 Vk Framework 1 EIVMTQTPVTLSVSPGERVTMSC

SEQ ID NO:469 Vk CDR1 KSSQSLLNSRTRKNYLA

SEQ ID NO:470 Vk Framework 2 WYQQKPGQAPRLLIY

SEQ ID NO:471 Vk CDR2 WASTRES

SEQ ID NO:472 Vk Framework 3 DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC

SEQ ID NO:473 Vk CDR 3 KQSSNLIS

SEQ ID NO:474 Vk Framework 4 FGQGTVLEIKR

SEQ ID NO:475
HuC6D4E5 EIVMTQSPATLSVSPGERVTMSC KSSQSLLNSRSRKNYLA WYQQKPGQAPRLLIY WASTRES
GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR

SEQ ID NO:476 Vk Framework 1 EIVMTQSPATLSVSPGERVTMSC

SEQ ID NO:478 Vk CDR1 KSSQSLLNSRSRKNYLA

SEQ ID NO:479 Vk Framework 2 WYQQKPGQAPRLLIY

SEQ ID NO:480 Vk CDR2 WASTRES

SEQ ID NO:481 Vk Framework 3 GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC

SEQ ID NO:482 Vk CDR 3 KQSYNLLS

SEQ ID NO:483 Vk Framework 4 FGQGTVLEIKR

SEQ ID NO:484
HuC6D4 EIVMTQSPATLSVSPGERVTMSC KSSQSLLNSRSRKNYLA WYQQKPGQAPRLLIY WASTRES
GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR

SEQ ID NO:485 Vk Framework 1 EIVMTQSPATLSVSPGERVTMSC

SEQ ID NO:486 Vk CDR1 KSSQSLLNSRSRKNYLA

SEQ ID NO:487 Vk Framework 2 WYQQKPGQAPRLLIY

SEQ ID NO:488 Vk CDR2 WASTRES

SEQ ID NO:489 Vk Framework 3 GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC

SEQ ID NO:490 Vk CDR 3 KQSYNLLS

SEQ ID NO:491 Vk Framework 4 FGQGTVLEIKR

SEQ ID NO:492
C6D4-RGD3 DIVMTQSPSSLAVSAGEKVTMSC KSSQSLLGRGDLGRLKKNALA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLS FGAGTKLELKR

SEQ ID NO:493 Vk Framework 1 DIVMTQSPSSLAVSAGEKVTMSC

SEQ ID NO:494 Vk CDR1 KSSQSLLGRGDLGRLKKNALA

SEQ ID NO:495 Vk Framework 2 WYQQKPGQSPRLLIY

SEQ ID NO:496 Vk CDR2 WASTRES

SEQ ID NO:497 Vk Framework 3 GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:498 Vk CDR 3 KQSYNLLS
SEQ ID NO:499 Vk Framework 4 FGAGTKLELKR

SEQ ID NO:500
HuC6D4-RGD3 EIVMTQSPATLSVSPGERVTMSC KSSQSLLGRGDLGRLKKNALA WYQQKPGQAPRLLIY WASTRES GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR

SEQ ID NO:501 Vk Framework 1 EIVMTQSPATLSVSPGERVTMSC
SEQ ID NO:502 Vk CDR1 KSSQSLLGRGDLGRLKKNALA
SEQ ID NO:503 Vk Framework 2 WYQQKPGQAPRLLIY
SEQ ID NO:504 Vk CDR2 WASTRES
SEQ ID NO:505 Vk Framework 3 GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC
SEQ ID NO:506 Vk CDR 3 KQSYNLLS
SEQ ID NO:507 Vk Framework 4 FGQGTVLEIKR

SEQ ID NO:508 HuC6D4V1 VH CDR1 DYSMH
SEQ ID NO:509 HuC6D4V1 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:510 HuC6D4V1 VH CDR3 FYYGRDS

SEQ ID NO:511 HuC6D4A3 VH CDR1 DYSMH
SEQ ID NO:512 HuC6D4A3 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:513 HuC6D4A3 VH CDR3 FYYGRDS

SEQ ID NO:514 HuC6D4B7 VH CDR1 DYSMH
SEQ ID NO:515 HuC6D4B7 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:516 HuC6D4B7 VH CDR3 FYYGRDT

SEQ ID NO:517 HuC6D4E5 VH CDR1 DYSMH
SEQ ID NO:518 HuC6D4E5 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:519 HuC6D4E5 VH CDR3 FYYGRDT

SEQ ID NO:520 HuC6D4 VH CDR1 DYSMH
SEQ ID NO:521 HuC6D4 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:522 HuC6D4 VH CDR3 FYYGRDT

SEQ ID NO:523 C6D4-RGD3 VH CDR1 DYSMH
SEQ ID NO:524 C6D4-RGD3 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:525 C6D4-RGD3 VH CDR3 FYYGRDS

SEQ ID NO:526 HuC6D4-RGD3 VH CDR1 DYSMH
SEQ ID NO:527 HuC6D4-RGD3 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:528 HuC6D4-RGD3 VH CDR3 FYYGRDT

SEQ ID NO:529 HuC6D4V1 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:530 HuC6D4V1 Vk CDR2 WASTRES
SEQ ID NO:531 HuC6D4V1 Vk CDR3 KQSYNLLS

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SEQ ID NO:532 HuC6D4A3 Vk CDR1 KSSQSLLNSRSRKNYLA
SEQ ID NO:533 HuC6D4A3 Vk CDR2 WASTRES
SEQ ID NO:534 HuC6D4A3 Vk CDR3 KQSYNLIS

SEQ ID NO:535 HuC6D4B7 Vk CDR1 KSSQSLLNSRTRKNYLA
SEQ ID NO:536 HuC6D4B7 Vk CDR2 WASTRES
SEQ ID NO:537 HuC6D4B7 Vk CDR3 KQSSNLIS

SEQ ID NO:538 HuC6D4E5 Vk CDR1 KSSQSLLNSRSRKNYLA
SEQ ID NO:539 HuC6D4E5 Vk CDR2 WASTRES
SEQ ID NO:540 HuC6D4E5 Vk CDR3 KQSYNLLS

SEQ ID NO:541 HuC6D4 Vk CDR1 KSSQSLLNSRSRKNYLA
SEQ ID NO:542 HuC6D4 Vk CDR2 WASTRES
SEQ ID NO:543 HuC6D4 Vk CDR3 KQSYNLLS

SEQ ID NO:544 C6D4-RGD3 Vk CDR1 KSSQSLLGRGDLGRLKKNALA
SEQ ID NO:545 C6D4-RGD3 Vk CDR2 WASTRES
SEQ ID NO:546 C6D4-RGD3 Vk CDR3 KQSYNLLS

SEQ ID NO:547 HuC6D4-RGD3 Vk CDR1 KSSQSLLGRGDLGRLKKNALA
SEQ ID NO:548 HuC6D4-RGD3 Vk CDR2 WASTRES
SEQ ID NO:549 HuC6D4-RGD3 Vk CDR3 KQSYNLLS

SEQ ID NO:550 **heavy chain FR1** QIQLVQSG(P/A)(E/K)(L/V)KKPG(E/A)(T/S)VKISCKASGYTFT
SEQ ID NO:551 **heavy chain FR2** WV(K/R)QAPG(K/Q)GL(K/E)WVA
SEQ ID NO:552 **heavy chain FR3** RF(A/T/S)V(S/T)L(E/D)TS(A/T)STAYL(Q/E)I(N/R/T)(N/S)L(K/R)(N/S)(E/D)DTA(T/V)YFCAI
SEQ ID NO:553 **heavy chain FR4** WGQGT(T/A)LTVSS

SEQ ID NO:554 **light chain FR1** (D/E)IVMTQ(S/T)P(S/A/V)(S/T)L(A/S)VS(A/P)GE(K/R/I)VTMSC
SEQ ID NO:555 **light chain FR2** WYQQKPGQ(S/A)PRLLIY
SEQ ID NO:556 **light chain FR3** (G/D)VP(D/A)RF(T/S)GSGSGT(D/E)FTLTISSVQ(A/S)ED(L/F)AVYYC
SEQ ID NO:557 **light chain FR4** FG(A/Q)GT(K/V)LE(L/I)KR

SEQ ID NO:558 heavy chain FR1 QIQLx1QSGx2x3x34KKPGx4x5VKISCKASGYTFT
SEQ ID NO:559 heavy chain FR2 WVx6QAPGx7GLx8Wx9x10
SEQ ID NO:560 heavy chain FR3
RFx17x18x19Lx20TSx21x22TAx23Lx24Ix25x26Lx27x28x29DTAx30YFCAI
SEQ ID NO:561 heavy chain FR4 WGQGTx33LVTVSS
SEQ ID NO:562 heavy chain CDR1 DYSMH
SEQ ID NO:563 heavy chain CDR2 x11Ix12TETx13EPTx14ADDFx15x16
SEQ ID NO:564 heavy chain CDR3 x31YYGRDx32
where x1 = V or L, x2 = A or P, x3 = E or K, x4 = A or E, x5 = S or T, x6 = R or K, x7 = Q or K, x8 = E or K, x9 = V or M, x10 = A or G, x11 = R or W, x12 = N or K, x13 = G or D, x14 = F or Y, x15 = R, N, K or G, x16 = G or E, x17 = T, A, or S, x18 = V or F, x19 = T or S, x20 = D or E,

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x21 = T or A, x22 = S or T, x23 = Y or N, x24 = E or Q, x25 = R, N, I or T, x26 = S or N, x27 = R or K, x28 = S or N, x29 = D or E, x30 = V, T, or K, x31 = F or Y, x32 = T or S, x33 = T or A. x34 = V or L.

SEQ ID NO:565 light chain FR1 x40IVMx41Qx42Px43x44Lx45VSx46GEx47VTMSC
SEQ ID NO:566 light chain FR2 WYQQKPGQx49PRLLIY
SEQ ID NO:567 light chain FR3
x50VPx51RFx52GSGSGTx53FTLTISSVQx54EDx55AVYYC
SEQ ID NO:568 light chain FR4 FGx56GTx57LEx58KR

SEQ ID NO:569 light chain CDR1 KSSQSLLNSRx48RKNYLA
SEQ ID NO:570 light chain CDR2 WASTRES
SEQ ID NO:571 light chain CDR3 KQSYNLLS
where x40 = E or D, x41 = T or S, x42 = S or T, x43 = A, S or V, x44 = T, S, x45 = S or A, x46 = P or A, x47 = R, K or I, x48 = S or T, x49 = A or S, x50 = G or D, x51 = A or D, x52 = S or T, x53 = E or D, x54 = S, D or A, x55 = F or L, x56 = Q or A, x57 = V or K, x58 = I or L.

SEQ ID NO:572	(C6D4)	KSSQSLLNSRSRKNYLA
SEQ ID NO:573	(RGD1)	KSSQSLLGRGDLGNALA
SEQ ID NO:574	(RGD2)	KSSQSLLNSGRGDLGNALA
SEQ ID NO:575	(RGD3)	KSSQSLLGRGDLGRLKKNALA
SEQ ID NO:576	(RGD3-1)	KSSQSLLGRGDLGRLKKQKDHNALA
SEQ ID NO:577	(RGD3-2)	KSSQSLLGRGDLGRLKKQKDNALA
SEQ ID NO:578	(RGD3-3)	KSSQSLLGRGDLGRLKKQKNALA
SEQ ID NO:579	(RGD3-4)	KSSQSLLGRGDLGRLKKQNALA
SEQ ID NO:580	(RGD3-6)	KSSQSLLGRGDLGRLKNALA
SEQ ID NO:581	(RGD3-7)	KSSQSLLGRGDLGRLNALA
SEQ ID NO:582	(RGD3-8)	KSSQSLLGRGDLGRNALA
SEQ ID NO:583	(RGD3-9)	KSSQSLLGRGDLGRLKKQKDHH
SEQ ID NO:584	(RGD3-10)	KSSQSLLGRGDLGRLKKQKDH
SEQ ID NO:585	(RGD3-11)	KSSQSLLGRGDLGRLKKQKD
SEQ ID NO:586	(RGD3-12)	KSSQSLLGRGDLGRLKKQK
SEQ ID NO:587	(RGD3-13)	KSSQSLLGRGDLGRLKKQ
SEQ ID NO:588	(RGD3-14)	KSSQSLLGRGDLGRLKK
SEQ ID NO:589	(RGD3-15)	KSSQSLLGRGDLGRLK
SEQ ID NO:590	(RGD3-16)	KSSQSLLGRGDLGRL

SEQ ID NO:591	Human αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:592	Chimp αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:593	Rhesus αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:594	Cyno αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ

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SEQ ID NO:595	Cow αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:596	Pig αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:597	Horse αv	FLQDGAKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:598	Mouse αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:599	Rat αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:600	Armadillo αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRV LLGGPGSF***Y***WQGQ
SEQ ID NO:601	Platypus αv	FLQDGTKTVEYAPCRSRSI***DADG***QGFCQGGFSIDFTKADRVL LGGPGSF***Y***WQGQ
SEQ ID NO:602	Human β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:603	Chimp β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFERA V***HR***QKIS
SEQ ID NO:604	Rhesus β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:605	Cyno β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:606	Cow β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:607	Pig β8	SASM***H***NNIEKLNTVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:608	Horse β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKA V***HR***QKIS
SEQ ID NO:609	Mouse β8	SASM***H***NNIEKLNSVGNDLSKKMALYSRDFRLGFGSYVDKT VSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEK AV***HR***QKIS
SEQ ID NO:610	Rat β8	SASM***H***NNIEKLNSVGNDLSKKMALFSHDFRLGFGSYVDKT VSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEK AV***HR***QKIS
SEQ ID NO:611	Armadillo β8	SASM***H***NNIEKLNSVGNDLSRKMAFFSLDFRLGFGSYVDKTV SPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFAK AV***HR***QKIS
SEQ ID NO:612	Platypus β8	SASM***H***NNIEKLNSVGNDLSQKMADFTRDFRLGFGSYVDKT VSPYISIHPGRIRNQC***S***QY***D******LD***CMPPHGYIHVLPLTENVTEFE KAVNKQKIS

SEQ ID NO:613	C6D4 Vh CDR1	**Y**TFTDY**S**MH
SEQ ID NO:614	C6D4 Vh CDR2	RINTETGEPTFADDFRG

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SEQ ID NO:615	C6D4 Vh CDR3	FYYGRDS
SEQ ID NO:616	C6D4 Vk CDR1	KSSQSL**L**N**S**R**T**R**K**N**Y**LA
SEQ ID NO:617	C6D4 Vk CDR2	**YW**ASTRES
SEQ ID NO:618	C6D4 Vk CDR3	KQ**S**Y**N**LLS
SEQ ID NO:619	β8, α1 helix	SASM**H**NNIEKLNSVGNDLSRKMAFFS
SEQ ID NO:620	β8, SDL	TVSPYISIHPERIHNQC**SDYNLD**CMPPH
SEQ ID NO:621	β8, α2 helix	NITEFEKAV**HR**
SEQ ID NO:622	αV, β-propeller domain blade W3	KQDKILACAPLYHWRTEMKQEREPVGTCFLQD GTKTVEYAPCRSQDI**DADG**QGFCQGGFSIDFT KADRVLLGGPGSF**Y**WQGQLISDQ VAEIVSKYDPNVYSIKYNNQLATRTAQAIFD

SEQ ID NO:623: head sequence of integrin αv
FNLDVDSPAEYSGPEGSYFGFAVDFFVPSASSRMFLLVGAPKANTTQPGIVEGGQVLKC
DWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWFGASVRSKQDKILACAPLYHWRTE
MKQEREPVGTCFLQDGTKTVEYAPCRSQDIDADGQGFCQGGFSIDFTKADRVLLGGPGS
FYWQGQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAIFDDSYLGYSVAVGDFNGD
GIDDFVSGVPRAARTLGMVYIYDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYAD
VFIGAPLFMDRGSDGKLQEVGQVSVSLQRASGDFQTTKLNGFEVFARFGSAIAPLGDLD
QDGFNDIAIAAPYGGEDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSMPPSFGYSMKG
ATDIDKNGYPDLIVGAFGVDRAILYRARP

SEQ ID NO:624
4F1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTNYLIE WVKQRPGQGLEWIG VINPGTGGTNYNKKFKV
KATLTADKSSSTAYMQLGGLTFDDSAVYFCAR EGNARTYYYAMDY WGQGTSVTVSS

SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:628 **VH CDR1** AFTNYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:634 **VH CDR2** VINPGTGGTNYNKKFKV
SEQ ID NO:637 **VH Framework 3** KATLTADKSSSTAYMQLGGLTFDDSAVYFCAR
SEQ ID NO:651 **VH CDR3** EGNARTYYYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:656
6B9 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVKQRPGQGLEWIG VINPETGGTNYNAKFKG
KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS

SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:635 **VH CDR2** VINPETGGTNYNAKFKG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:652 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:657
6B9.1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR AGNYIYAMDY
WGQGTSVTVSS

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SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:653 **VH CDR3** AGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:658
A1 VH QVQLQQSGAELVRPGASVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG KATLTADKSSSSVYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:626 **VH Framework 1** QVQLQQSGAELVRPGASVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:639 **VH Framework 3** KATLTADKSSSSVYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:659
A2 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG KATLTADKSSSTAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:640 **VH Framework 3** KATLTADKSSSTAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:660
A8 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:641 **VH Framework 3** KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:661
A11 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDNLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:630 **VH CDR1** AFTDNLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR

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SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:662
B1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVKQRPGQGLEWIG VINPETGGTNYNAKFRG
KATLTADKSSSSAYMQLSSLSSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:642 **VH Framework 3** KATLTADKSSSSAYMQLSSLSSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:663
B3 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:643 **VH Framework 3** KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:664
C4=F10 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:644 **VH Framework 3** RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:665
C7=D1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KATLTADKSSGSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:644 **VH Framework 3** RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:666
D3=F1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KATLTADKSSSSAYMQLSSLTSDDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS

SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:645 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSDDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:667
D10=E5 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:646 **VH Framework 3** KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:668
G4 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KVTLTADKSSSSAYMQLNSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:647 **VH Framework 3** KVTLTADKSSSSAYMQLNSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:669
C4 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:650 **VH Framework 3** RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:670
D10 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVRQRPGQGLEWIG VINPETGGTNYNAKFRG
KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:633 **VH Framework 2** WVRQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:646 **VH Framework 3** KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR

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SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:671
4F1A11 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:650 **VH Framework 3** RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:672
4F1E1 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIQ WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:631 **VH CDR1** AFTDYLIQ
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:673
4F1G3 VH QVQLQQSGAELVRPGTSVRVSCKASGY AFTDYLIQ WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTANKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:631 **VH CDR1** AFTDYLIQ
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:648 **VH Framework 3** KATLTANKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:674
4F1E10 VH QVQLQQSGAELVRPGTSVKVPCKASGY AFTDYLIQ WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:627 **VH Framework 1** QVQLQQSGAELVRPGTSVKVPCKASGY
SEQ ID NO:631 **VH CDR1** AFTDYLIQ
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:675
4F1E9 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIE WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS

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SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:629 **VH CDR1** AFTDYLIE
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:676
4F1H12 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIQ WVKQRPGQGLEWIG
VINPETGGTNYNAKFRG KATLTADKSSSSAYLQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:631 **VH CDR1** AFTDYLIQ
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:649 **VH Framework 3** KATLTADKSSSSAYLQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:677
F9 VH QVQLQQSGAELVRPGTSVKVSCKASGY AFTDYLIQ WVKQRPGQGLEWIG VINPETGGTNYNAKFRG
KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR EAGNYIYAMDY WGQGTSVTVSS
SEQ ID NO:625 **VH Framework 1** QVQLQQSGAELVRPGTSVKVSCKASGY
SEQ ID NO:631 **VH CDR1** AFTDYLIQ
SEQ ID NO:632 **VH Framework 2** WVKQRPGQGLEWIG
SEQ ID NO:636 **VH CDR2** VINPETGGTNYNAKFRG
SEQ ID NO:638 **VH Framework 3** KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR
SEQ ID NO:654 **VH CDR3** EAGNYIYAMDY
SEQ ID NO:655 **VH Framework 4** WGQGTSVTVSS

SEQ ID NO:678
4F1 VL DIQMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:692 **VL** **Framework 1** DIQMTQSPASLSASVGETVTITC
SEQ ID NO:693 **VL** **CDR1** RASVNIYSYLV
SEQ ID NO:694 **VL** **Framework 2** WYQQKQGKSPQLLVH
SEQ ID NO:695 **VL** **CDR2** NAKTLAE
SEQ ID NO:696 **VL** **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 **VL** **CDR3** QHHHGTPYT
SEQ ID NO:698 **VL** **Framework 4** FGGGTKLEIKA

SEQ ID NO:679
6B9 VL DIEMTQTPASLSASVGETVTITC RASENIYSYLV WYQQKQGKSPQVLVY NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHNGTPYT FGGGTKLEIKA
SEQ ID NO:699 **VL** **Framework 1** DIEMTQTPASLSASVGETVTITC
SEQ ID NO:700 **VL** **CDR1** RASENIYSYLV
SEQ ID NO:701 **VL** **Framework 2** WYQQKQGKSPQVLVY
SEQ ID NO:695 **VL** **CDR2** NAKTLAE
SEQ ID NO:696 **VL** **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC

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SEQ ID NO:702 VL CDR3 QHHNGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:680
6B9.1 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:681
A1 = A2 = C4 = C7 = D1 = D10 = E5 = F1 = F10 = G4 VL DIVMTQSPASLSASVGETVTITC
RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:682
A8 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSVQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:683
A11 VL HIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:704 VL Framework 1 HIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:684

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B1 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDVGSYYC QHHHGTPYT FGGGTKLEIKA

SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:685
B3 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA

SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:686
D10=E5 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA

SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:698 VL Framework 4 FGGGTKLEIKA

SEQ ID NO:687
C4 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKR

SEQ ID NO:703 VL Framework 1 DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE
SEQ ID NO:696 VL Framework 3 GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL CDR3 QHHHGTPYT
SEQ ID NO:706 VL Framework 4 FGGGTKLEIKR

SEQ ID NO:688
D10 VL DIEMTQTPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE
GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKR

SEQ ID NO:699 VL Framework 1 DIEMTQTPASLSASVGETVTITC
SEQ ID NO:693 VL CDR1 RASVNIYSYLV
SEQ ID NO:694 VL Framework 2 WYQQKQGKSPQLLVH
SEQ ID NO:695 VL CDR2 NAKTLAE

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SEQ ID NO:696 VL **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL **CDR3** QHHHGTPYT
SEQ ID NO:706 VL **Framework 4** FGGGTKLEIKR

SEQ ID NO:689
4F1E1 = 1F1G3 = 4F1B5 = 4F1G11 = 4F1A9 = 4F1B9 = 4F1H9 = 4F1D10 = 4F1E9 = 4F1F10 = 4F1H11 = 4F1H12 VL DIVMTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:703 VL **Framework 1** DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL **CDR1** RASVNIYSYLV
SEQ ID NO:694 VL **Framework 2** WYQQKQGKSPQLLVH
SEQ ID NO:695 VL **CDR2** NAKTLAE
SEQ ID NO:696 VL **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL **CDR3** QHHHGTPYT
SEQ ID NO:698 VL **Framework 4** FGGGTKLEIKA

SEQ ID NO:690
4FA11 VL DIVVTQSPASLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKA
SEQ ID NO:705 VL **Framework 1** DIVVTQSPASLSASVGETVTITC
SEQ ID NO:693 VL **CDR1** RASVNIYSYLV
SEQ ID NO:694 VL **Framework 2** WYQQKQGKSPQLLVH
SEQ ID NO:695 VL **CDR2** NAKTLAE
SEQ ID NO:696 VL **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL **CDR3** QHHHGTPYT
SEQ ID NO:698 VL **Framework 4** FGGGTKLEIKA

SEQ ID NO:691
F9 VL DIVMTQSPAFLSASVGETVTITC RASVNIYSYLV WYQQKQGKSPQLLVH NAKTLAE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC QHHHGTPYT FGGGTKLEIKR
SEQ ID NO:703 VL **Framework 1** DIVMTQSPASLSASVGETVTITC
SEQ ID NO:693 VL **CDR1** RASVNIYSYLV
SEQ ID NO:694 VL **Framework 2** WYQQKQGKSPQLLVH
SEQ ID NO:695 VL **CDR2** NAKTLAE
SEQ ID NO:696 VL **Framework 3** GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
SEQ ID NO:697 VL **CDR3** QHHHGTPYT
SEQ ID NO:706 VL **Framework 4** FGGGTKLEIKR

SEQ ID NO:707	C6D4 Vh CDR1	DYSMH
SEQ ID NO:615	C6D4 Vh CDR3	FYYGRDS
SEQ ID NO:620	β8, SDL	TVSPYISIHPERIHNQC**SDYNLD**CMPPH
SEQ ID NO:616	C6D4 Vk CDR1	KSSQSL**LNSRTR**KNYLA
SEQ ID NO:708	C6D4 Vk CDR2	**W**ASTRES
SEQ ID NO:618	C6D4 Vk CDR3	KQSY**N**LLS

SEQ ID NO:709 αVβ6: GRGDLGRLKK
SEQ ID NO:710 αIIbβ3: GRGDSP
SEQ ID NO:711 αIIbβ3: AKQRGDV

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SEQ ID NO:712: RGDLGRLKK - loop of L-TGFβ

SEQ ID NO:713: DDHGRGDLGRLK (TGFB3 sequence)

SEQ ID NO: 714 TGBF1
MPPSGLRLLLLLLPLLWLLVLTPGRPAAGLSTCKTIDMELVKRKRIEAIRGQILSKLRLASPPSQGE
VPPGPLPEAVLALYNSTRDRVAGESAEPEPEPEADYYAKEVTRVLMVETHNEIYDKFKQSTHSIY
MFFNTSELREAVPEPVLLSRAELRLLRLKLKVEQHVELYQKYSNNSWRYLSNRLLAPSDSPEWL
SFDVTGVVRQWLSRGGEIEGFRLSAHCSCDSRDNTLQVDINGFTTGRRGDLATIHGMNRPFLLL
MATPLERAQHLQSSRHRRALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCL
GPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSC
KCS

SEQ ID NO: 715 TGFB2
MHYCVLSAFLILHLVTVALSLSTCSTLDMDQFMRKRIEAIRGQILSKLKLTSPPEDYPEPEEVPPEV
ISIYNSTRDLLQEKASRRAAACERERSDEEYYAKEVYKIDMPPFFPSENAIPPTFYRPYFRIVRFDV
SAMEKNASNLVKAEFRVFRLQNPKARVPEQRIELYQILKSKDLTSPTQRYIDSKVVKTRAEGEWL
SFDVTDAVHEWLHPSYRLESQQTNRRKKRALDAAYCFRVQDNCCLRPLYIDFKRDLGWKWIHEP
KGYNANFCAGACPYLWSSDTQHSRVLSLYNTINPEASASPCCVSQDLEPLTILYYIGKTPKIEQLS
NMIVKSCKCS

SEQ ID NO: 716 TGFB3
MKMHLQRALVVLALLNFATVSLSLSTCTTLDFGHIKKKRVEAIRGQILSKLRLTSPPEPTVTHVPY
QVLALYNSTRELLEEMHGEREEGCTQENTESEYYAKEIHKFDMIQGLAEHNELAVCPKGITSKVF
RFNVSSVEKNRTNLFRAEFRVLRVPNPSSKRNEQRIELFQILRPDEHIAKQRYIGGKNLPTRGTAE
WLSFDVTDTVREWLLRRESNLGLEISIHCPCHTFQPNGDILENIHEVMEIKFKGVDNEDDHGRGD
LGRLKKQKQHHNPHLILMMIPPHRLDNPGQGGQRKKRALDTNYCFRNLEENCCVRPLYIDFRQD
LGWKWVHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCCVPQDLEPLTILYY
VGRTPKVEQLSNMVVKSCKCS

SEQ ID NO: 717 C6D4 vk
DIVMTQSPSSLAVSAGEKVTMSCKSSQSLLNSRTRKNYLAWYQQKPGQSPRLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQ
AEDLAVYYCKQSYNLLSFGAGTKLELKAADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD
QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

SEQ ID NO:718 C6D4-RDG1 KSSQSLLGRGDLGNALA
SEQ ID NO:719 C6D4-RDG2 KSSQSLLNSGRGDLGNALA
SEQ ID NO:720 C6D4-RDG3 KSSQSLLGRGDLGRLKKNALA

SEQ ID NO:721 – GRGDLGRLK

SEQ ID NO:722
C6D4 VH QIQLVQSGPELKKPGETVKISCKASGYTFT DYSMH WVKQAPGKGLKWVA RINTETGEPTFADDFRG
RFAVSLETSASTAYLQINNLKNEDTATYFCAI FYYGRDS WGQGTTLTVSS

SEQ ID NO:732 VH Framework 1 QIQLVQSGPELKKPGETVKISCKASGYTFT
SEQ ID NO:733 VH CDR1 DYSMH
SEQ ID NO:734 VH Framework 2 WVKQAPGKGLKWVA
SEQ ID NO:735 VH CDR2 RINTETGEPTFADDFRG
SEQ ID NO:736 VH Framework 3 RFAVSLETSASTAYLQINNLKNEDTATYFCAI

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SEQ ID NO:737 **VH** **CDR3** FYYGRDS
SEQ ID NO:738 **VH** **Framework 4** WGQGTTLTVSS

SEQ ID NO:723
HuC6D4 V1 VH QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA
RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDS WGQGTTLTVSS
SEQ ID NO:739 **VH** **Framework 1** QIQLVQSGAEVKKPGASVKISCKASGYTFT
SEQ ID NO:733 **VH** **CDR1** DYSMH
SEQ ID NO:740 **VH** **Framework 2** WVRQAPGQGLEWVA
SEQ ID NO:735 **VH** **CDR2** RINTETGEPTFADDFRG
SEQ ID NO:741 **VH** **Framework 3** RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:737 **VH** **CDR3** FYYGRDS
SEQ ID NO:738 **VH** **Framework 4** WGQGTTLTVSS

SEQ ID NO:724
Mutclone A3 VH QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA
RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDS WGQGTTLTVSS
SEQ ID NO:739 **VH** **Framework 1** QIQLVQSGAEVKKPGASVKISCKASGYTFT
SEQ ID NO:733 **VH** **CDR1** DYSMH
SEQ ID NO:740 **VH** **Framework 2** WVRQAPGQGLEWVA
SEQ ID NO:735 **VH** **CDR2** RINTETGEPTFADDFRG
SEQ ID NO:741 **VH** **Framework 3** RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:737 **VH** **CDR3** FYYGRDS
SEQ ID NO:738 **VH** **Framework 4** WGQGTTLTVSS

SEQ ID NO:725
Mutclone B7 VH QIQLVQSGAKVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA
RINTETGEPTFADDFRG RFSVTLDTSTSTAYLEITSLRSDDTAVYFCAI FYYGRDT WGQGTTLTVSS
SEQ ID NO:742 **VH** **Framework 1** QIQLVQSGAKVKKPGASVKISCKASGYTFT
SEQ ID NO:733 **VH** **CDR1** DYSMH
SEQ ID NO:740 **VH** **Framework 2** WVRQAPGQGLEWVA
SEQ ID NO:735 **VH** **CDR2** RINTETGEPTFADDFRG
SEQ ID NO:743 **VH** **Framework 3** RFSVTLDTSTSTAYLEITSLRSDDTAVYFCAI
SEQ ID NO:744 **VH** **CDR3** FYYGRDT
SEQ ID NO:738 **VH** **Framework 4** WGQGTTLTVSS

SEQ ID NO:726
Mutclone E5 VH QIQLVQSGAEVKKPGASVKISCKASGYTFT DYSMH WVRQAPGQGLEWVA
RINTETGEPTFADDFRG RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI FYYGRDT WGQGTTLTVSS
SEQ ID NO:739 **VH** **Framework 1** QIQLVQSGAEVKKPGASVKISCKASGYTFT
SEQ ID NO:733 **VH** **CDR1** DYSMH
SEQ ID NO:740 **VH** **Framework 2** WVRQAPGQGLEWVA
SEQ ID NO:735 **VH** **CDR2** RINTETGEPTFADDFRG
SEQ ID NO:741 **VH** **Framework 3** RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI
SEQ ID NO:744 **VH** **CDR3** FYYGRDT
SEQ ID NO:738 **VH** **Framework 4** WGQGTTLTVSS

SEQ ID NO:727
C6D4 VK DIVMTQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPRLLIY WASTRES
GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLLS FGAGTKLELKR

SEQ ID NO:745 **VK** **Framework 1** DIVMTQSPSSLAVSAGEKVTMSC
SEQ ID NO:746 **VK** **CDR1** KSSQSLLNSRTRKNYLA
SEQ ID NO:747 **VK** **Framework 2** WYQQKPGQSPRLLIY
SEQ ID NO:748 **VK** **CDR2** WASTRES
SEQ ID NO:749 **VK** **Framework 3** GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC
SEQ ID NO:750 **VK** **CDR3** KQSYNLLS
SEQ ID NO:751 **VK** **Framework 4** FGAGTKLELKR

SEQ ID NO:728
HuC6D4 V1 VK EIVMTQSPATLSVSPGERVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQAPRLLIY WASTRES GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR
SEQ ID NO:752 **VK** **Framework 1** EIVMTQSPATLSVSPGERVTMSC
SEQ ID NO:746 **VK** **CDR1** KSSQSLLNSRTRKNYLA
SEQ ID NO:747 **VK** **Framework 2** WYQQKPGQSPRLLIY
SEQ ID NO:748 **VK** **CDR2** WASTRES
SEQ ID NO:753 **VK** **Framework 3** GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC
SEQ ID NO:750 **VK** **CDR3** KQSYNLLS
SEQ ID NO:754 **VK** **Framework 4** FGQGTVLEIKR

SEQ ID NO:729
Mutclone A3 VK EIVMTQSPATLSVSPGEIVTMSC KSSQSLLNSRSRKNYLA WYQQKPGQAPRLLIY WASTRES GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR
SEQ ID NO:755 **VK** **Framework 1** EIVMTQSPATLSVSPGEIVTMSC
SEQ ID NO:756 **VK** **CDR1** KSSQSLLNSRSRKNYLA
SEQ ID NO:747 **VK** **Framework 2** WYQQKPGQSPRLLIY
SEQ ID NO:748 **VK** **CDR2** WASTRES
SEQ ID NO:753 **VK** **Framework 3** GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC
SEQ ID NO:750 **VK** **CDR3** KQSYNLLS
SEQ ID NO:754 **VK** **Framework 4** FGQGTVLEIKR

SEQ ID NO:730
Mutclone B7 VK EIVMTQTPVTLSVSPGERVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQAPRLLIY WASTRES DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSSNLLS FGQGTVLEIKR
SEQ ID NO:757 **VK** **Framework 1** EIVMTQTPVTLSVSPGERVTMSC
SEQ ID NO:746 **VK** **CDR1** KSSQSLLNSRTRKNYLA
SEQ ID NO:747 **VK** **Framework 2** WYQQKPGQSPRLLIY
SEQ ID NO:748 **VK** **CDR2** WASTRES
SEQ ID NO:758 **VK** **Framework 3** DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC
SEQ ID NO:750 **VK** **CDR3** KQSYNLLS
SEQ ID NO:754 **VK** **Framework 4** FGQGTVLEIKR

SEQ ID NO:731
Mutclone E5 VK EIVMTQSPATLSVSPGERVTMSC KSSQSLLNSRSRKNYLA WYQQKPGQAPRLLIY WASTRES GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC KQSYNLLS FGQGTVLEIKR
SEQ ID NO:752 **VK** **Framework 1** EIVMTQSPATLSVSPGERVTMSC
SEQ ID NO:756 **VK** **CDR1** KSSQSLLNSRSRKNYLA
SEQ ID NO:747 **VK** **Framework 2** WYQQKPGQSPRLLIY
SEQ ID NO:748 **VK** **CDR2** WASTRES
SEQ ID NO:753 **VK** **Framework 3** GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC

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SEQ ID NO:750 VK CDR3 KQSYNLLS
SEQ ID NO:754 VK Framework 4 FGQGTVLEIKR

SEQ ID NO:755 – E8 - VL Framework 3 - GVPSRFSGSGSGTRFSLKINSLQPEDFGSYYC

SEQ ID NO:756 - RGDL

SEQ ID NO:757	αv	DADGQ
SEQ ID NO:758	αv	SFYWQ
SEQ ID NO:759	αv	FDDSY

SEQ ID NO:760
KQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAPCRSQDIDADGQGFCQGG
FSIDFTKADRVLLGGPGSFYWQGQLISDQVAEIVSKYDPNVYSIKYNNQLATRTAQAIFD

SEQ ID NO:761	β8	YNLDC
SEQ ID NO:762	β8	QCSDYNL
SEQ ID NO:763	β8	SMHNN
SEQ ID NO:764	β8	AVHRQ

SEQ ID NO:765 - KSSQSLLGRGDLGRLKK

SEQ ID NO:766 – C6H - VH CDR1 – TFTDYSMH
SEQ ID NO:767 – C6H - VH CDR2 – RINTETGEPTFADDFRG
SEQ ID NO:768 – C6H – VH CDR3 - FYYGRDS

SEQ ID NO:877 heavy chain FR2 WV(K/R)QAPG(K/Q)GL(K/E)W(V/M)(A/G)
SEQ ID NO:878 heavy chain FR3
RF(A/T/S)(V/F)(S/T)L(E/D)TS(A/T)(S/T)TA(Y/N)L(Q/E)I(N/R/I/T)(N/S)L(K/R)(N/S)(E/D)DTA(T/V/K)YFCAI
SEQ ID NO:879 heavy chain FR4 WGQGT(T/A)LTVSS

SEQ ID NO:880 light chain FR1
(D/E)IVM(T/S)Q(S/T)P(S/A/V)(S/T)L(A/S)VS(A/P)GE(K/R/I)VTMSC
SEQ ID NO:881 light chain FR2 WYQQKPGQ(S/A)PRLLIY
SEQ ID NO:882 light chain FR3
(G/D)VP(D/A)RF(T/S)GSGSGT(D/E)FTLTISSVQ(A/S/D)ED(L/F)AVYYC
SEQ ID NO:883 light chain FR4 FG(A/Q)GT(K/V)LE(i/LI)KR

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WHAT IS CLAIMED IS:

1. An antibody that specifically binds human αvβ8 and blocks binding of TGFβ peptide to αvβ8, wherein the antibody binds to an epitope on human αvβ8 comprising amino acids D148, A149, D150, G151, and Y178 of human αv as occurs in SEQ ID NO:393 and amino acids H118, S170, D171, Y172, N173 L174, D175, H200, and R201 of human β8 as occurs in SEQ ID NO:394.

2. The antibody of claim 1, wherein the antibody comprises heavy chain CDRs SEQ ID NO:562, SEQ ID NO: 563, and SEQ ID NO; 564 and light chain CDRs SEQ ID NO:569, SEQ ID NO: 570, and SEQ ID NO: 571.

3. The antibody of claim 1, wherein the antibody comprises:
heavy chain CDRs SEQ ID NO:313, SEQ ID NO:314, and SEQ ID NO:315; and light chain CDRs SEQ ID NO:334, SEQ ID NO:335, and SEQ ID NO:336; or
heavy chain CDRs SEQ ID NO:319, SEQ ID NO:320, and SEQ ID NO:321; and light chain CDRs SEQ ID NO:340, SEQ ID NO:341, and SEQ ID NO:342; or
heavy chain CDRs SEQ ID NO:316, SEQ ID NO:317, and SEQ ID NO:318; and light chain CDRs SEQ ID NO:337, SEQ ID NO:338, and SEQ ID NO:339; or
heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:343, SEQ ID NO:344, and SEQ ID NO:345; or
heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:346, SEQ ID NO:347, and SEQ ID NO:348; or
heavy chain CDRs SEQ ID NO:322, SEQ ID NO:323, and SEQ ID NO:324; and light chain CDRs SEQ ID NO:349, SEQ ID NO:350, and SEQ ID NO:351; or
heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:352, SEQ ID NO:353, and SEQ ID NO:354; or
heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:355, SEQ ID NO:356, and SEQ ID NO:357; or
heavy chain CDRs SEQ ID NO:325, SEQ ID NO:326, and SEQ ID NO:327; and light chain CDRs SEQ ID NO:358, SEQ ID NO:359, and SEQ ID NO:360; or

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heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:364, SEQ ID NO:365, and SEQ ID NO:366; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:367, SEQ ID NO:368, and SEQ ID NO:369; and light chain CDRs SEQ ID NO:376, SEQ ID NO:377, and SEQ ID NO:378; or

heavy chain CDRs SEQ ID NO:370, SEQ ID NO:371, and SEQ ID NO:372; and light chain CDRs SEQ ID NO:373, SEQ ID NO:374, and SEQ ID NO:375; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:382, SEQ ID NO:383, and SEQ ID NO:384; or

heavy chain CDRs SEQ ID NO:379, SEQ ID NO:380, and SEQ ID NO:381; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:331, SEQ ID NO:332, and SEQ ID NO:333; and light chain CDRs SEQ ID NO:361, SEQ ID NO:362, and SEQ ID NO:363; or

heavy chain CDRs SEQ ID NO:508, SEQ ID NO:509, and SEQ ID NO:510; and light chain CDRs SEQ ID NO:529, SEQ ID NO:530, and SEQ ID NO:531; or

heavy chain CDRs SEQ ID NO:511, SEQ ID NO:512, and SEQ ID NO:513; and light chain CDRs SEQ ID NO:532, SEQ ID NO:533, and SEQ ID NO:534; or

heavy chain CDRs SEQ ID NO:514, SEQ ID NO:515, and SEQ ID NO:516; and light chain CDRs SEQ ID NO:535, SEQ ID NO:536, and SEQ ID NO:537; or

heavy chain CDRs SEQ ID NO:517, SEQ ID NO:518, and SEQ ID NO:519; and light chain CDRs SEQ ID NO:538, SEQ ID NO:539, and SEQ ID NO:540; or

heavy chain CDRs SEQ ID NO:520, SEQ ID NO:521, and SEQ ID NO:522; and light chain CDRs SEQ ID NO:541, SEQ ID NO:542, and SEQ ID NO:543; or

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:544, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528; and light chain CDRs SEQ ID NO:547, SEQ ID NO:548, and SEQ ID NO:549.

4. The antibody of claim 2 or 3, wherein the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 558, SEQ ID NO: 559, SEQ ID NO: 560, and SEQ ID NO: 561, respectively, and light chain framework sequences

FR1, FR2, FR3,and FR4 as SEQ ID NO: 565, SEQ ID NO: 566, SEQ ID NO: 567, and SEQ ID NO: 568, respectively.

5. The antibody of claim 2 or 3, wherein the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 550, SEQ ID NO: 551, SEQ ID NO: 552, and SEQ ID NO: 553, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 554, SEQ ID NO: 555, SEQ ID NO: 556, and SEQ ID NO: 557, respectively.

6. The antibody of any of claims 1-3, wherein the antibody is humanized.

7. The antibody of any of claims 1-3, wherein the antibody is linked to a detectable label.

8. An antibody that specifically binds human αvβ8 and blocks binding of TGFβ peptide to αvβ8, wherein the antibody binds to the specificity determining loop (SDL) of human β8.

9. The antibody of claim 8, wherein the antibody further binds to one, two, or all three of the human αv-head domain, the α1 helix of human β8, or the α2 helix of human β8.

10. The antibody of claim 8 or 9, wherein the antibody is humanized.

11. The antibody of claim 8 or 9, wherein the antibody is linked to a detectable label.

12. An antibody that binds to αvβ8 and αvβ6 and comprising a light chain CDR1 comprising the sequence RGDL.

13. The antibody of claim 12, comprising

heavy chain CDRs SEQ ID NO:523, SEQ ID NO:524, and SEQ ID NO:525; and light chain CDRs SEQ ID NO:544, SEQ ID NO:545, and SEQ ID NO:546; or

heavy chain CDRs SEQ ID NO:526, SEQ ID NO:527, and SEQ ID NO:528; and light chain CDRs SEQ ID NO:547, SEQ ID NO:548, and SEQ ID NO:549.

14. The antibody of claim 13, wherein the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 558, SEQ ID NO: 559, SEQ ID NO: 560, and SEQ ID NO: 561, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 565, SEQ ID NO: 566, SEQ ID NO: 567, and SEQ ID NO: 568, respectively.

15. The antibody of claim 13, wherein the antibody further comprises heavy chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 550, SEQ ID NO: 551, SEQ ID NO: 552, and SEQ ID NO: 553, respectively, and light chain framework sequences FR1, FR2, FR3,and FR4 as SEQ ID NO: 554, SEQ ID NO: 555, SEQ ID NO: 556, and SEQ ID NO: 557, respectively.

16. The antibody of claim 12 or 13, wherein the antibody is humanized.

17. The antibody of claim 12 or 13, wherein the antibody is linked to a detectable label.

18. A pharmaceutical composition comprising the antibody of any of claims 1-6 or 8-17 in a pharmaceutically acceptable excipient.

19. A method of enhancing an immune response to a viral infection in a human individual, the method comprising administering a sufficient amount of the antibody of any of claims 1-6 or 8-17 to the individual, thereby enhancing an immune response to the viral infection.

20. The method of claim 19, wherein the viral infection is a hepatitis infection.

21. The method of claim 20, wherein the viral infection is a hepatitis B infection.

22. A method of enhancing an immune response to a viral infection in a human individual, the method comprising administering a sufficient amount of the antibody to the individual, wherein the antibody specifically binds to human $\alpha v\beta 8$ and blocks binding of

TGFβ peptide to αvβ8 or blocks activation of αvβ8 by binding of TGFβ human αvβ8, thereby enhancing an immune response to the viral infection.

23. A method of enhancing an immune response to cancer in a human individual, the method comprising administering a sufficient amount of the antibody of any of claims 1-6 or 8-17 to the individual, thereby enhancing an immune response to the cancer.

24. The method of claim 23, wherein the cancer is lung cancer.

25. The method of claim 23, wherein the cancer is a metastatic cancer.

26. The method of claim 23, wherein the cancer is a primary cancer.

27. A method of enhancing an immune response to *H. pyroli* in a human individual, the method comprising administering a sufficient amount of the antibody of any of claims 1-6 or 8-17 to the individual, thereby enhancing an immune response to *H. pyroli*.

28. The method of claim 27, wherein the human individual has a peptide ulcer, gastric carcinoma or MALT lymphoma.

29. An antibody that specifically binds to human αvβ8 and that comprises human heavy chain CDRs SEQ ID NO:299, SEQ ID NO:301, and SEQ ID NO:303; and light chain CDRs SEQ ID NO:307, SEQ ID NO:309, and SEQ ID NO:311.

30. The antibody of claim 29, wherein the antibody is linked to a detectable label.

31. A method of detecting the presence, absence, or quantity of human in a sample, the method comprising,

contacting the antibody of 29-30 to the sample, and

detecting or quantifying binding of the antibody to the sample.

32. The method of claim 31, wherein the sample is a formalin-fixed sample.

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VH	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
(Mouse Hybridoma Name)							
B13C4 15-8	EVQLQQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
B13C4 15-10	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
B13H3.2	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWMG	WIKTETDEPTYADDFKG	RFAFSLETSASTANLQIINLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B13C1231015	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFNG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B15B11Vh	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
B2B2 15-9	QIQLLQSGPELKKPGETVKISCLASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEFTFADDFGG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
R11D12715.3	EVQLVESGGGLVQPGGSLKLSCAASGF	TFSSFGMS	WVRQTPDKRLELVA	TINSNGGSTYYPDNMKG	RFTISRDNAKNTLYLQMSSLKSEDTAMYYCAS	ACYRYGAFFDY	WGQGTTLTVSS
(Produced Rabbit IgG clone name)							
RSDLVH-1	EVQLLESGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFKG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTVTVSS
RSDLVH-3	QVQLMQSGPELKKPGETVKISCKASGY	TFTDYSIH	WVKQAPGKGLKWMG	WIKTETGEPTYADDFNG	RFAFSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
RSDLVH-16	QIQLQQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
(scFv clone from Yeast Display library)							
29	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
44	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEFTFADDFRG	RFAVSLETSATTAYLQINNLKNEDTAKYFCAI	YYYGRDS	WGQGTTLTVSS
A1=B4=F9	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDT	WGQGTTLSVSS
A5=C6	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTALTVSS
D4=E6	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	YYYGRDS	WGQGTTLTVSS
Final clone for in vivo/in vitro Functional test in IgG format							
C6D4	QIQLLQSGPELKKPGETVKISCKASGY	TFTDYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTTLTVSS

FIG. 1

VH	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
(Mouse Hybridoma Name)							
B2B2 35-20	DIVMSQSPSSMYASLGERVTITC	KASQDINSYLS	WFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPPLT	FGAGTKLELKA
B2B2 35- 26	QIVLTQSPSSMYASLGERVTITC	KASQDINSYLS	WFQQKPGKSPKTLIY	RANRLVD	GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC	LQYDEFPPLT	FGAGTKLELKA
B15B1lvk34-26	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSYMH	WYQQKPGTSPKLWIY	DTSNLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPLT	FGSGTKLEIKA
B15B1lvk33-24	EIVLTQSPAIMSASPGEKVTMTC	SASSSVSYMH	WYQQKPGSSPKLWIY	DTSNLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPLT	FGDGTRLEIKA
B15B1lvk35-26	QIVLTQSPAIMSASPGEKVTMTC	SASSSVSYMH	WYQQKSGTSPKLWIY	DTSNLAS	GVPARFSGSGSGTSYSLTISSMEADDAATYYC	QQWSSNPPT	FGAGTKLELKA
B13C12134-25	DIKMTQSPAIMSASPGEKVTMTC	SASSSVSYMH	WYQQKSGTSPKRWIY	DTSKLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPTT	FGSGTKLEIKA
B13C12133-26	QMVLTHSPAIMSASPGEKVTMTC	SASSSVSYMH	WYQQKPGSSPKPWIY	GTSNLAS	GVPARFSGSGSGTSYSLTISRMEAEDAATYYC	QQWSSNPPT	FGDGTRLEIKA
B13C4 35-20	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
B15B1lvk35-20	DIVMSQSPSSLAVSAGENVTVSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYFC	KQSYNLLT	FGAGTKLELKA
B13C12335-25	DIKMTQSPSSLAVSPGEKVTMSC	KSSQSLLHSRTRKNYLA	WYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
B13C1233520	DIVMSQSPSSLAVSPGEKVTMSC	KSSQSLLHSRTRKNYLA	WYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
(Produced Rabbit IgG clone name)							
RSDLVK-1	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKR
RSDLVK-6	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTRLEIKR
RSDLVK-10	DIVMTQSPSSLAVSAGENVTVSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTGFTLTISSVQAEDLAVYFC	KQSYNLLT	FGAGTRLEIKR
RSDLVK-13	DIVMSQSPSSLAVSPGEKVTMSC	KSSQSLLHSRTRKNYLA	WYQQKPGQSPKLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKR
(scFv clone from Yeast Display library)							
29	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
44	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC	KQSYNLLT	FGAGTKLELKA
A1=B4=F9	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
A5=C6	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLT	FGAGTKLELKA
D4=E6	DIVMSQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQXPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQDEDLAVYYC	KQSYNLLS	FGAGTKLELKA
Final clone for in vivo/in vitro Functional test in IgG format							
C6D4	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLS	FGAGTKLELKR

FIG. 2

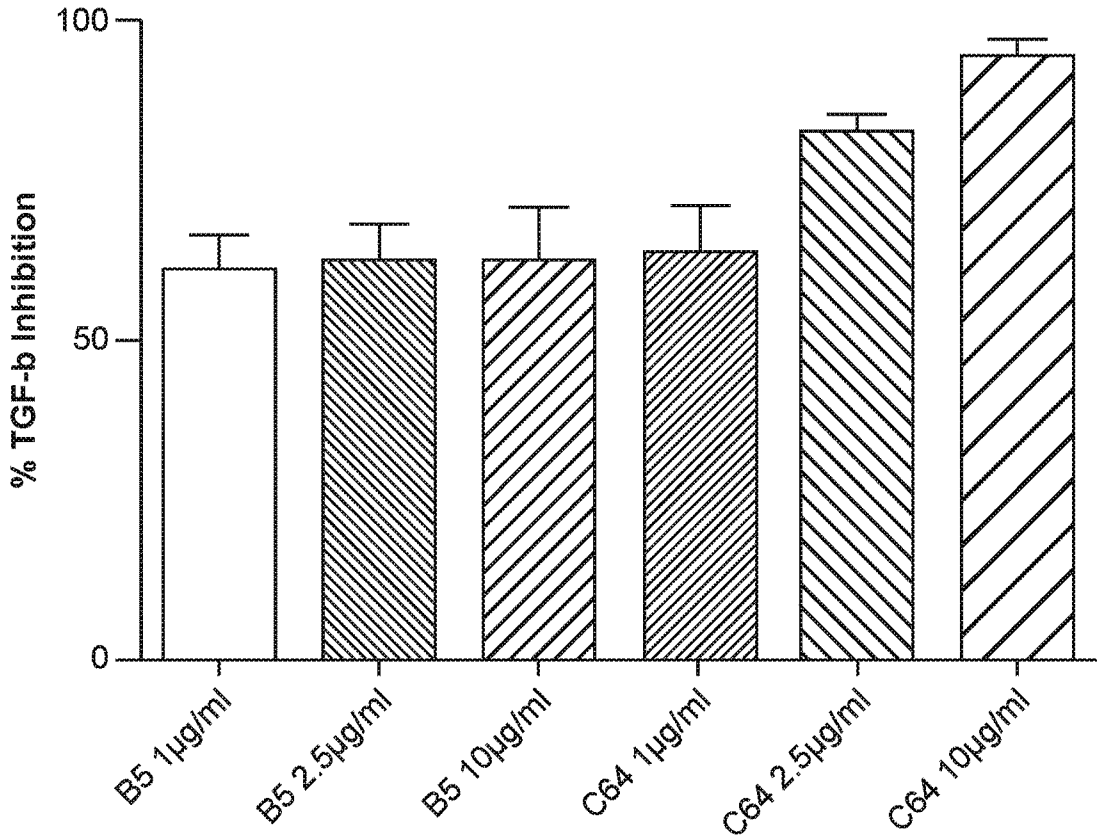


FIG. 3

Date Reçue/Date Received 2023-12-19

Human	αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Chimp	αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Rhesus	αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Cyno	αv	FLQDGTKTVEYAPCRSQDI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Cow	αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Pig	αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Horse	αv	FLQDGAKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Mouse	αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Rat	αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Armadillo	αv	FLQDGTKTVEYAPCRSKNI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ
Platypus	αv	FLQDGTKTVEYAPCRSRSI***DADG***QGFCQGGFSIDFTKADRVLLGGPGSF**Y**WQGQ

Integrin αv: Epitope for C6D4 in Bold Underlined Italics

Human	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Chimp	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFERAV***HR***QKIS
Rhesus	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Cyno	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Cow	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Pig	β8	SASM**H**NNIEKLNTVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Horse	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Mouse	β8	SASM**H**NNIEKLNSVGNDLSKKMALYSRDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Rat	β8	SASM**H**NNIEKLNSVGNDLSKKMALFSHDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFEKAV***HR***QKIS
Armadillo	β8	SASM**H**NNIEKLNSVGNDLSRKMAFFSLDFRLGFGSYVDKTVSPYISIHPERIHNQC***SDYNLD***CMPPHGYIHVLSLTENITEFAKAV***HR***QKIS
Platypus	β8	SASM**H**NNIEKLNSVGNDLSQKMADFTRDFRLGFGSYVDKTVSPYISIHPGRIRNQC***SQYDLD***CMPPHGYIHVLPLTENVTEFEKAVNKQKIS

FIG. 4

```
1    FNLDVDSPAEYSGPEGSYFGFAVDFFVPSASSRMFLLVGAPKANTTQPGI 50
51   VEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDPLEFKSHQWFGASVRS 100
101  KQDKILACAPLYHWRTEMKQEREPVGTCFLQDGTKTVEYAPCRSQDIDAD 150
151  GQGFCQGGFSIDFTKADRVLLGGPGSFYWQGQLISDQVAEIVSKYDPNVY 200
201  SIKYNNQLATRTAQAIFDDSYLGYSVAVGDFNGDGIDDFVSGVPRAARTL 250
251  GMVYIYDGKNMSSLYNFTGEQMAAYFGFSVAATDINGDDYADVFIGAPLF 300
301  MDRGSDGKLQEVGQVSVSLQRASGDFQTTKLNGFEVFARFGSAIAPLGDL 350
351  DQDGFNDIAIAAPYGGEDKKGIVYIFNGRSTGLNAVPSQILEGQWAARSM 400
401  PPSFGYSMKGATDIDKNGYPDLIVGAFGVDRAILYRARPVITVNAGLEVY 450
451  PSILNQDNKTCSLPGTALKVSCFNVRFCLKADGKGVLPRKLNFQVELLLD 500
501  KLKQKGAIRRALFLYSRSPSHSKNMTISRGGLMQCEELIAYLRDESEFRD 550
551  KLTPITIFMEYRLDYRTAADTTGLQPILNQFTPANISRQAHILLDCGEDN 600
601  VCKPKLEVSVDSDQKKIYIGDDNPLTLIVKAQNQGEGAYEAELIVSIPLQ 650
651  ADFIGVVRNNEALARLSCAFKTENQTRQVVCDLGNPMKAGTQLLAGLRFS 700
701  VHQQSEMDTSVKFDLQIQSSNLFDKVSPVVSHKVDLAVLAAVEIRGVSSP 750
751  DHVFLPIPNWEHKENPETEEDVGPVVQHIYELRNNGPSSFSKAMLHLQWP 800
801  YKYNNNTLLYILHYDIDGPMNCTSDMEINPLRIKISSLQTTEKNDTVAGQ 850
851  GERDHLITKRDLALSEGDIHTLGCGVAQCLKIVCQVGRLDRGKSAILYVK 900
901  SLLWTETFMNKENQNHSYSLKSSASFNVIEFPYKNLPIEDITNSTLVTTN 950
951  VTWGIQPAPMPVPVWVIILAVLAGLLLLAVLVFVMYRMGFFKRVRPPQEE 1000
1001 QEREQLQPHENGEGNSET                                1018
```

Integrin AlphaV (Human, No Signal Peptide) –
Epitope for C6D4 in ***Bold Underlined Italics***

```
1    EDNRCASSNAASCARCLALGPECGWCVQEDFISGGSRSERCDIVSNLISK 50
51   GCSVDSIEYPSVHVIIPTENEINTQVTPGEVSIQLRPGAEANFMLKVHPL 100
101  KKYPVDLYYLVDVSASMHNNIEKLNSVGNDLSRKMAFFSRDFRLGFGSYV 150
151  DKTVSPYISIHPERIHNQCSDYNLDCMPPHGYIHVLSLTENITEFEKAVH 200
201  RQKISGNIDTPEGGFDAMLQAAVCESHIGWRKEAKRLLLVMTDQTSHLAL 250
251  DSKLAGIVVPNDGNCHLKNNVYVKSTTMEHPSLGQLSEKLIDNNINVIFA 300
301  VQGKQFHWYKDLLPLLPGTIAGEIESKAANLNNLVVEAYQKLISEVKVQV 350
351  ENQVQGIYFNITAICPDGSRKPGMEGCRNVTSNDEVLFNVTVTMKKCDVT 400
401  GGKNYAIIKPIGFNETAKIHIHRNCSCQCEDNRGPKGKCVDETFLDSKCF 450
451  QCDENKCHFDEDQFSSESCKSHKDQPVCSGRGVCVCGKCSCHKIKLGKVY 500
501  GKYCEKDDFSCPYHHGNLCAGHGECEAGRCQCFSGWEGDRCQCPSAAAQH 550
551  CVNSKGQVCSGRGTCVCGRCECTDPRSIGRFCEHCPTCYTACKENWNCMQ 600
601  CLHPHNLSQAILDQCKTSCALMEQQHYVDQTSECFSSPSYLRIFFIIFIV 650
651  TFLIGLLKVLIIRQVILQWNSNKIKSSSDYRVSASKKDKLILQSVCTRAV 700
701  TYRREKPEEIKMDISKLNAHETFRCNF                        727
```

Integrin Beta8 (Human, No Signal Peptide) –
Epitope for C6D4 in ***Bold Underlined Italics***

FIG. 5

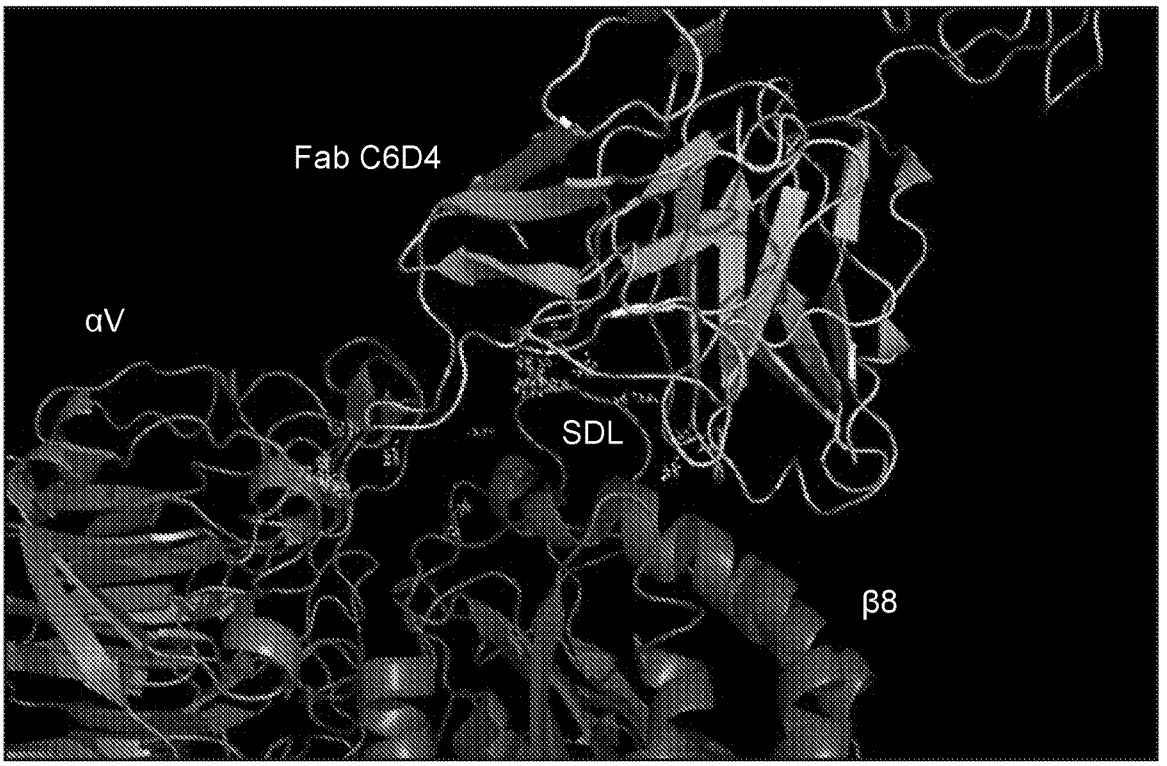


FIG. 6

Date Reçue/Date Received 2023-12-19

Residues making interactions are in bold

FIG. 7

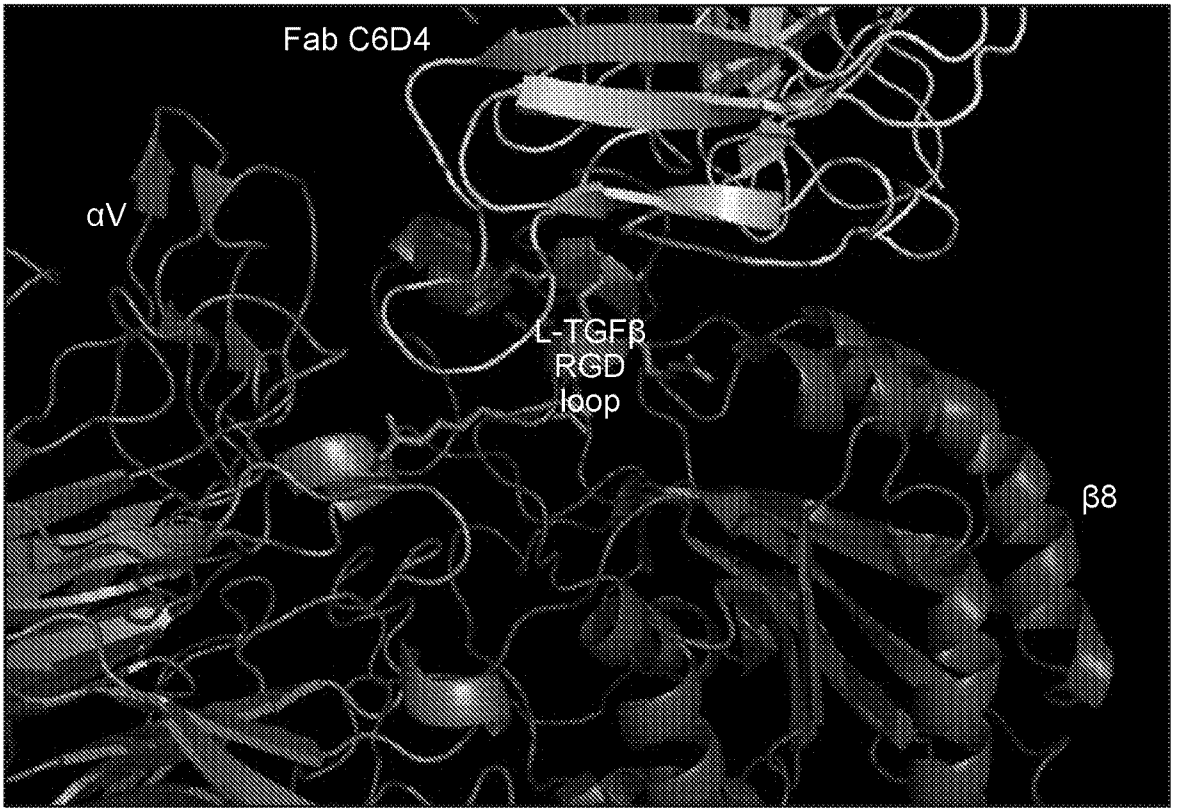
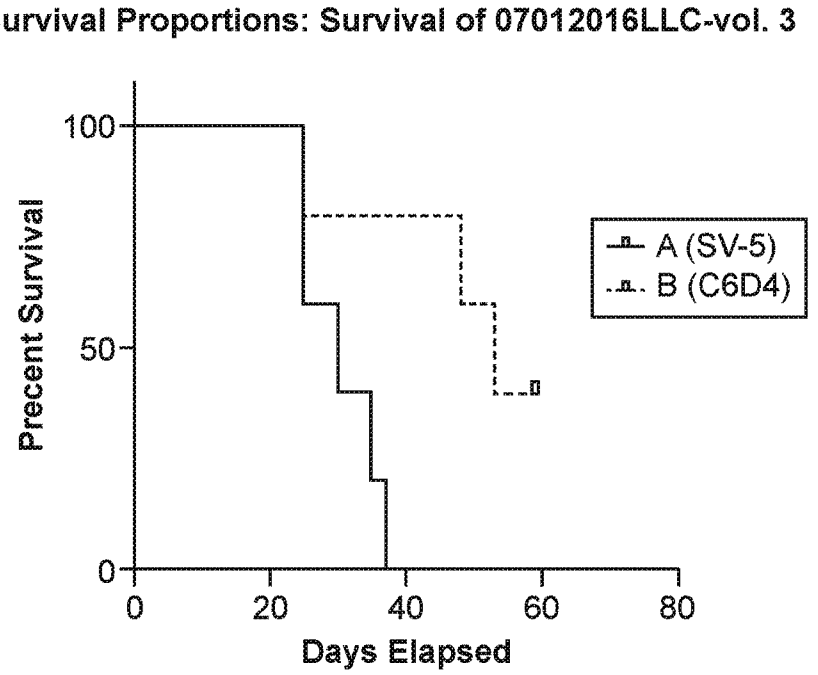


FIG. 8

Date Reçue/Date Received 2023-12-19



A (n=5), cause; 1 died (and had local rec), 1 local rec, 3 weight loss
B (n=5), 1 local rec. 2 weight loss (1 died)

Log-rank (Mantel-Cox) test	
Chi square	5.322
df	1
P value	0.0211
P value summary	*

Gehan-Breslow -Wilcoxon test	
Chi square	3.510
df	1
P value	0.0610
P value summary	ns

FIG. 9

PBS	ALT Day 0	HBSag ELISA	ALT Day 7	HBSag ELISA	ALT Day 14	HBSag ELISA	
1	71	POS	33	POS	68	POS	
2	77	POS	10	POS	27	POS	
3	20	POS	16	POS	38	POS	
4	33	POS	17	POS	51	POS	
5	28	POS	14	POS	31	POS	
C6D4							
1	38	POS	23	**NEG**	26	**NEG**	
2	31	POS	24	**NEG**	20	**NEG**	
3	24	POS	59	**NEG**	31	**NEG**	
4	28	POS	24	POS	20	POS	

FIG. 10

Date Reçue/Date Received 2023-12-19

VH (Mouse Hybridoma clone Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
4F1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTNYLIE	WVKQRPGQGLEWIG	VINPGTGGTNYNKKFKV	KATLTADKSSSTAYMQLGGLTFDDSAVYFCAR	EGNARTYYYAMDY	WGQGTSVTVSS
6B9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFKG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
(scFv clone Name from yeast display libra1y)							
6B9.1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A1	QVQLQQSGAELVRPGASVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSVYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A2	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSTAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A8	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDNLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
B1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLSSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
B3	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
C4=F10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
C7=D1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSGSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D3=F1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSDDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D10=E5	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
G4	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKSSSSAYMQLNSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
(Produced Rabbit IgG clone name)							
C4	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
(scFv clone from Phage Dispiay library)							
4F1A11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1E1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1G3	QVQLQQSGAELVRPGTSVRVSCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTANKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1E10	QVQLQQSGAELVRPGTSVKVPCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1E9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1H12	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYLQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
Final clone for in vitro Functional test in IgG format							
F9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS

FIG. 11A

VL	Framework 1	CDR1	Framework2	CDR2	Framework3	CDR3	Framework 4
(Mouse Hybridoma clone Name)							
4F1	DIQMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
689	DIEMTQTPASLSASVGETVTITC	RASENIYSYLV	WYQQKQGKSPQVLVY	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHNGTPYT	FGGGTKLEIKA
(scFv clone Name from yeast display library)							
6B9.1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
A1 = A2 = C4 = C7 = D1 = D10 = E5 = F1 = F10 = G4 :							
	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
A8	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSVQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
A11	HIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYCY	QHHHGTPYT	FGGGTKLEIKA
B1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDWGSYYC	QHHHGTPYT	FGGGTKLEIKA
B3	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAA	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
D10=E5	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
(Produced Rabbit IgG clone name)							
C4	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
D10	DIEMTQTPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
(scFv clone from Phage Display library)							
4F1E1 = 4F1G3 = 4F1B5 = 4F1G11 = 4F1A9 = 4F1A9 = 4F1F9 = 4F1H9 = 4F1D10 = 4F1E9 = 4F1E10 = 4F1F10 = 4F1H11 = 4F1H12 :							
	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
4FA11	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
Final clone for in vitro Functional test in IgG format							
E9	DIVMTQSPATLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR

FIG. 11B

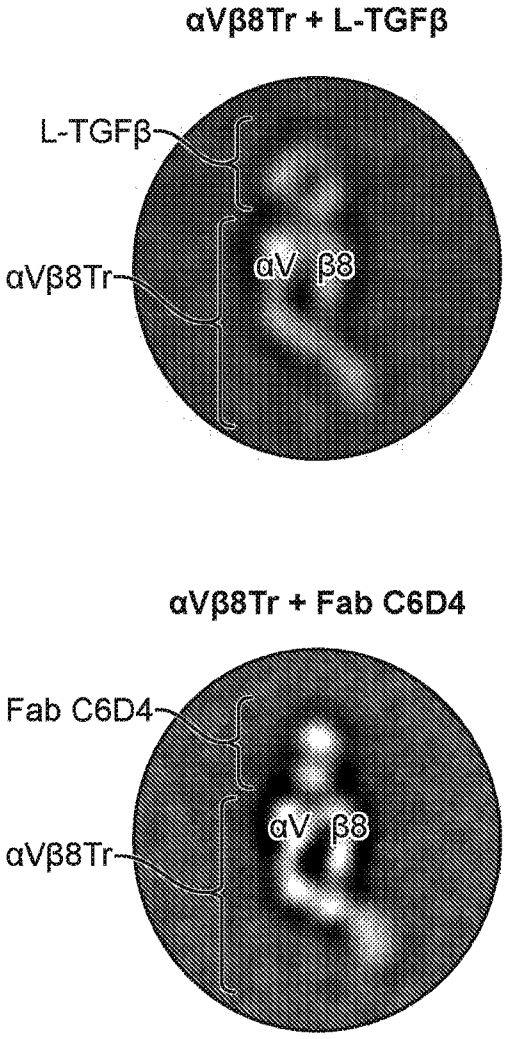
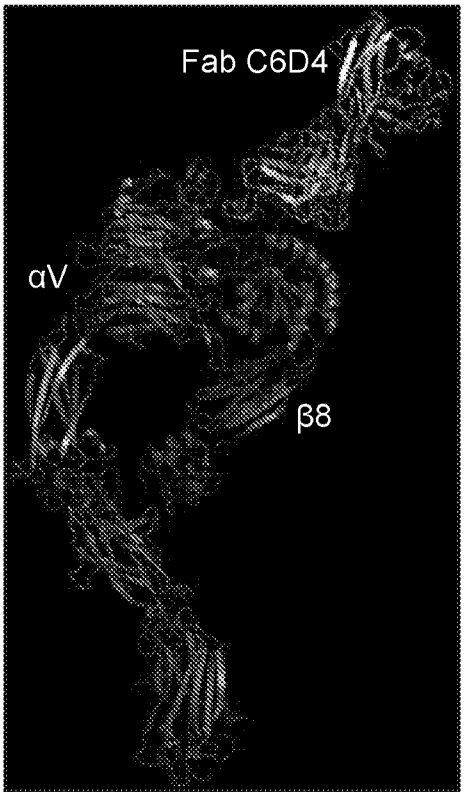
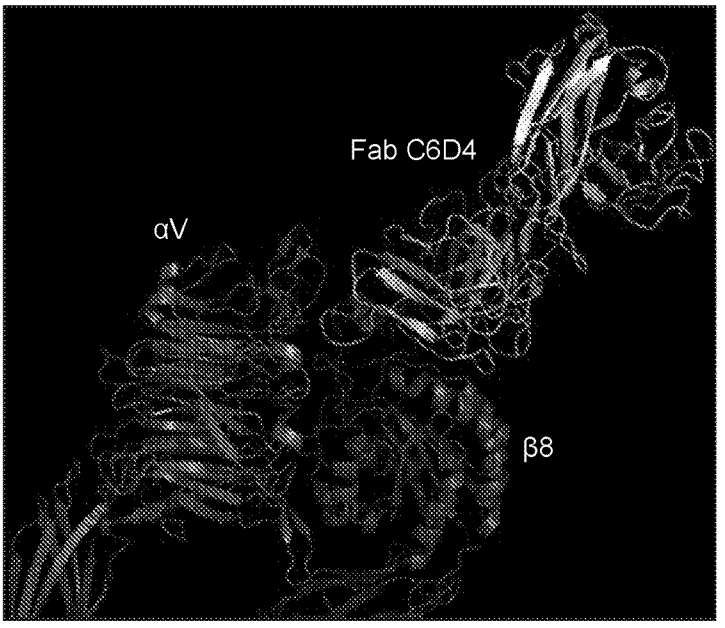


FIG. 12



C6D4 binds integrin αVβ8 at the head domain

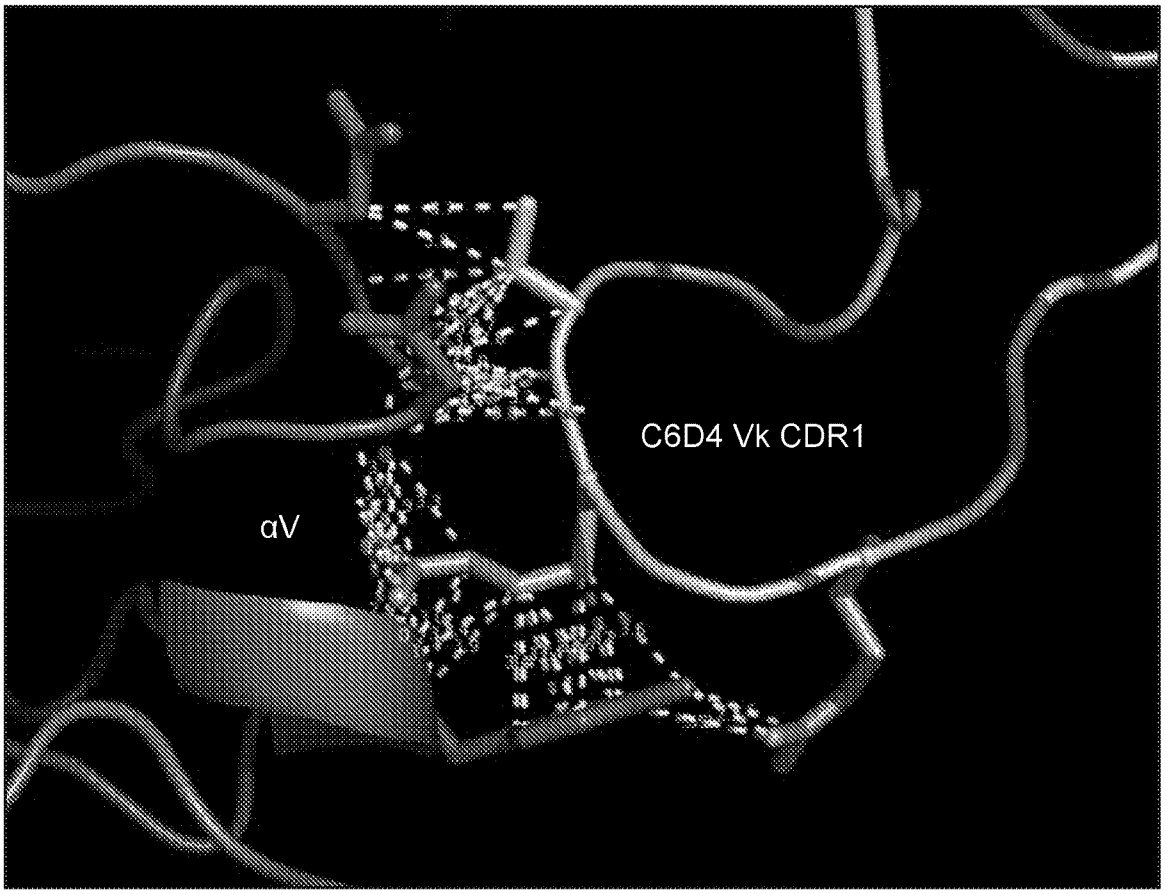
FIG. 13A



Zoom-in onto the integrin αVβ8 head domains and bound Fab C6D4

FIG. 13B

Date Reçue/Date Received 2023-12-19



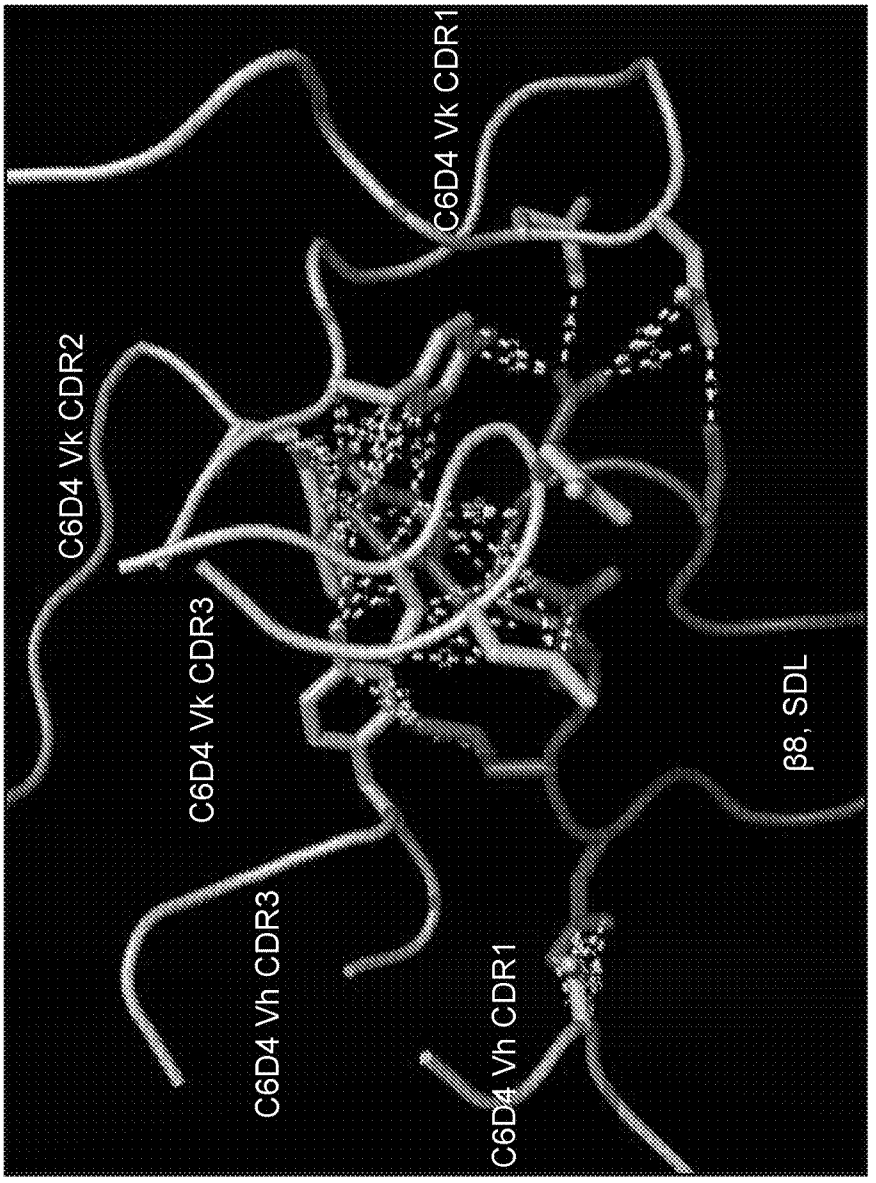
C6D4, Vk, CDR1: KSSQSLLN**SR**T**R**KNYLA

αV, β-propeller domain, blade W3: …DI**DADG**QG…SF**Y**WQ…

Interacting residues are in **bold**

FIG. 14

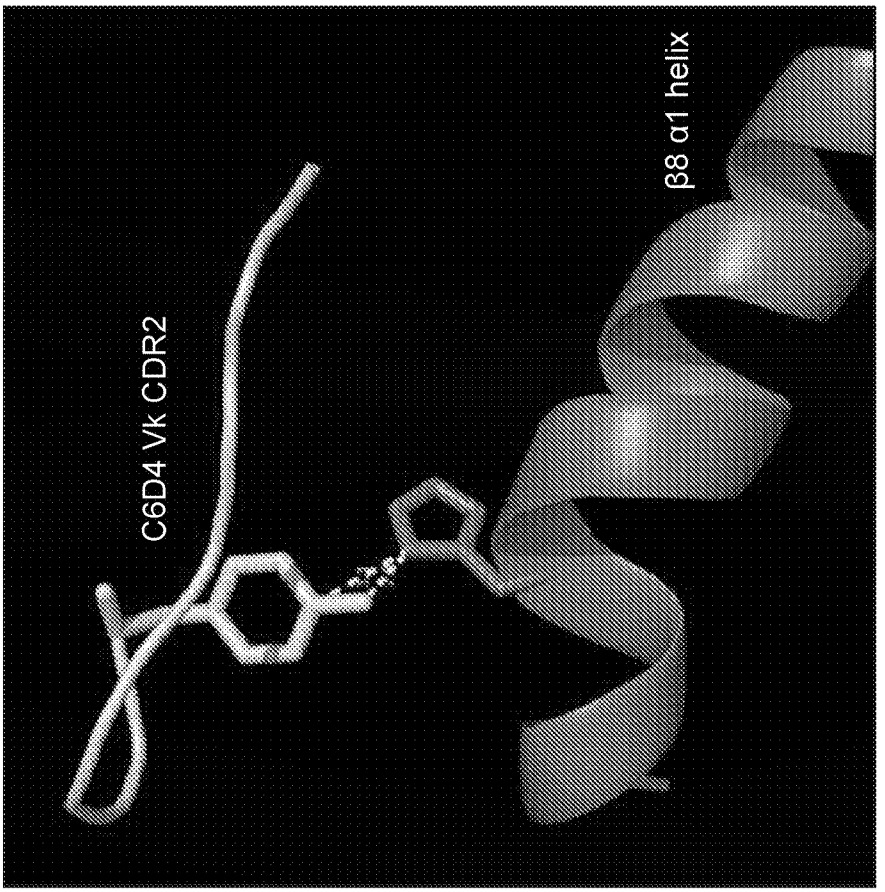
Date Reçue/Date Received 2023-12-19



C6D4, Vh, CDR1: DY**S**MH CDR3: FYYGRDS
β8, SDL: 153 TVSPYISIHPERIHNQC**SDYNLD**CMPPH 180
C6D4, Vk, CDR1: KSSQSL**LN**SRTRKNYLA CDR2: **W**ASTRES CDR3: KQ**SYNLL**S

Interacting residues are in **bold**

FIG. 15



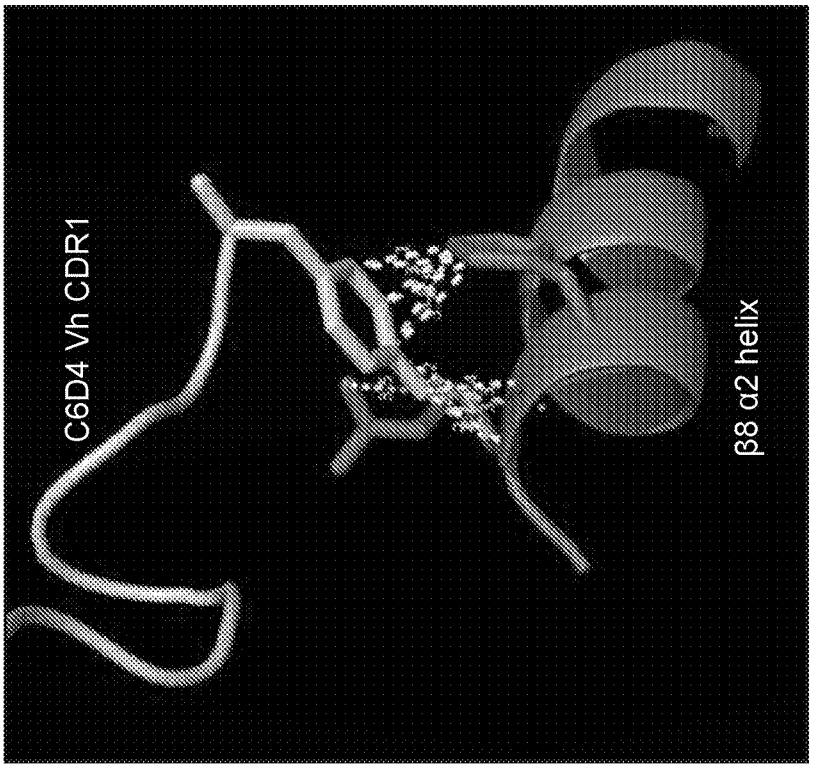
This residue is technically outside of the CDR

C6D4, Vk, CDR2: YWASTRES

β8, α1 helix: 114 SASM**H**N**N**IEKLNSVGNDLSRKMAFFS 139

Interacting residues are in **bold**

FIG. 16



This residue is technically outside of the CDR

C6D4, Vh, CDR1: YTFTDYSMH

β8, α2 helix: 191 NITEFEKAV**HR** 201

Interacting residues are in **bold**

FIG. 17

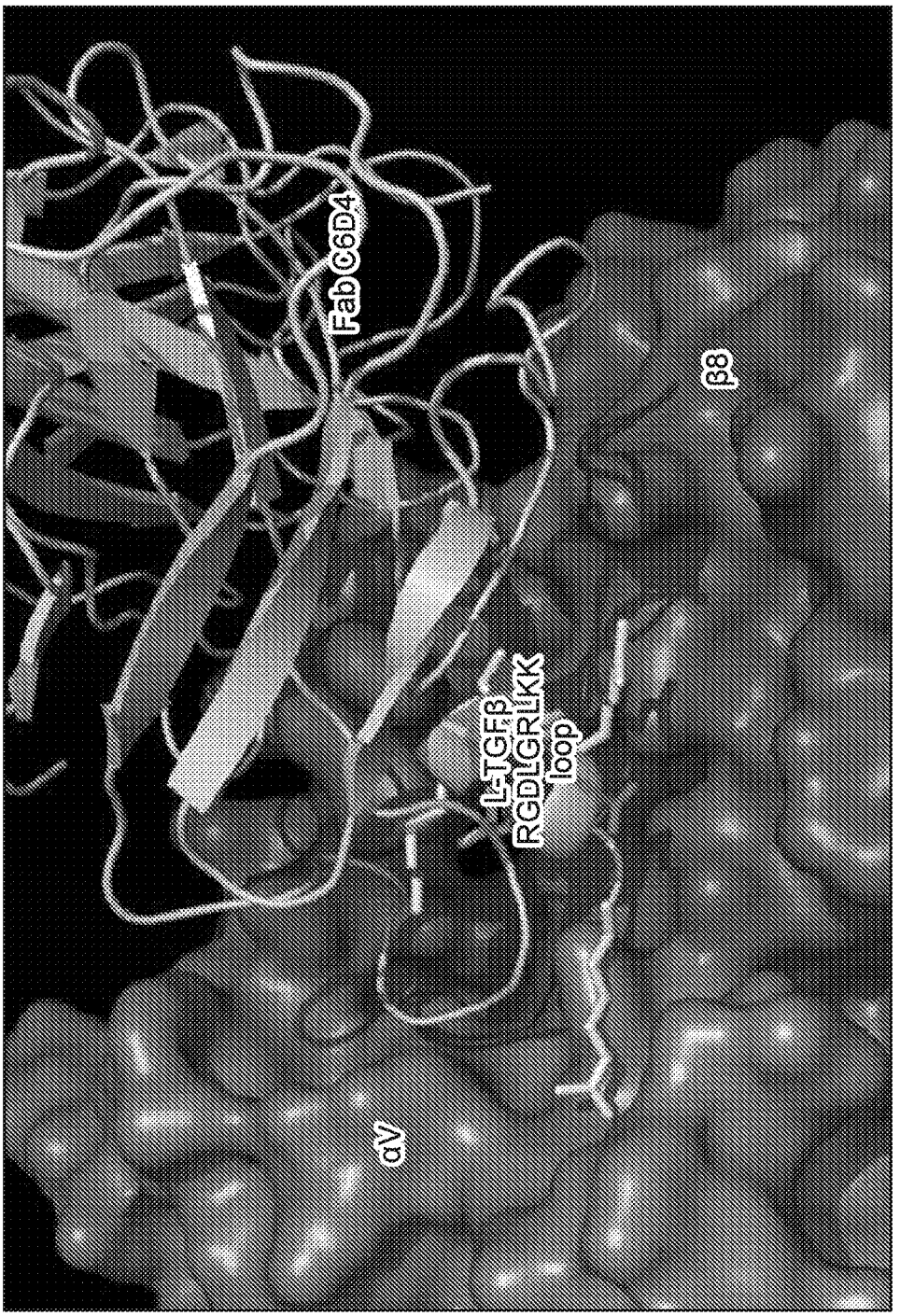
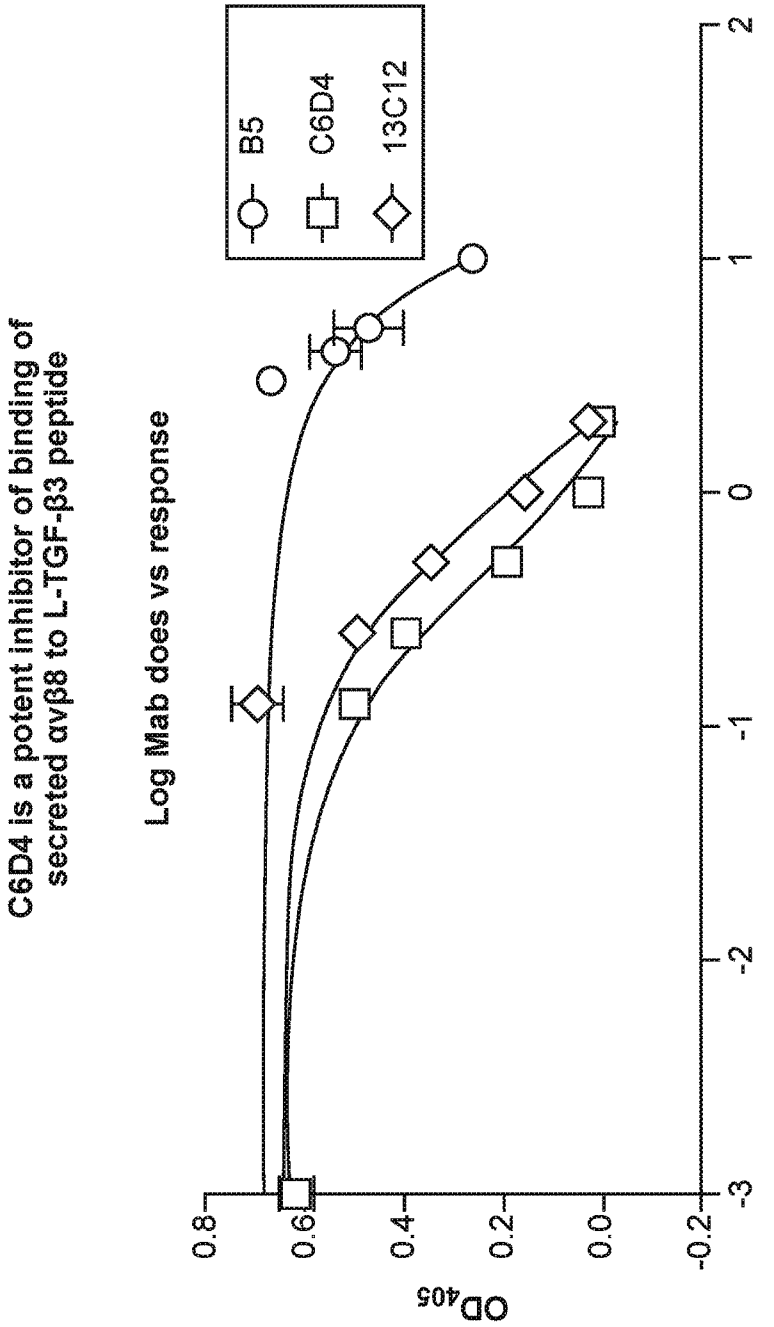


FIG. 18



	B5	C6D4	13C12
IC50	6.886e+006	0.4940	1.183

FIG. 19

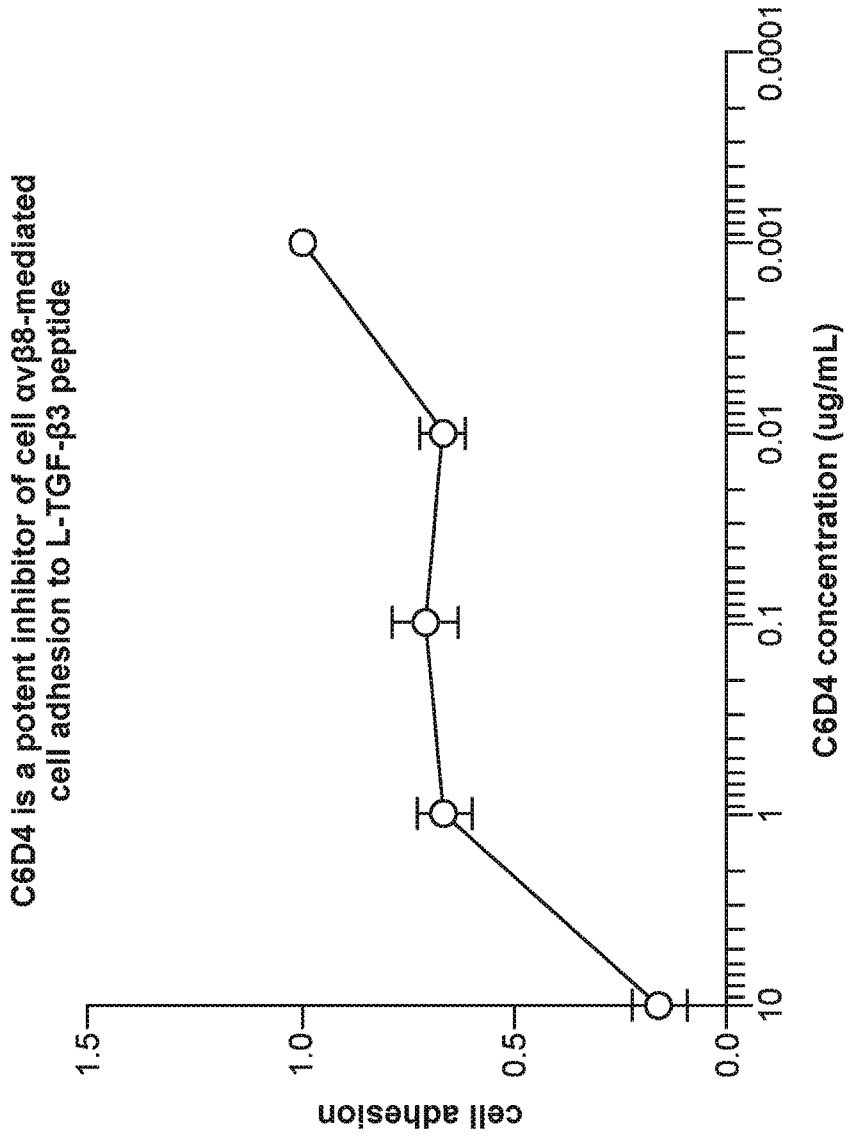


FIG. 20

β8 integrin subunit is increased in expression in the crypt epithelial cells of patients infected with H. Pylori

H. Pylori

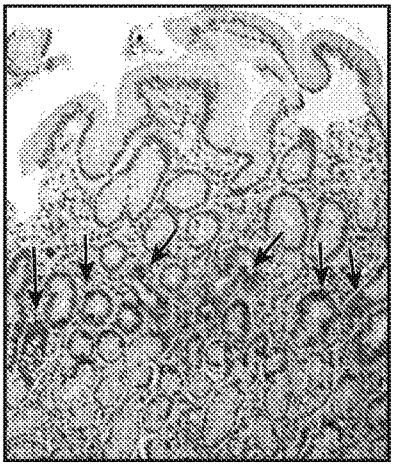


FIG. 21A

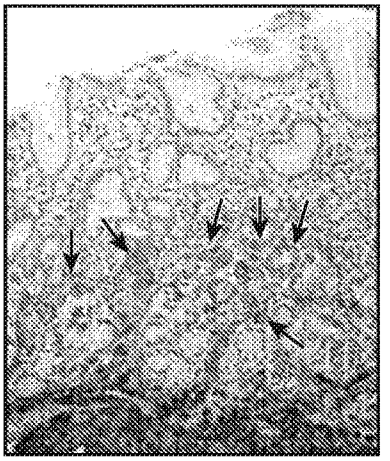


FIG. 21B

Normal

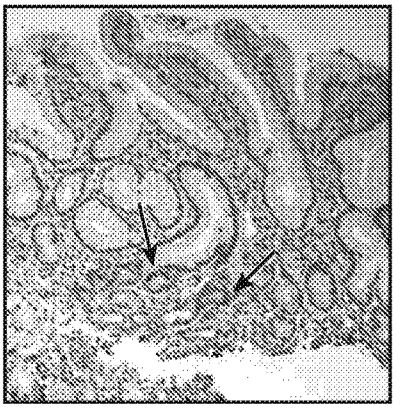


FIG. 21C

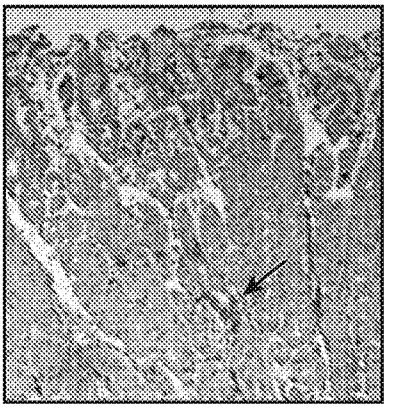


FIG. 21D

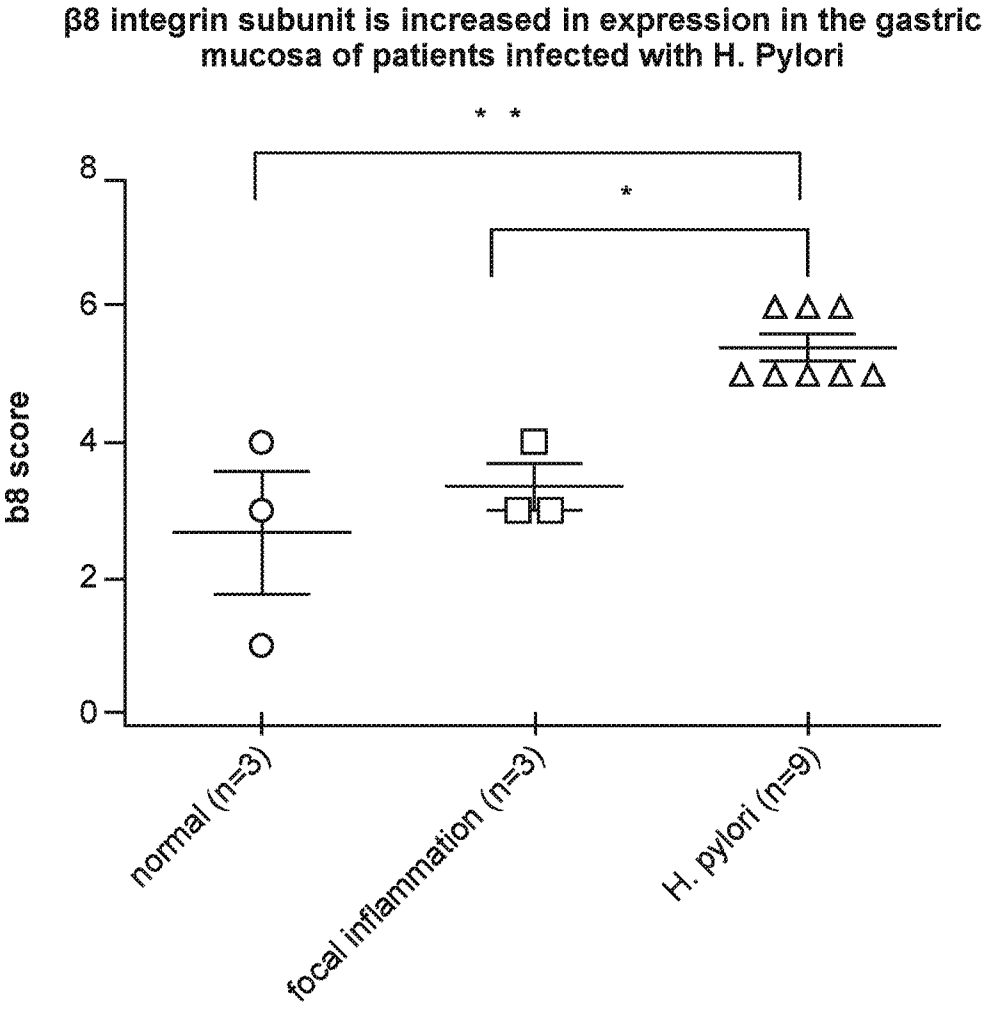


FIG. 22

Date Reçue/Date Received 2023-12-19

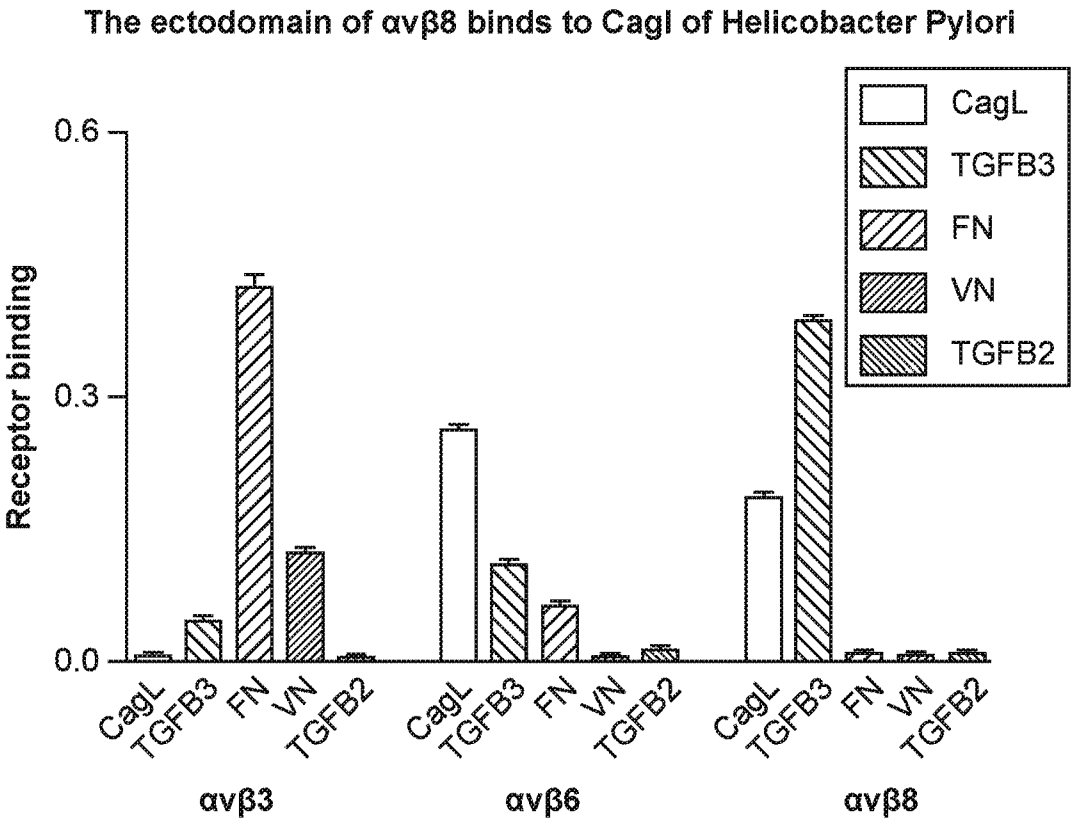


FIG. 23

Date Reçue/Date Received 2023-12-19

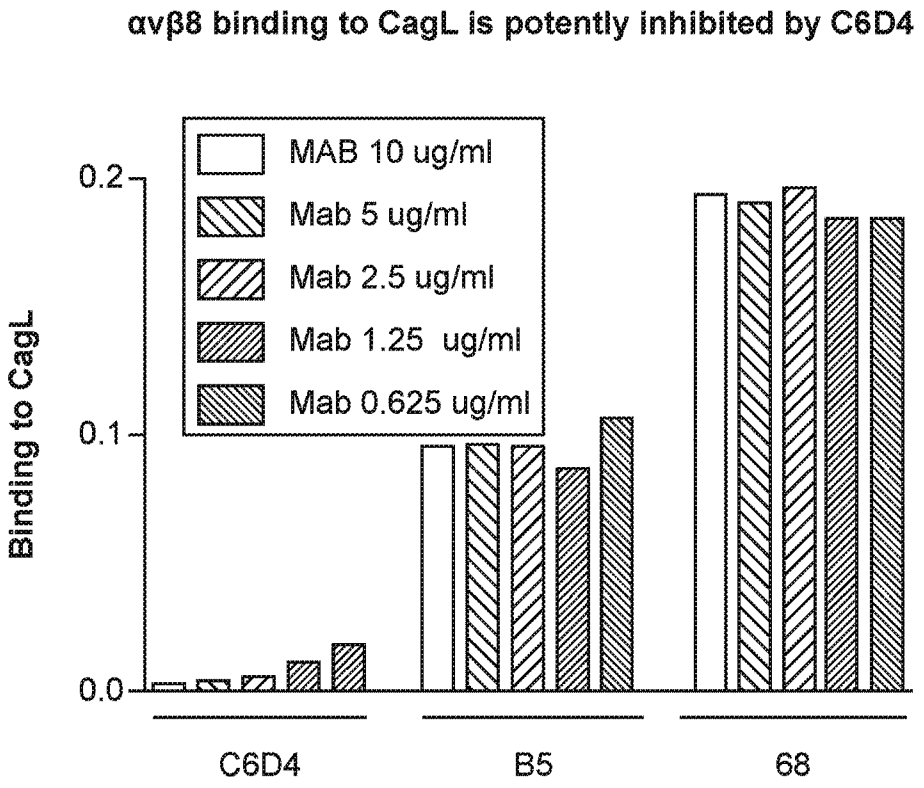


FIG. 24

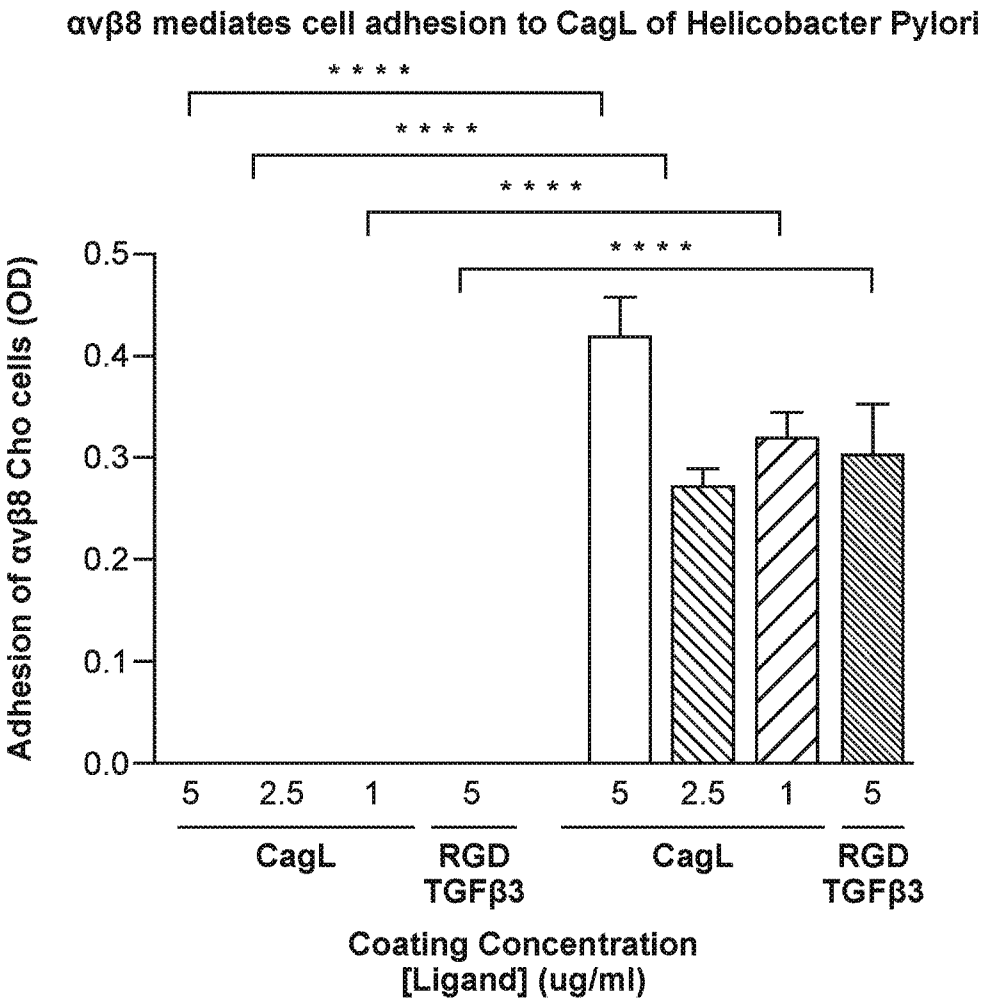


FIG. 25

Date Reçue/Date Received 2023-12-19

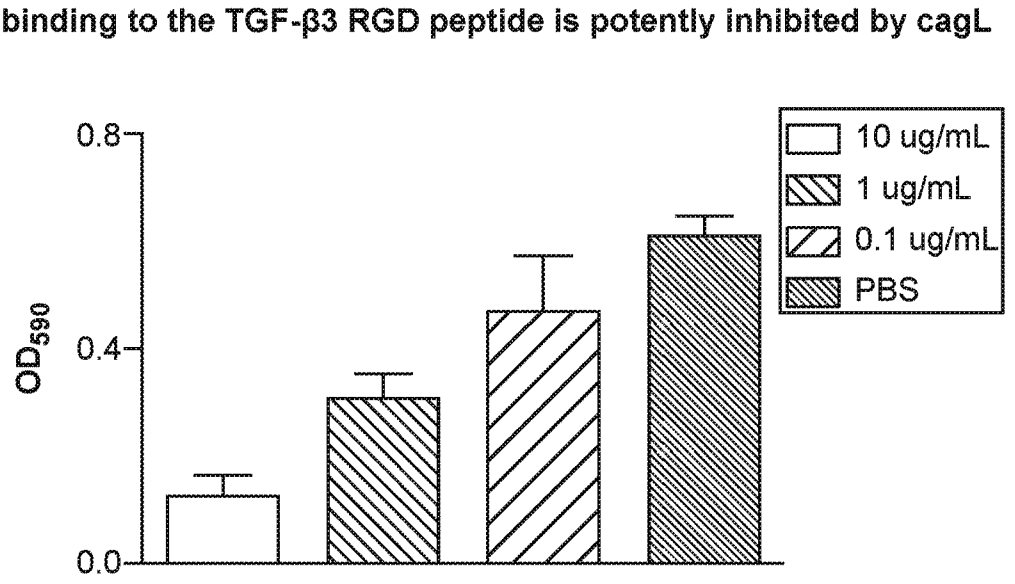


FIG. 26

Date Reçue/Date Received 2023-12-19

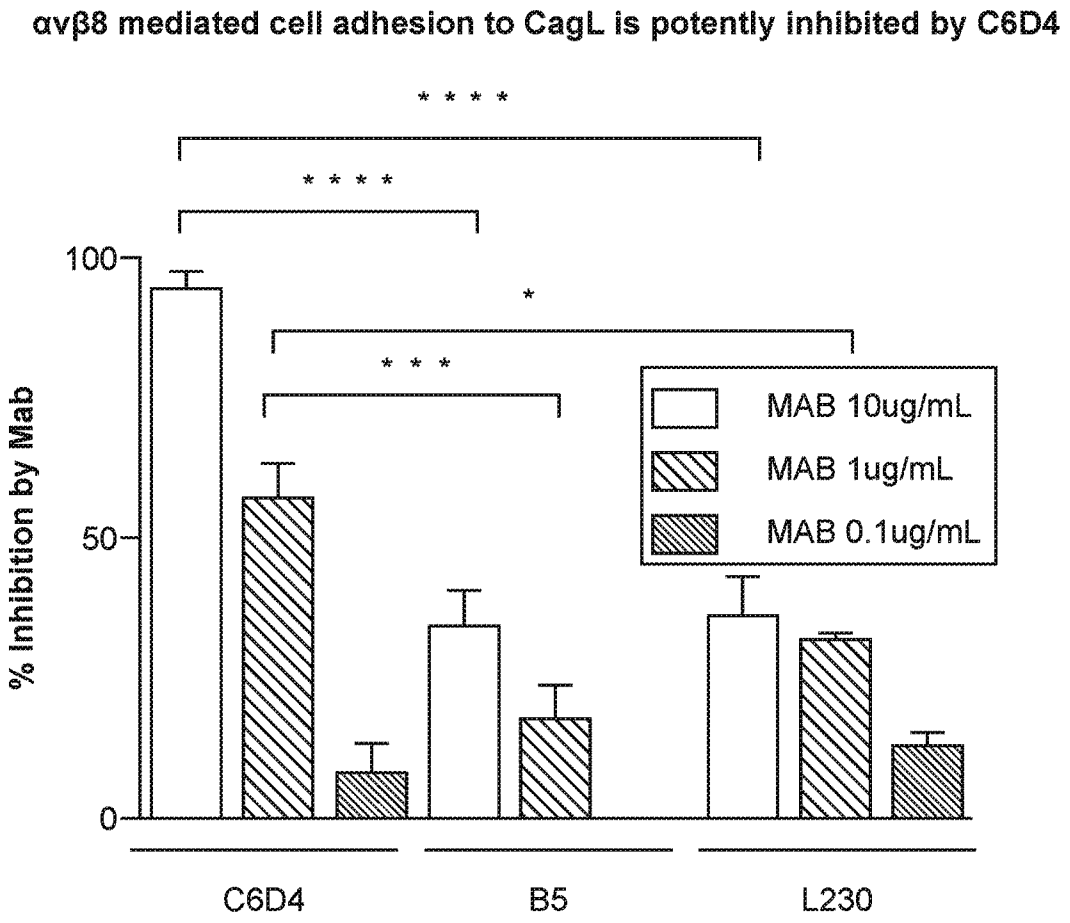


FIG. 27

Date Reçue/Date Received 2023-12-19

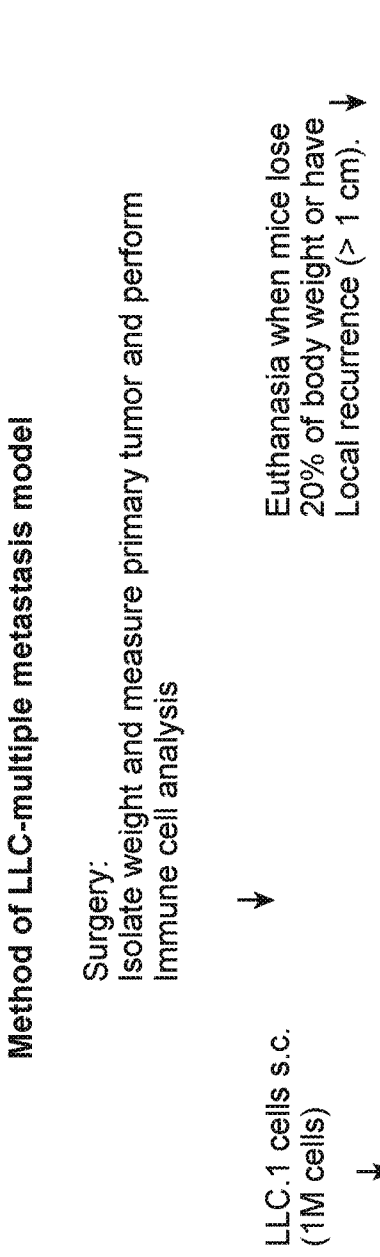
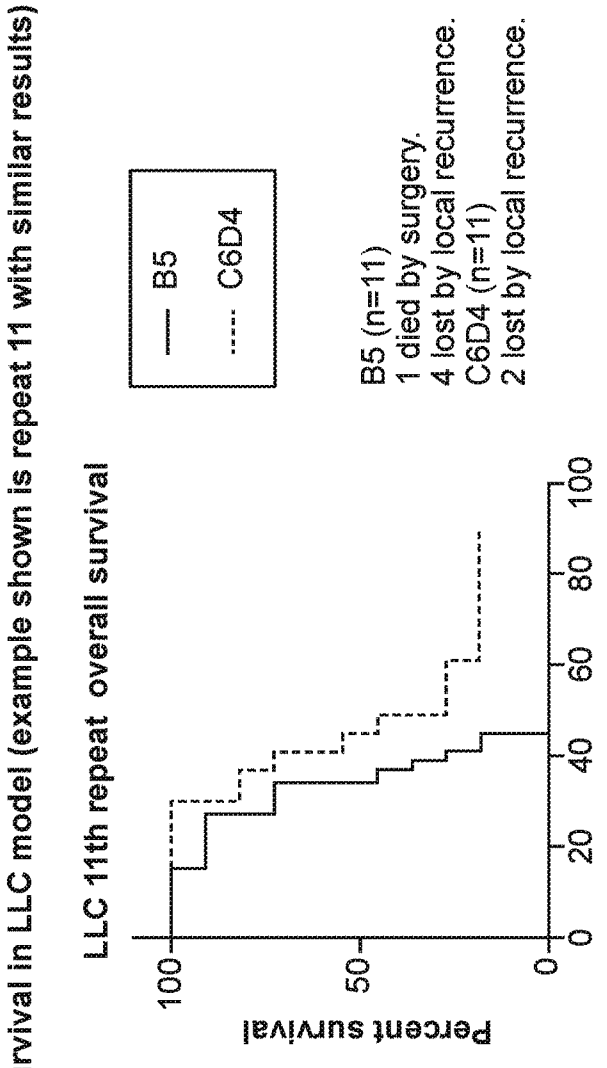


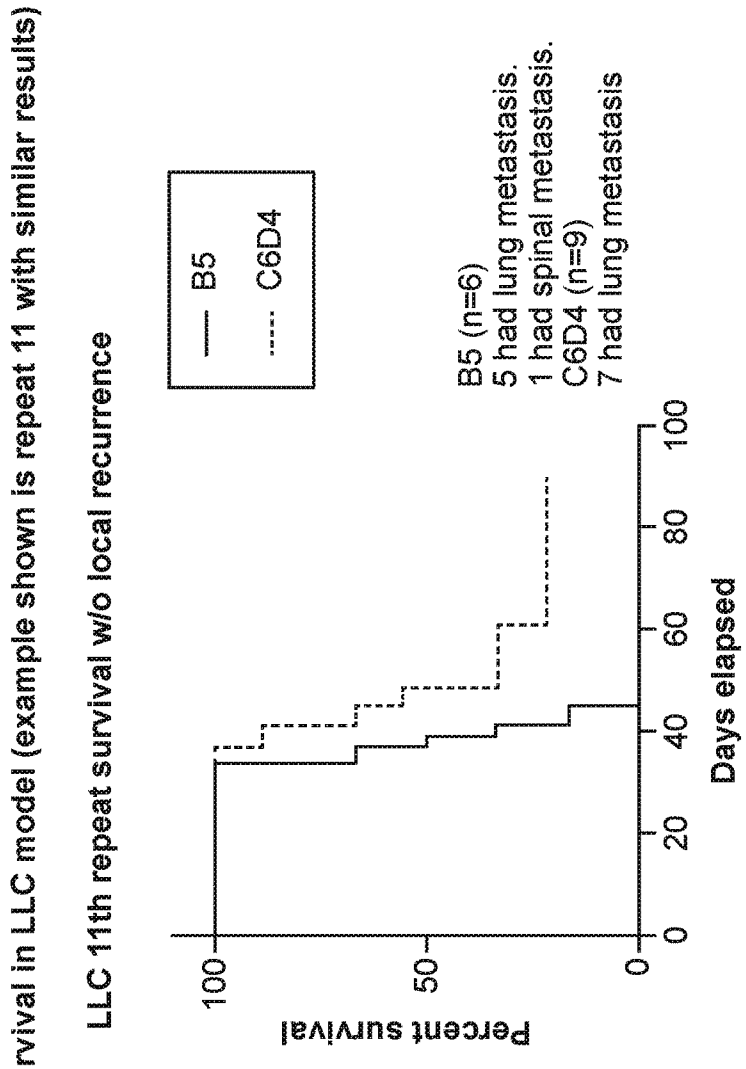
FIG. 28



Gehan-Breslow-Wilcoxon test	
Chi square	5.233
df	1
P value	0.0222

Log-rank (Mantel-Cox) test	
Chi square	6.508
df	1
P value	0.0107

FIG. 29A



Gehan-Breslow-Wilcoxon test	
Chi square	6.733
df	1
P value	0.0095

Log-rank (Mantel-Cox) test	
Chi square	7.282
df	1
P value	0.0070

FIG. 29B

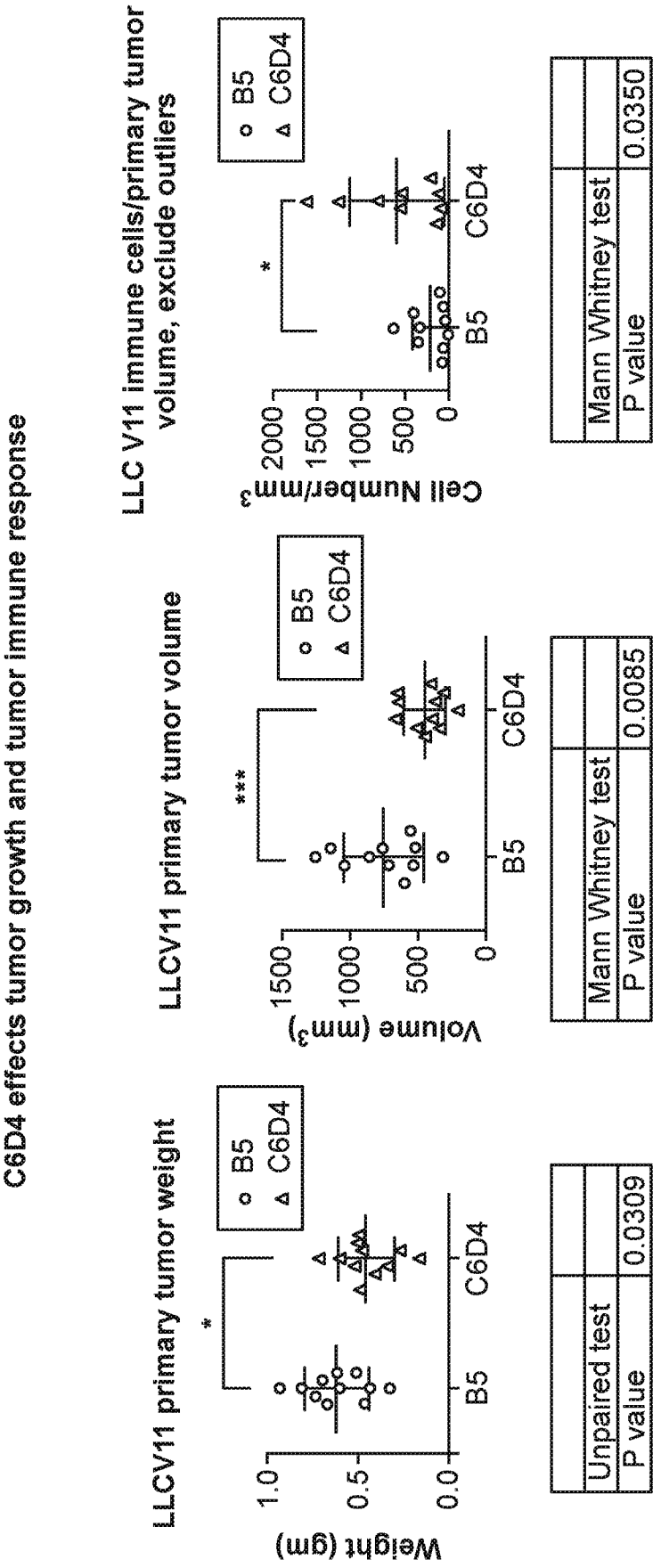


FIG. 30A FIG. 30B FIG. 30C

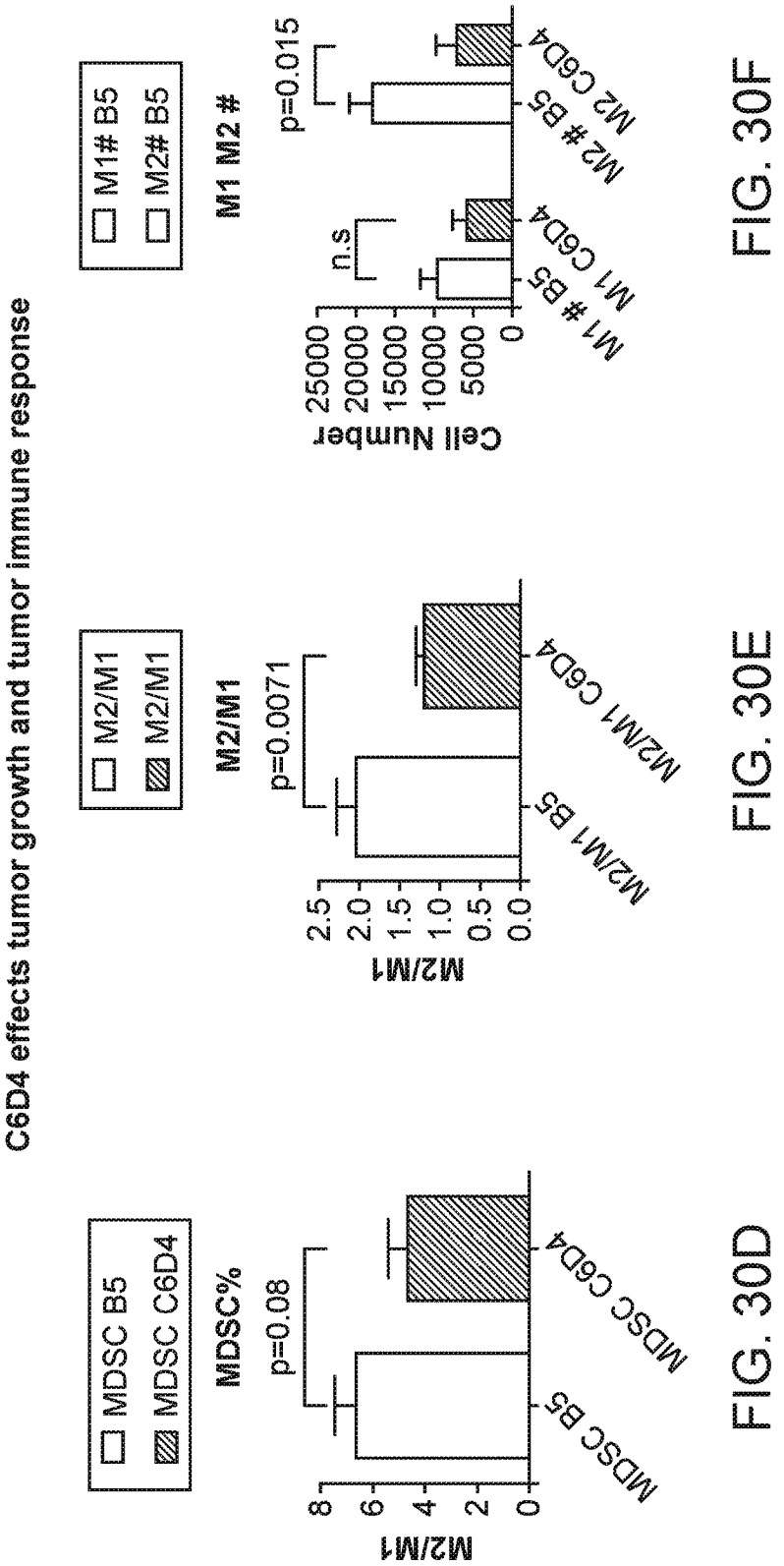


FIG. 30D

FIG. 30E

FIG. 30F

FIG. 31

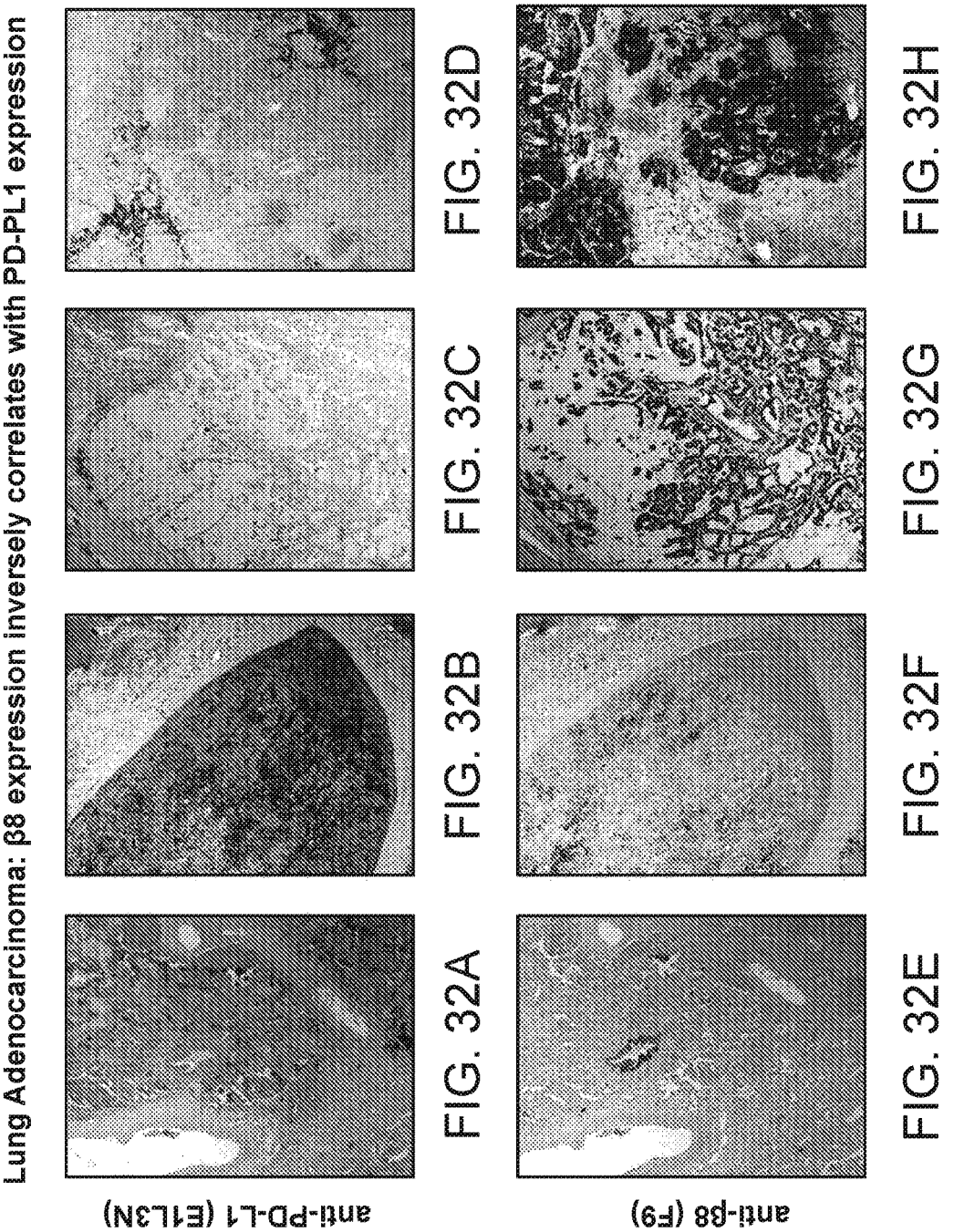
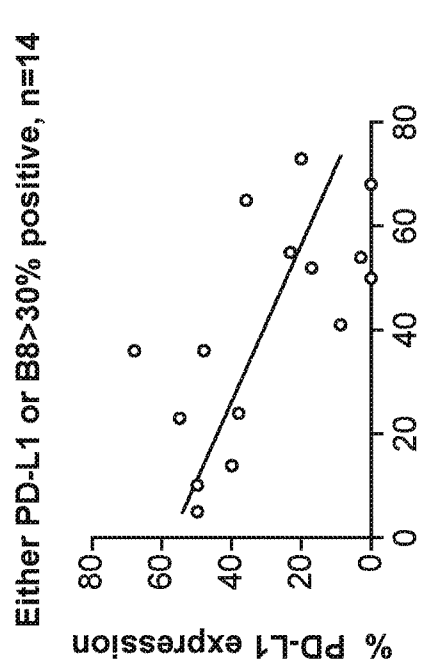


FIG. 32A FIG. 32B FIG. 32C FIG. 32D

FIG. 32E FIG. 32F FIG. 32G FIG. 32H



	B8 vs. PDL1 either >30%
Spearman r	
r	-0.6983
95% confidence interval	-0.895 to -0.2743
P value	
P (two-tailed)	0.0049

FIG. 33B

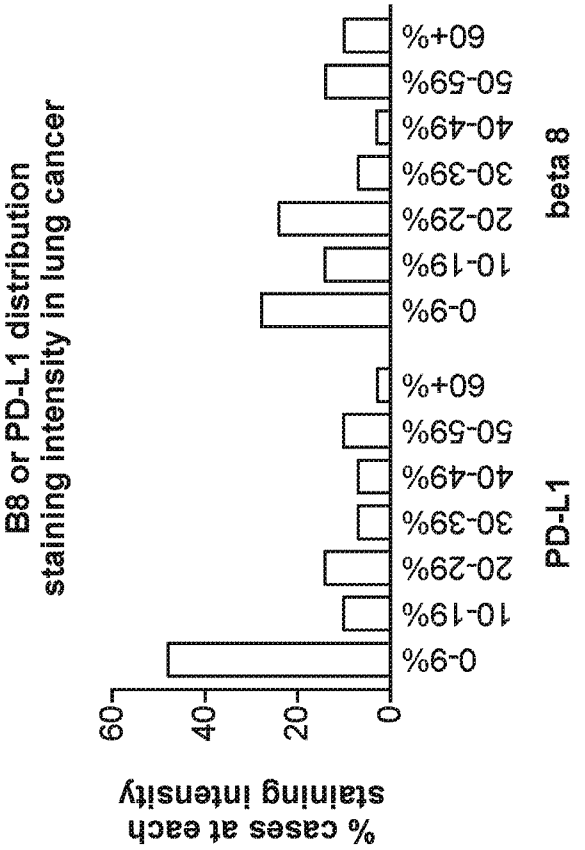


FIG. 33A

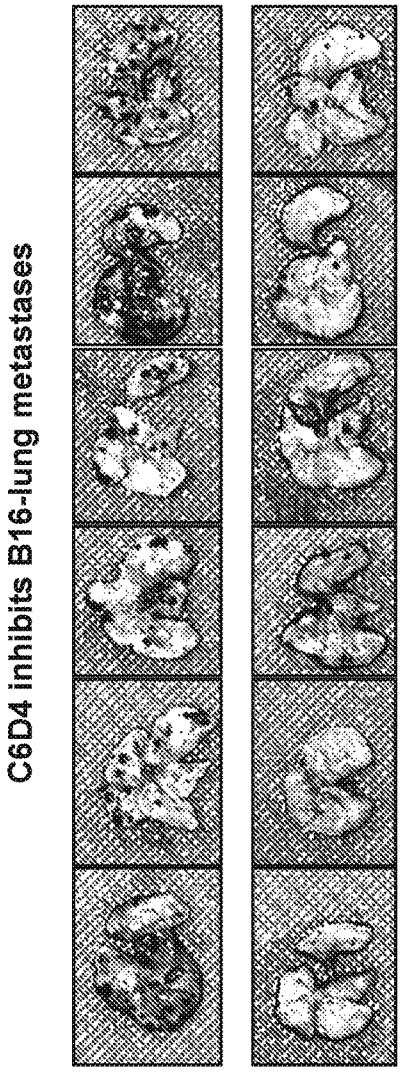


FIG. 34A

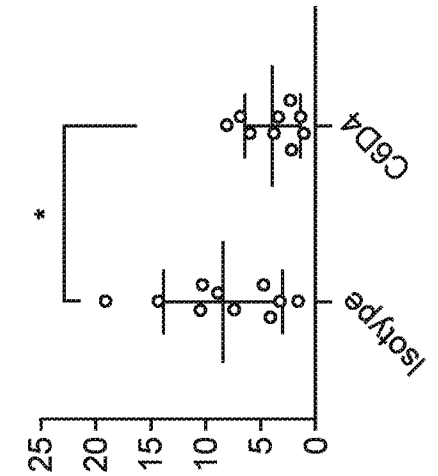


FIG. 34C

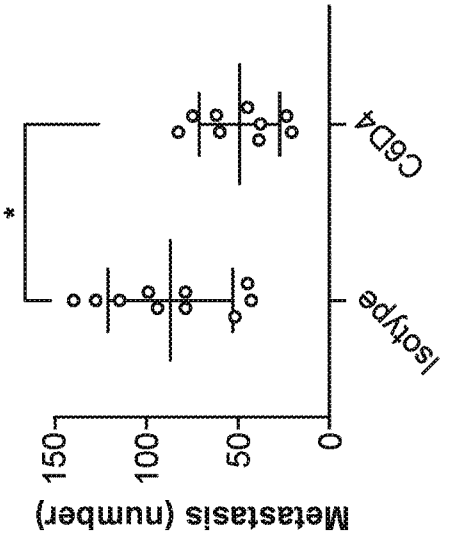


FIG. 34B

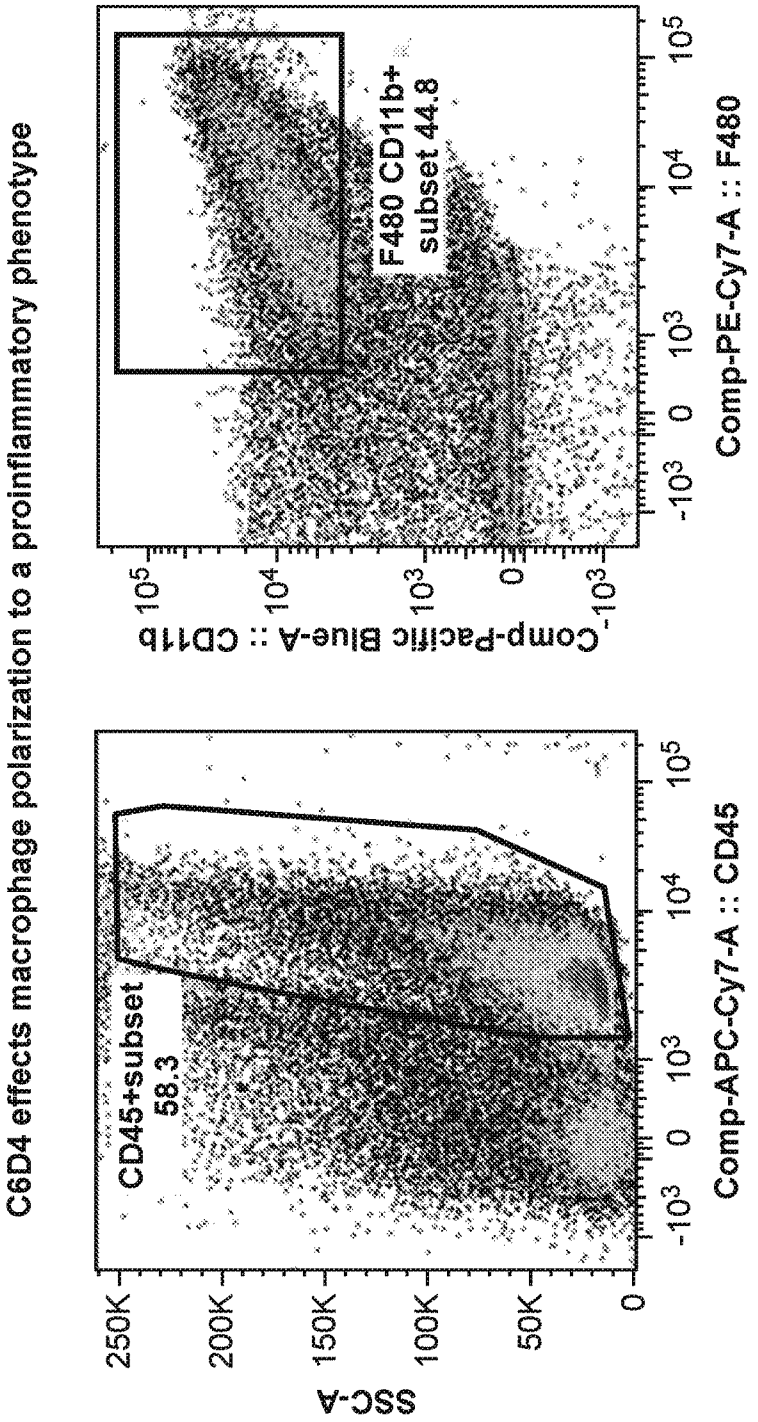


FIG. 35A

FIG. 35B

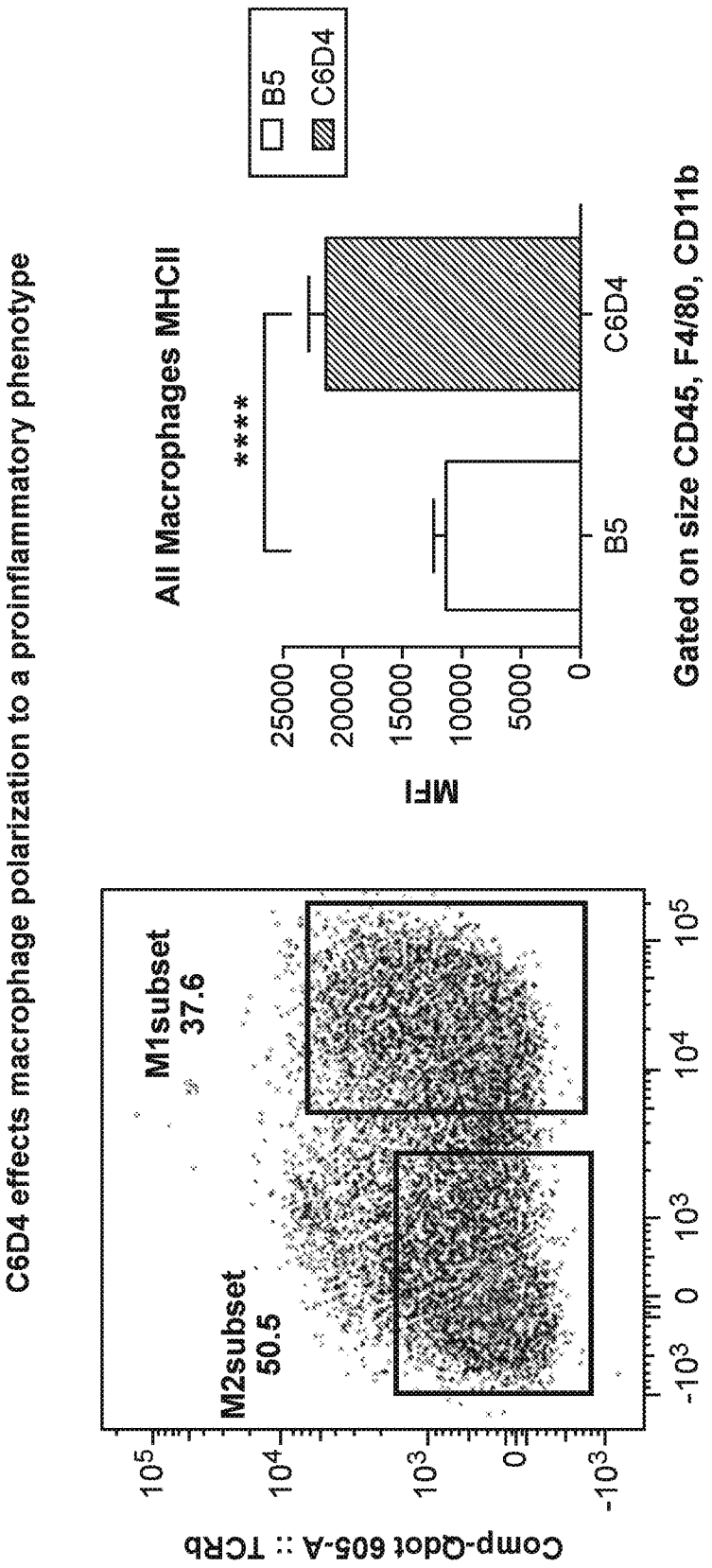


FIG. 35C

FIG. 35D

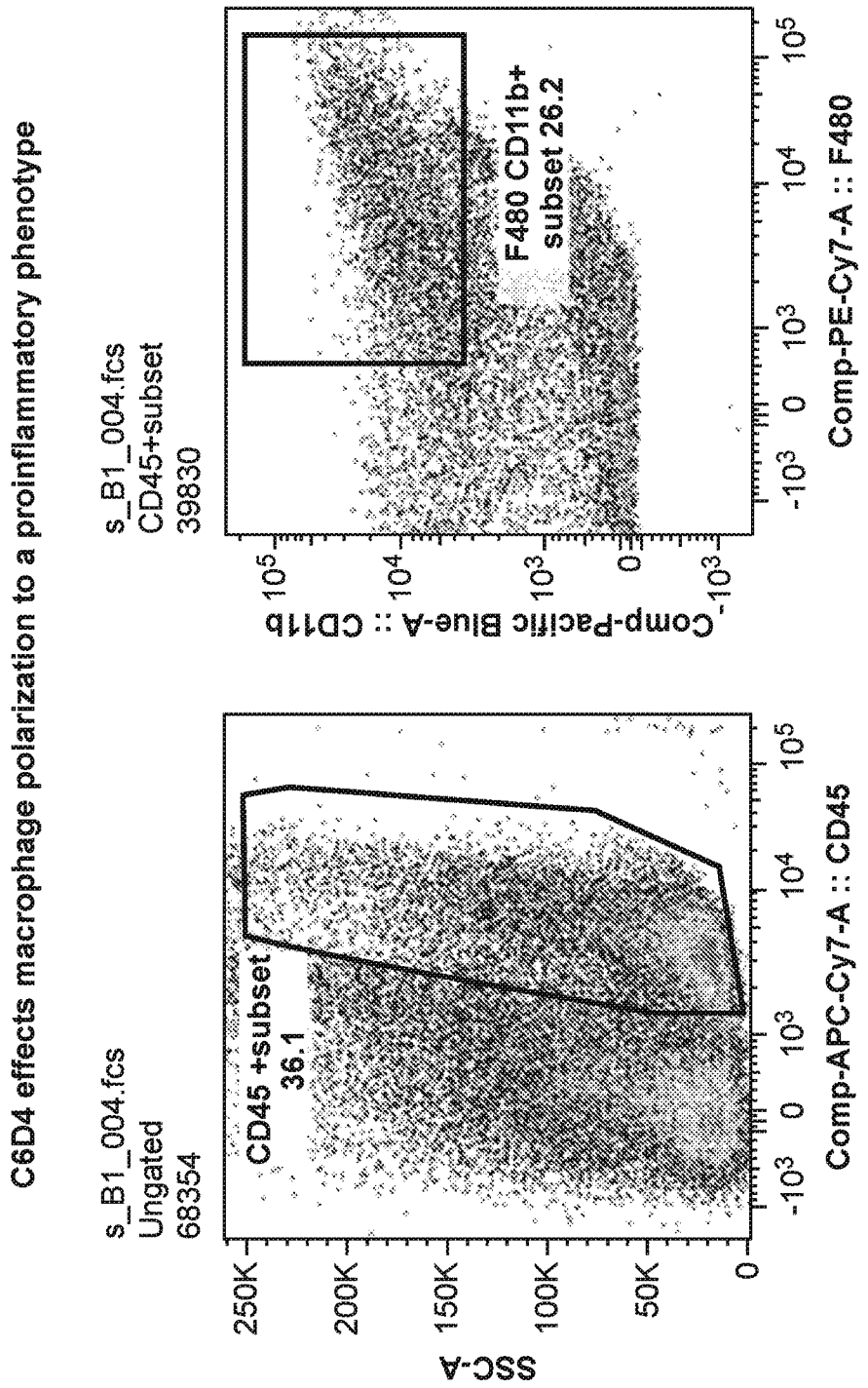


FIG. 35E

FIG. 35F

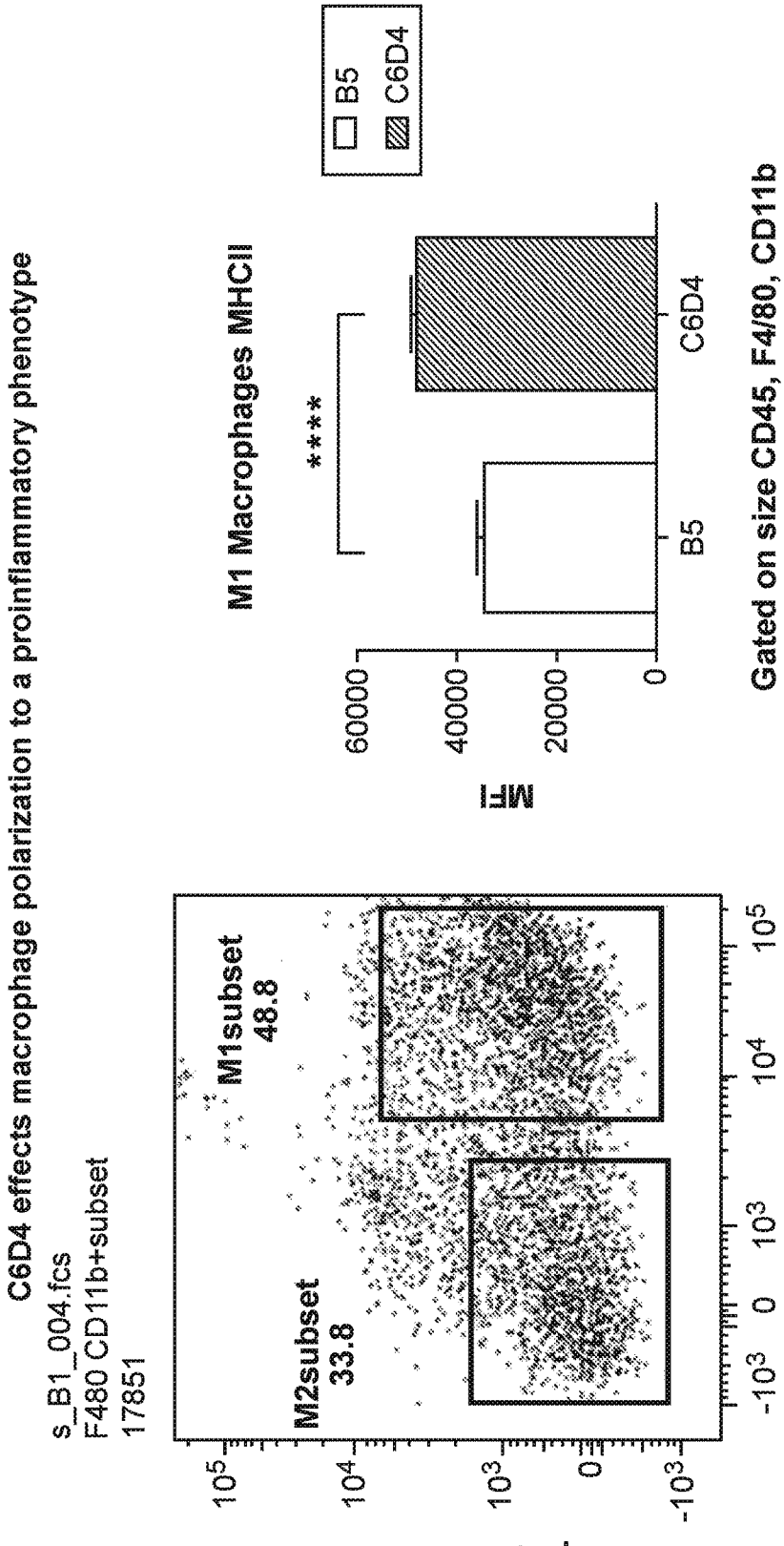


FIG. 35G

FIG. 35H

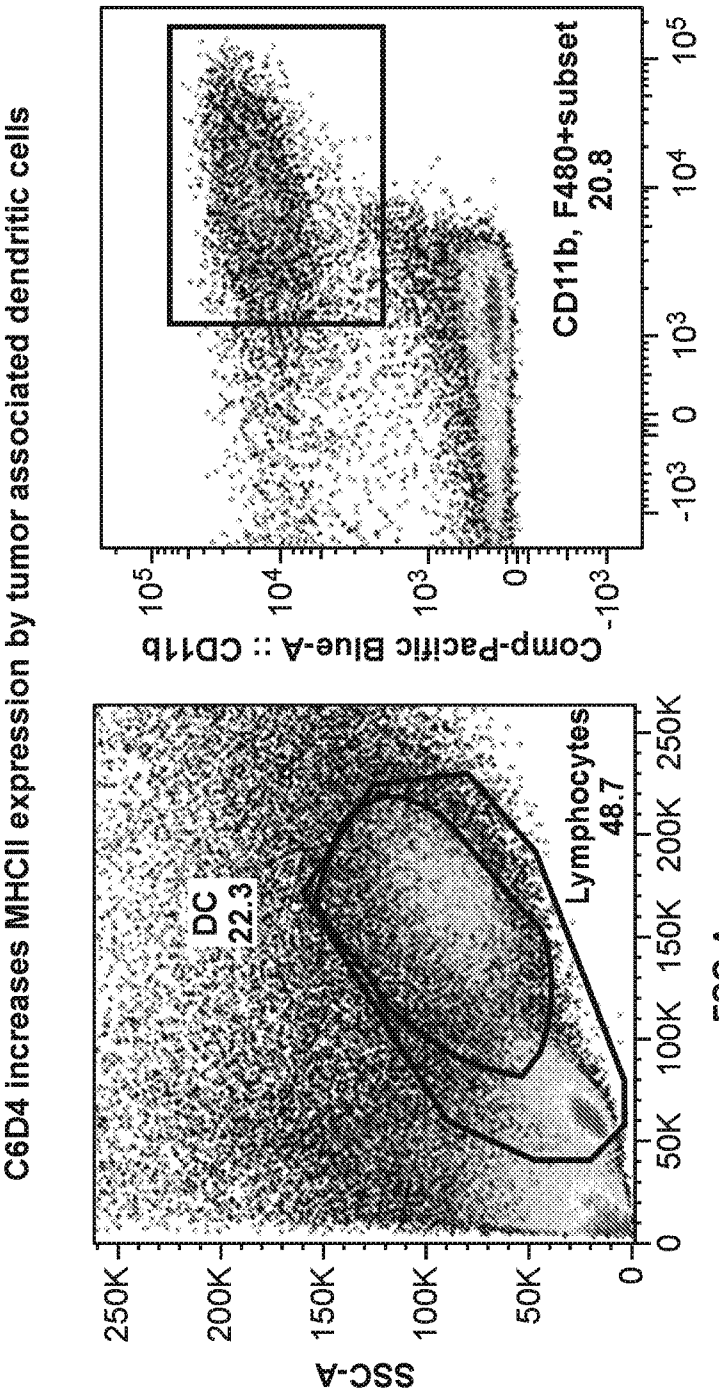


FIG. 36A

FIG. 36B

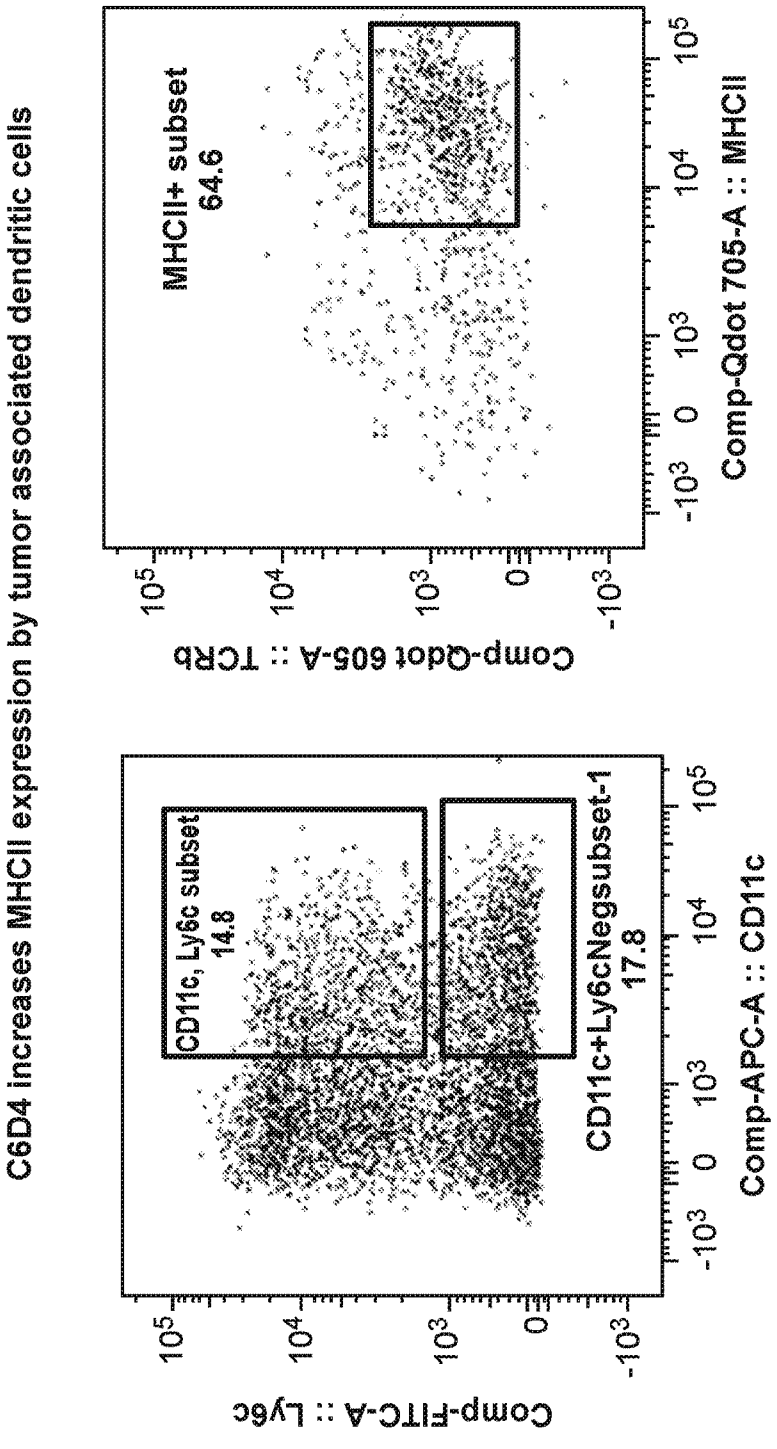


FIG. 36C

FIG. 36D

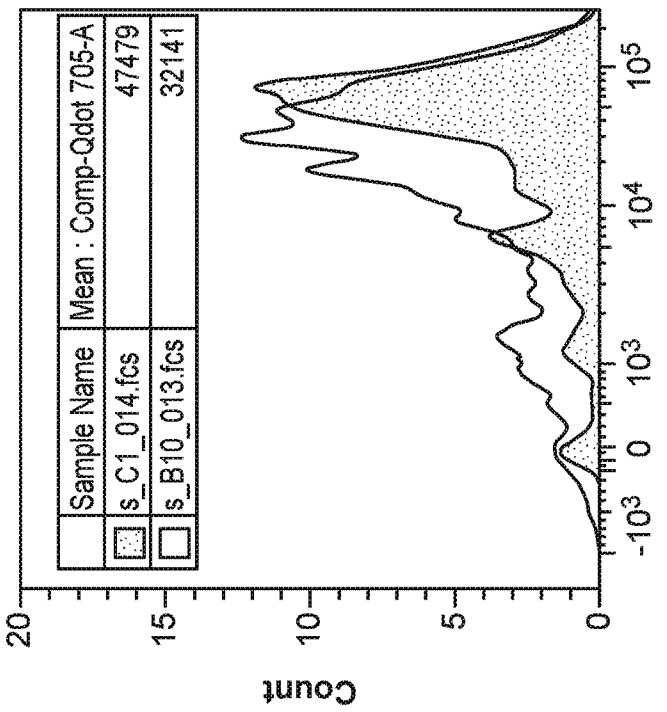


FIG. 36E

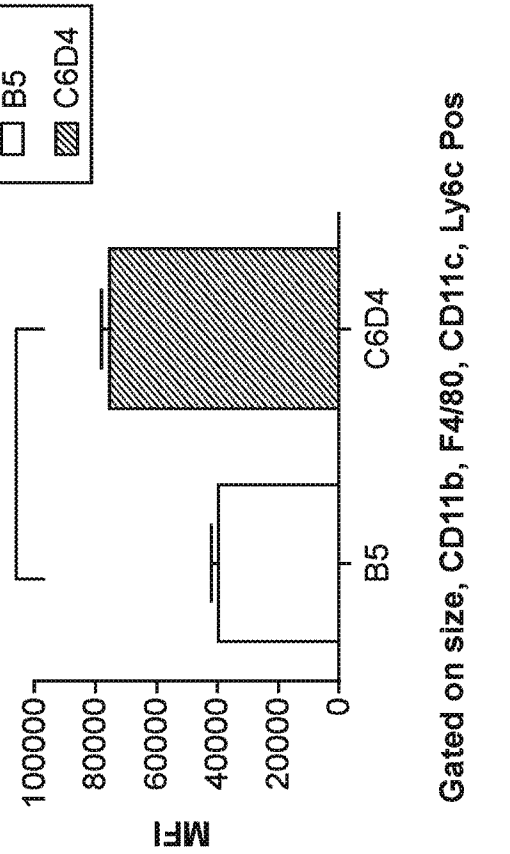
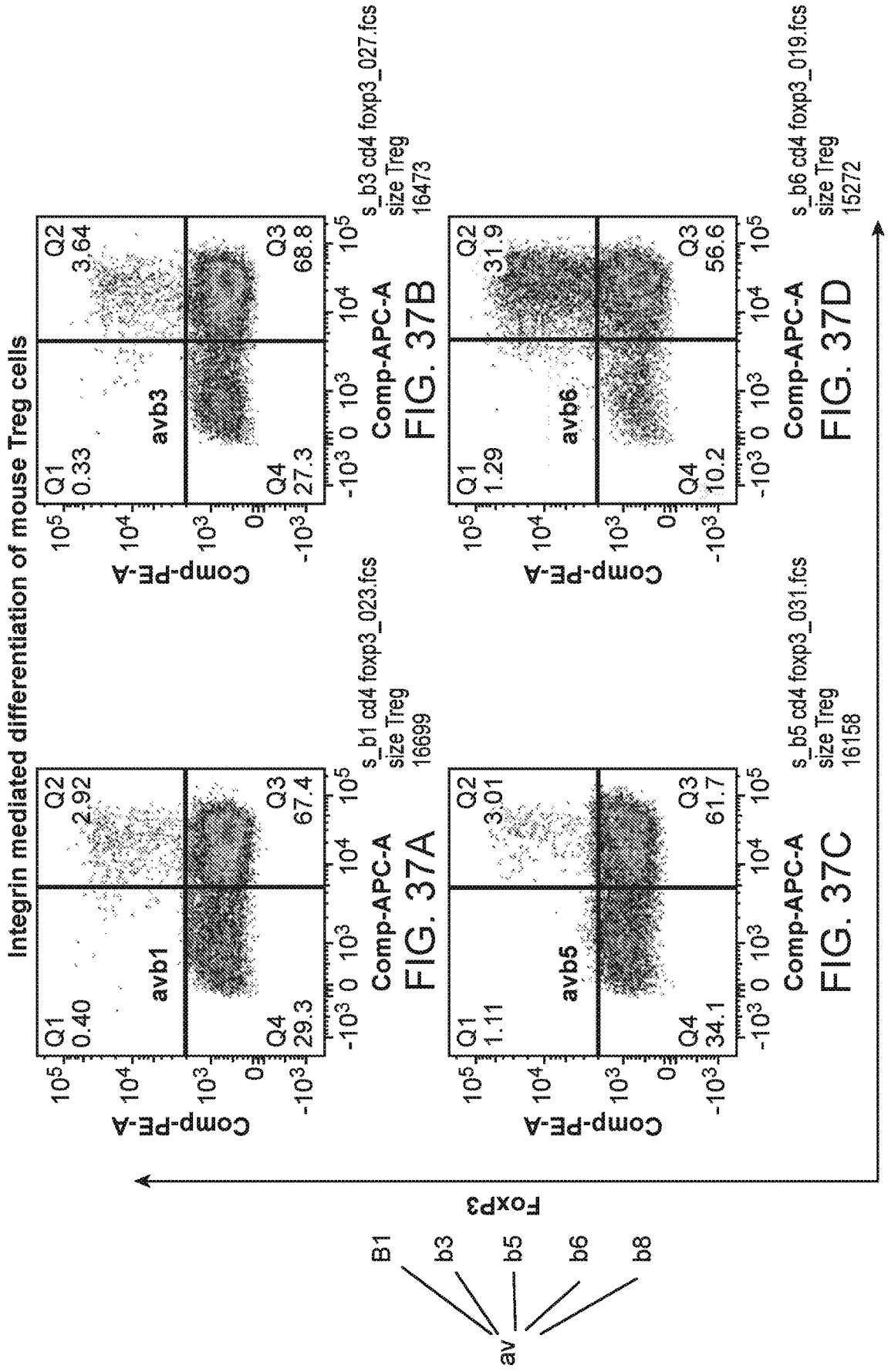
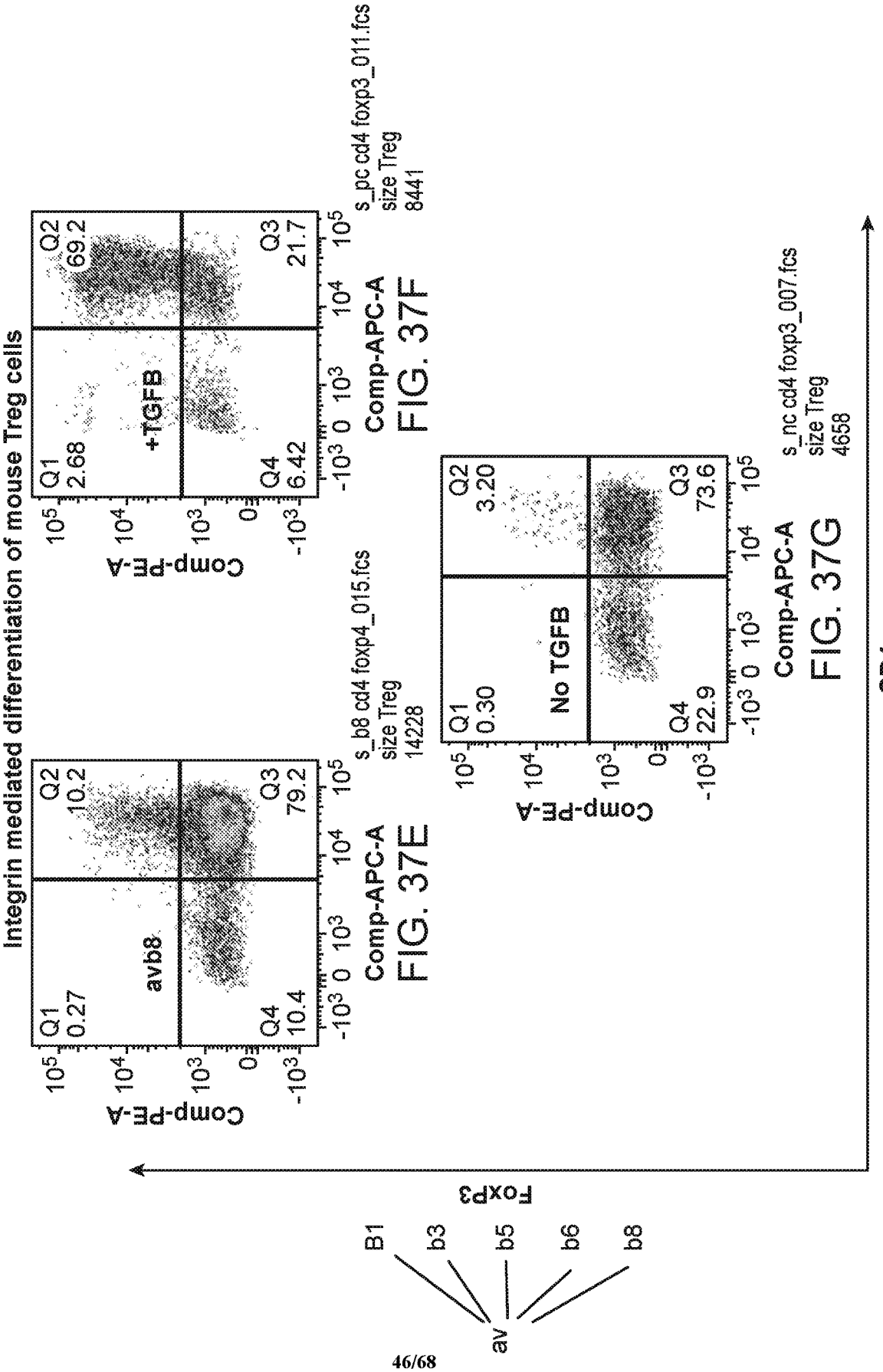


FIG. 36F





Structure based development of a C6D4 derivative (C6D4-RGD3) that is cross-reactive to both avb6 and avb8

αVβ6: GRGDLGRLKK
αIIbβ3: GRGDSP
αIIbβ3: AKQRGDV

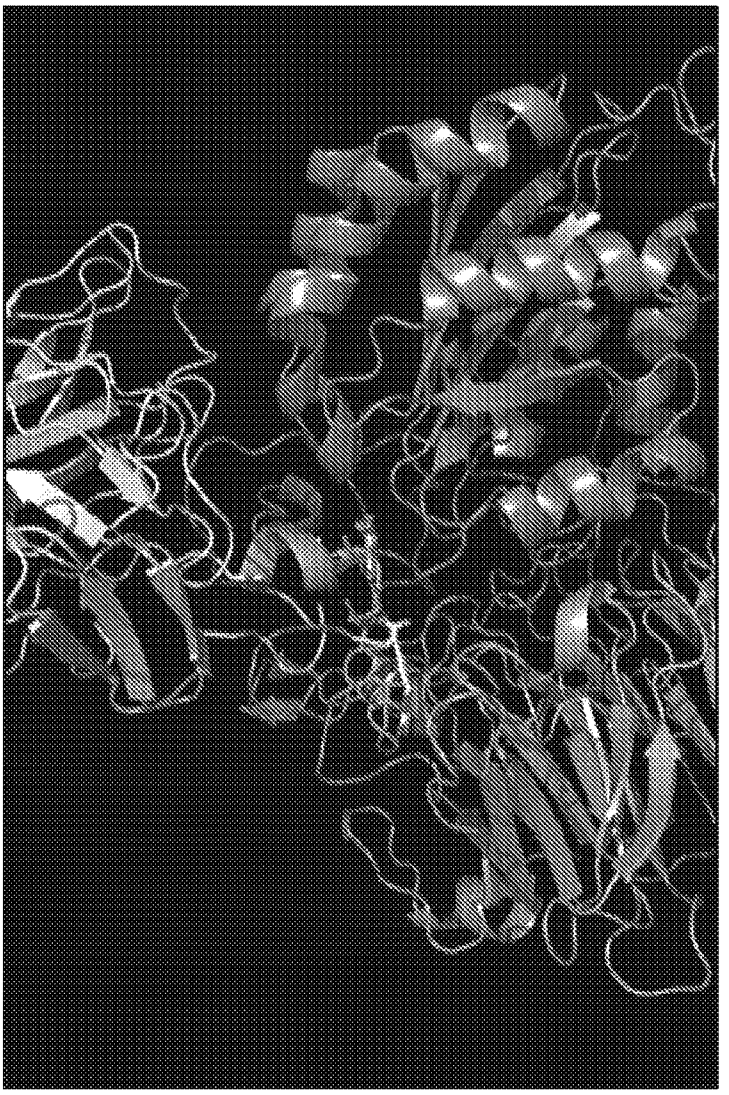


FIG. 38A

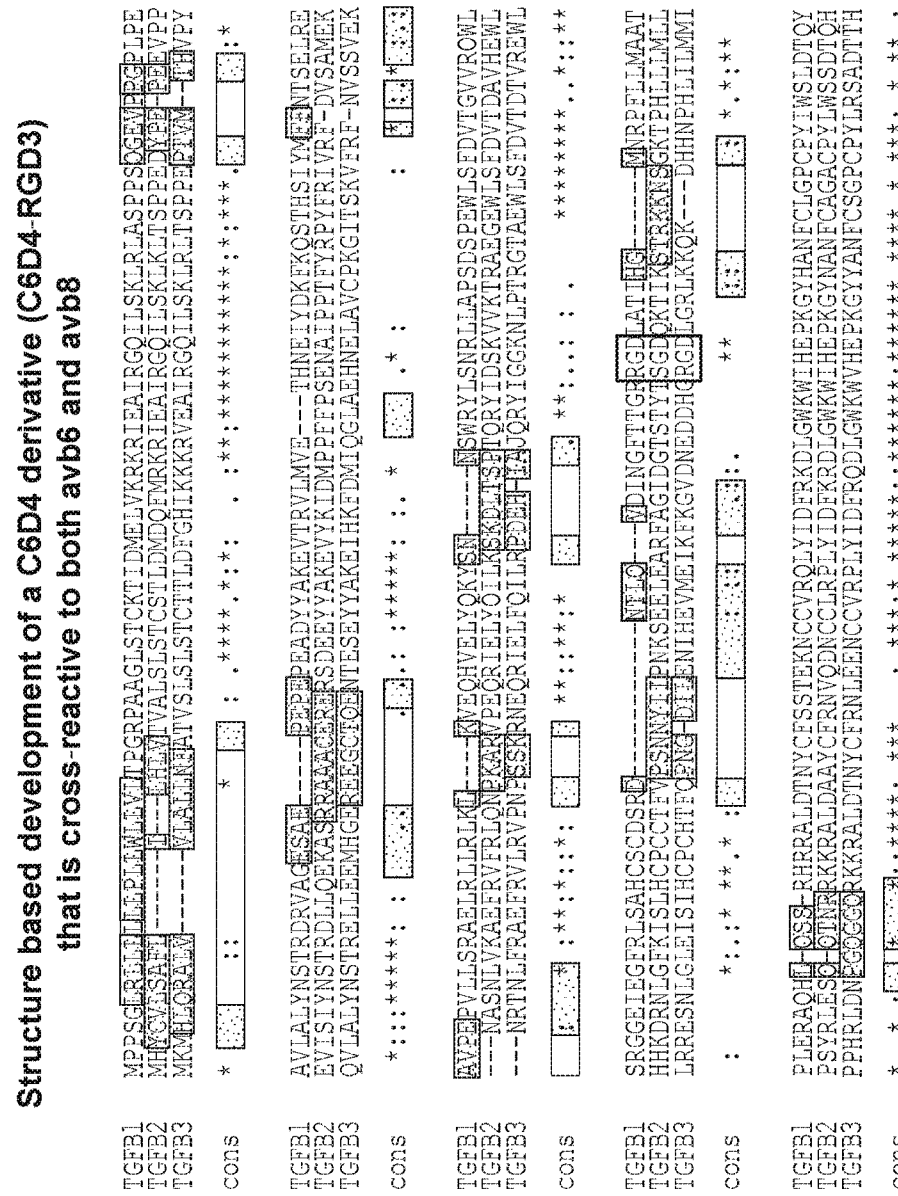


FIG. 38B

Structure based development of a C6D4 derivative (C6D4-RGD3) that is cross-reactive to both avb6 and avb8

C6D4_vk

DIVMTQSPSSLAVSAGEKVTMSCKSSQSLLNSRTRKNYLAWYQQKPGQSPRLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCKQSYNLLSFGAGTKLE
LKAADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

C6D4-RGD1 KSSQSLLGRGDLGNALA (17aa)
C6D4-RGD2 KSSQSLLNSGRGDLGNALA (19aa)
C6D4-RGD3 KSSQSLLGRGDLGRLKKNALA (21aa)

FIG. 38C

FIG. 38D

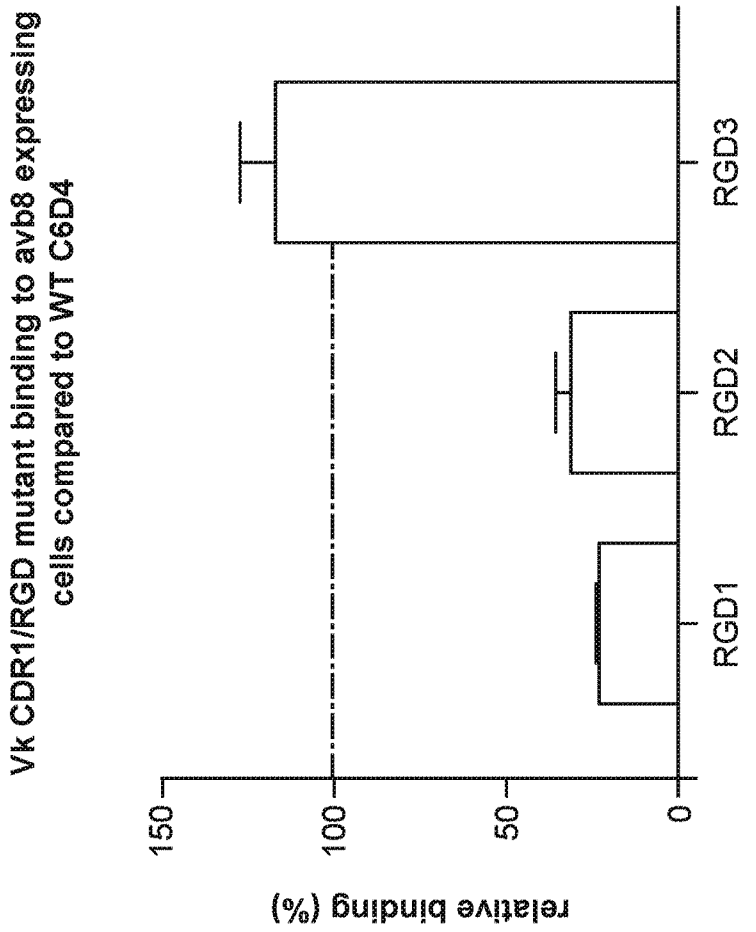


FIG. 39

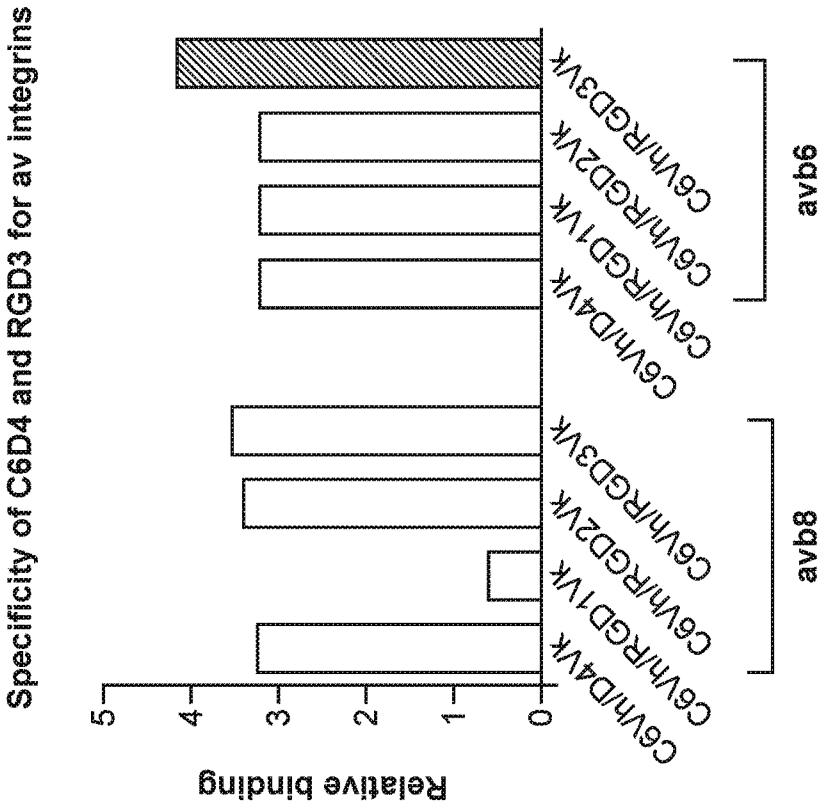


FIG. 40

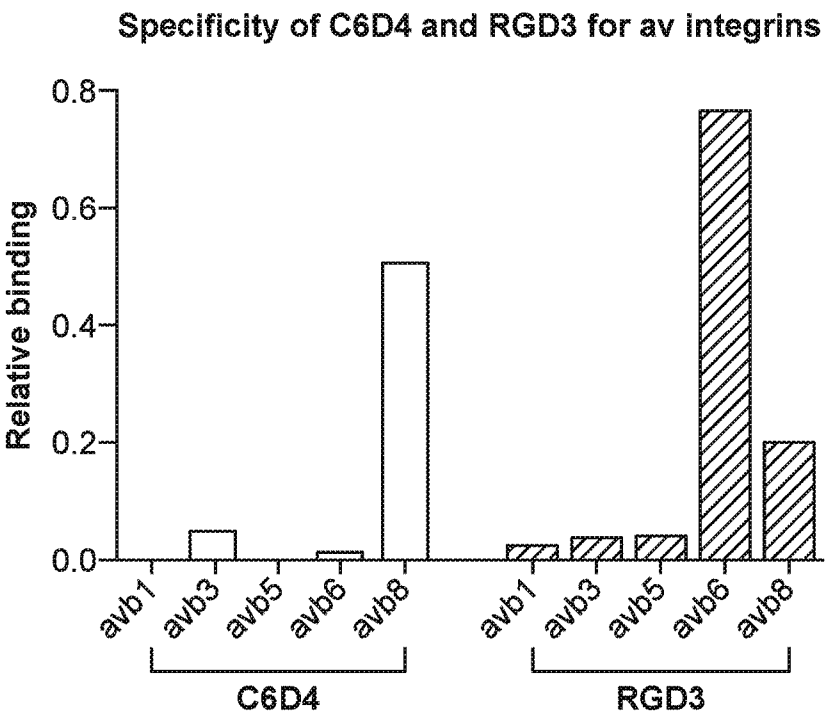


FIG. 41

C6D4 binding to αvβ8 is not enhanced by cations C6D4-RGD3 binding to αvβ8 is enhanced by cations and cation-dependent to αvβ6

Mab (5 ug/ml)	Receptor	Binding in EDTA buffer (% compared with binding to anti-av clone 11D12V2)	Binding in Mg buffer relative to clone 68 (% compared with binding to anti-av clone 11D12V2
C6D4	avb8	105%	103%
C6D4	avb6	0%	0%
RGD3	avb8	11%	98%
RGD3	avb6	0%	120%

FIG. 42

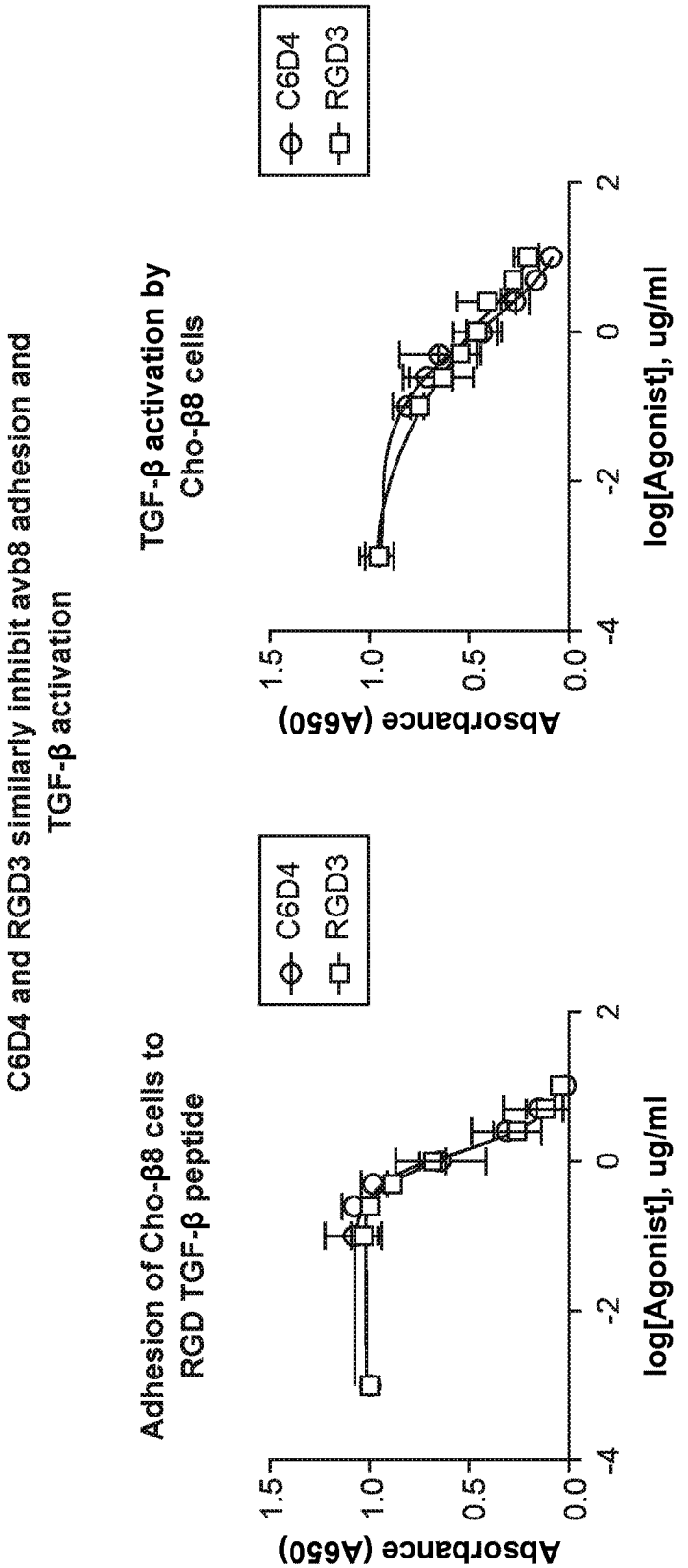


FIG. 43A

FIG. 43B

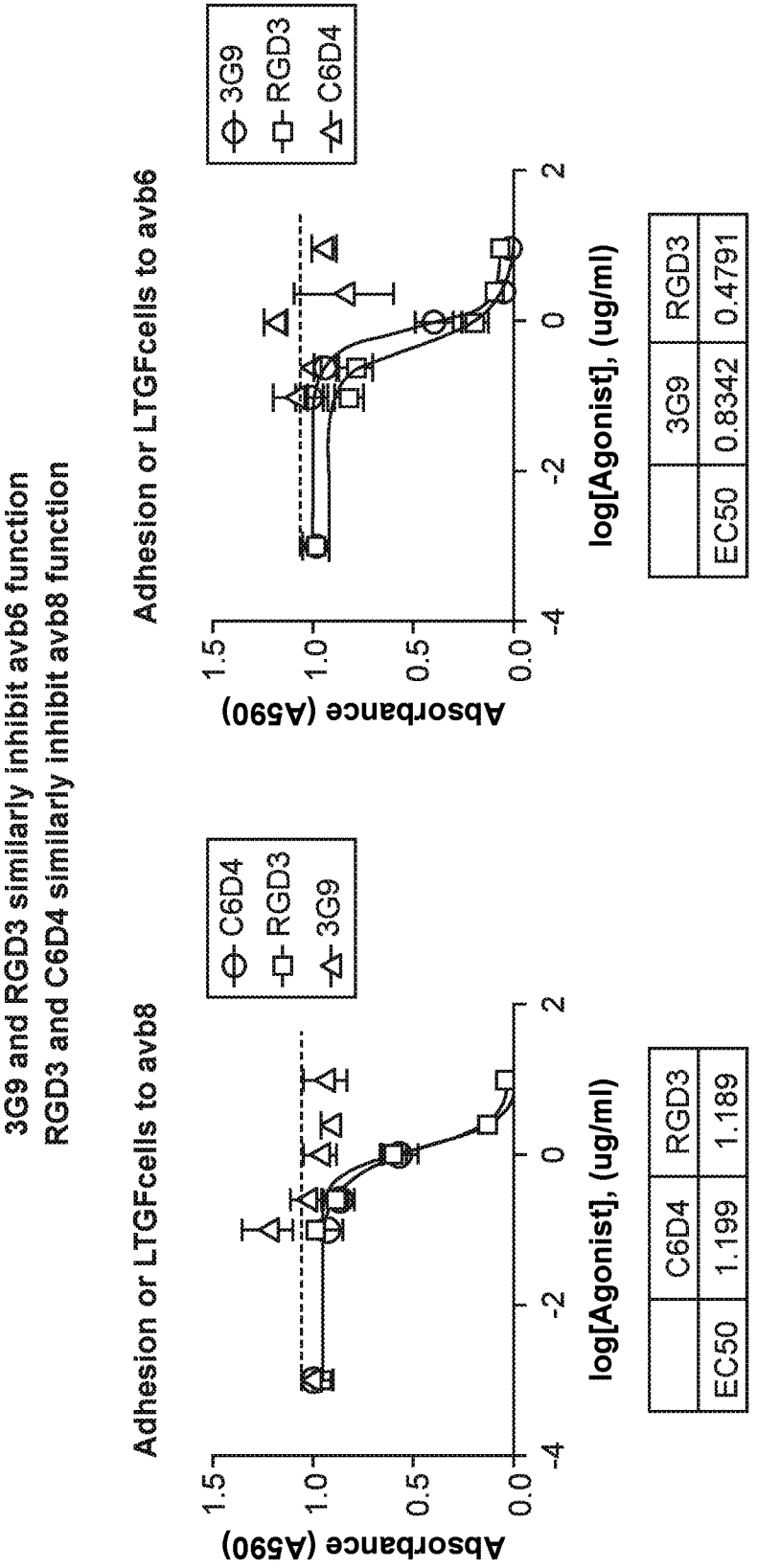


FIG. 44A

FIG. 44B

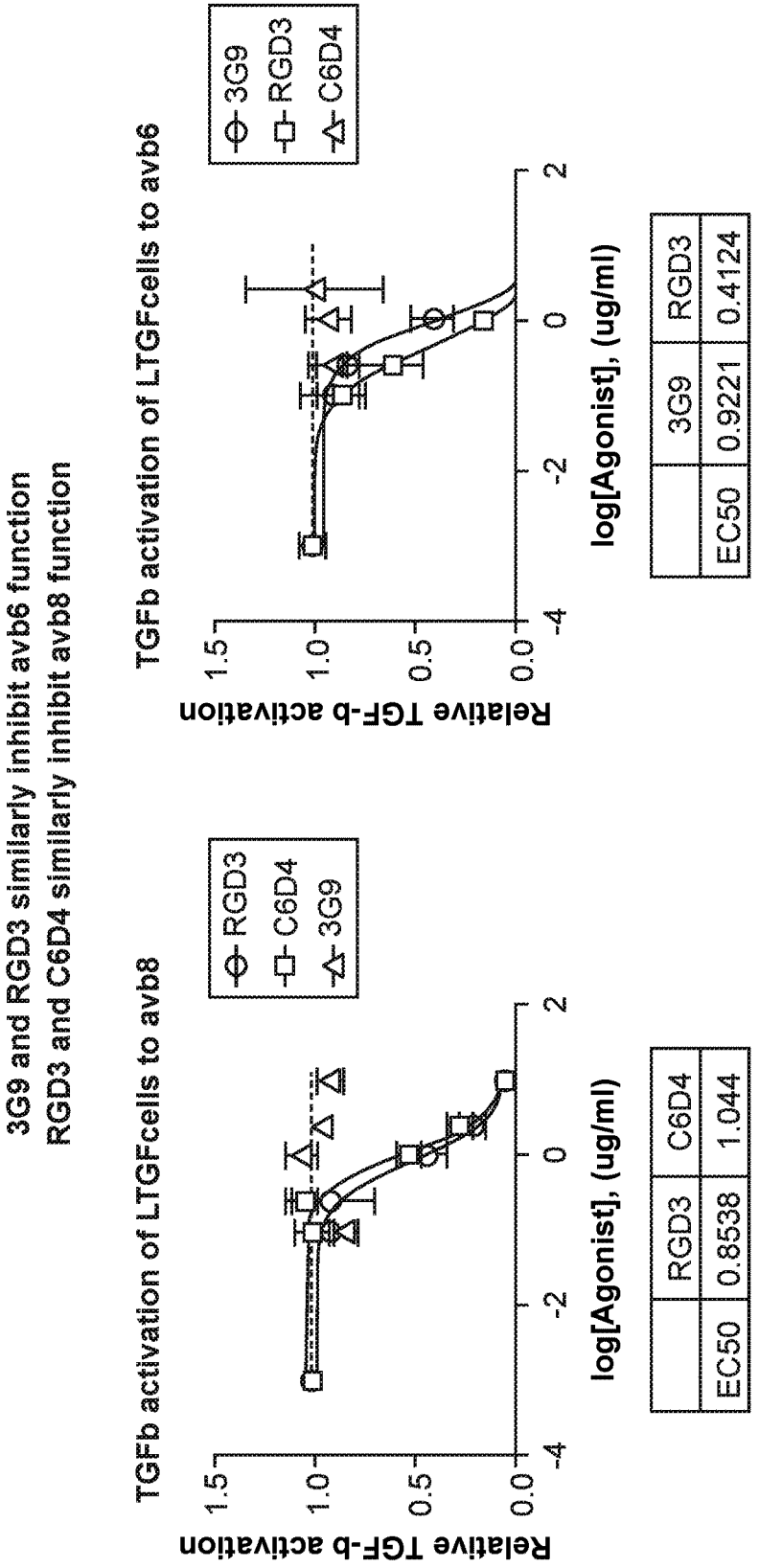
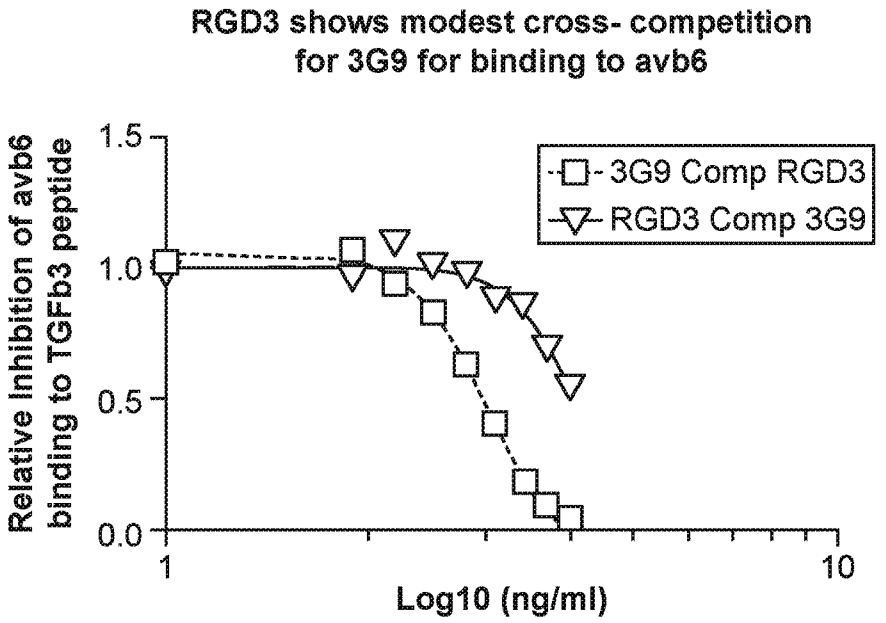


FIG. 44C

FIG. 44D



	3G9 Comp RGD3	RGD3 Comp 3G9
LogEC50	2.927	3.777

FIG. 45

Humanization of C6D4

C6D4 Humanization design and FACS Screened based on risk factor and germline (VH1/VK3) picking results with yeast scFv KD data

VH (Mouse IgG2a)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4	scFv KD (nM)
C6D4	QIQLVQSGPELKKPGETVKISCKASGYTFT	DYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTTLTVSS	7.2507
HuC6D4 V1	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDS	WGQGTTLTVSS	15.571
Mutclone A3	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDS	WGQGTTLTVSS	7.4638
Mutclone B7	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFSVTLDTSTSTAYLETMSLRSDDTAVYFCAI	FYYGRDT	WGQGTALTVSS	6.9373
Mutclone E5	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDT	WGQGTTLTVSS	6.5826

VK (Mouse IgG2a)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4	scFv KD (nM)
C6D4	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLS	FGAGTKLELKR	7.2507
HuC6D4 V1	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR	15.571
Mutclone A3	EIVMTQSPATLSVSPGEIVTMSC	KSSQSLLNSRSRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR	7.4638
Mutclone B7	EIVMTQTPVTLSVSPGERVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQAPRLLIY	WASTRES	DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSSNLLS	FGQGTVLEIKR	6.9373
Mutclone E5	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLNSRSRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR	6.5826

FIG. 46

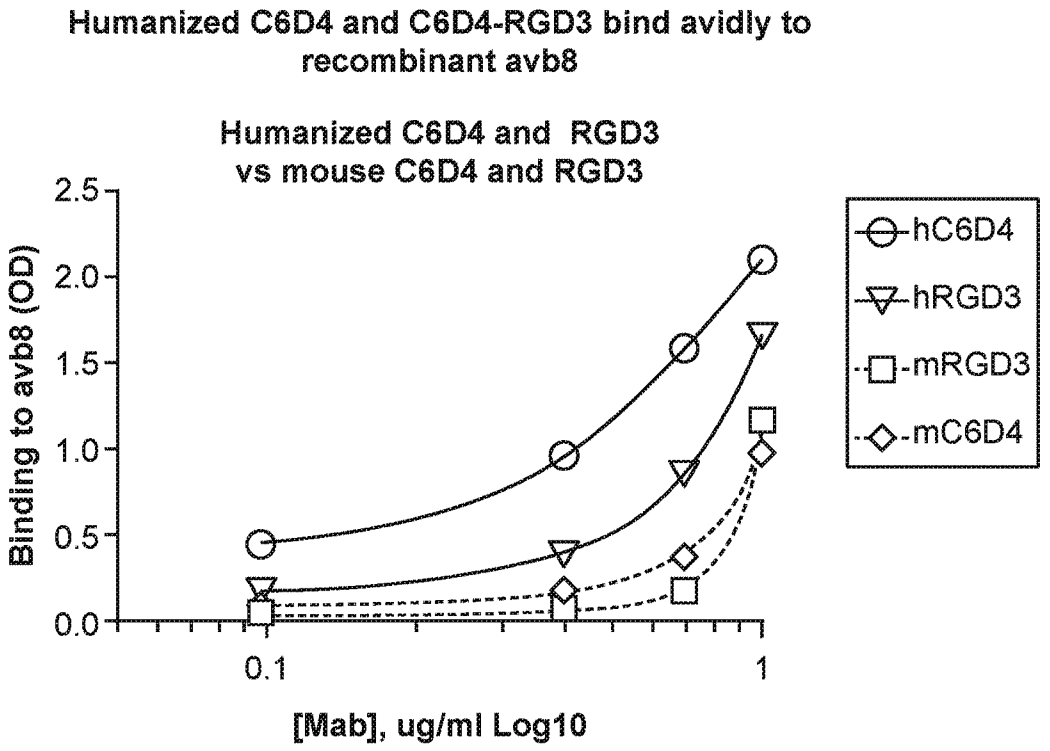


FIG. 47

Date Reçue/Date Received 2023-12-19

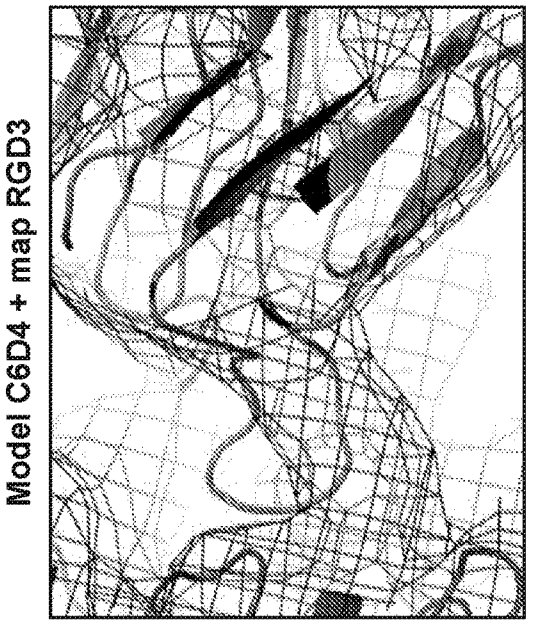


FIG. 48B

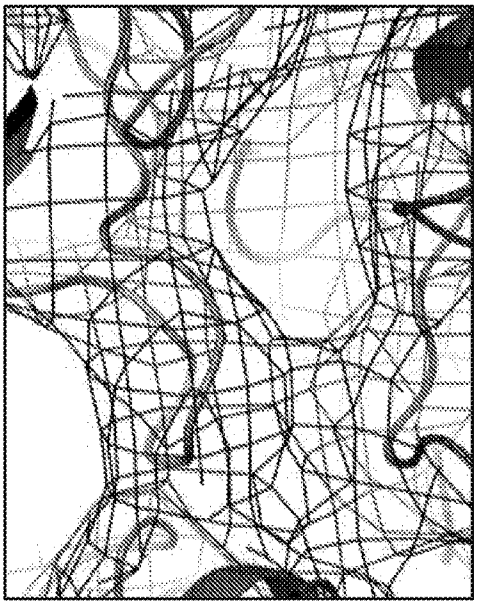


FIG. 48D

View from top

View from front

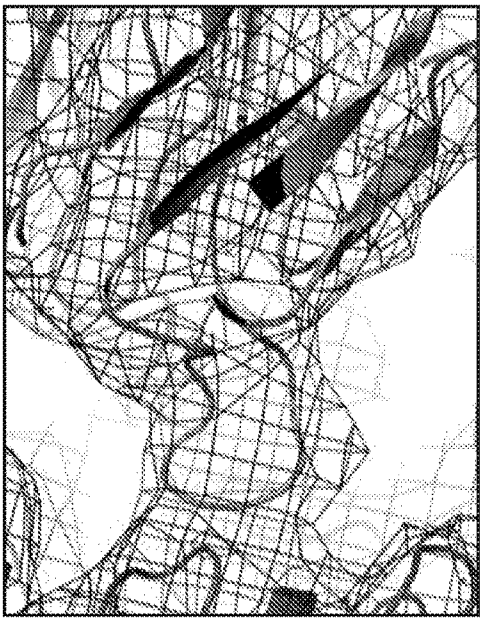


FIG. 48A

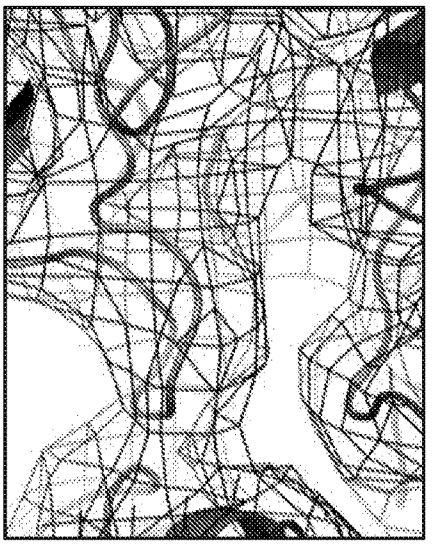


FIG. 48C

Date Reçue/Date Received 2023-12-19

FIG. 49A FIG. 49B FIG. 49C

VH (Mouse Hybridoma Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
HuC6D4V1	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDS	WGQGTTLTVSS
HuC6D4A3	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDS	WGQGTTLTVSS
HuC6D4B7	QIQLVQSGAKVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFSVTLDTSTSTAYLEITSLRSDDTAVYFCAI	FYYGRDT	WGQGTALTVSS
HuC6D4E5	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDT	WGQGTTLTVSS

Final clone for in vivo/in vitro Functional test in IgG format

VH (Mouse Hybridoma Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
C6D4	QIQLLQSGPELKKPGETVKISCKASGYTFT	DYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTTLTVSS
HuC6D4	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDT	WGQGTTLTVSS
C6D4-RGD3	QIQLLQSGPELKKPGETVKISCKASGYTFT	DYSMH	WVKQAPGKGLKWVA	RINTETGEPTFADDFRG	RFAVSLETSASTAYLQINNLKNEDTATYFCAI	FYYGRDS	WGQGTTLTVSS
HuC6D4-RGD3	QIQLVQSGAEVKKPGASVKISCKASGYTFT	DYSMH	WVRQAPGQGLEWVA	RINTETGEPTFADDFRG	RFTVTLDTSTSTAYLEIRSLRSDDTAVYFCAI	FYYGRDT	WGQGTTLTVSS

Consensus sequence of HuC6D4 related clones:

Consensus VH: QIQLx1QSGx2x3x34KKPGx4x5VKISCKASGYTFT DYSMH WVx6QAPGx7GxL8Wx9x10 x11Ix12TETx13EPTx14ADDFx15x16 RFx17x18x19Lx20TSx21x22TAx23Lx24Ix25x26Lx27x28x29DTAx30YFCAI x31YYGRDx32 WGQGTx33LVTVSS

where x1 = V or L, x2 = A or P, x3 = E or K, x4 = A or E, x5 = S or T, x6 = R or K, x7 = Q or K, x8 = E or K, x9 = V or M, x10 = A or G x11 = R or W, x12 = N or K, x13 = G or D, x14 = F or Y, x15 = R, N, K or G, x16 = G or E, x17 = T, A, or S, x18 = V or F, x19 = T or S, x20 = D or E, x21 = T or A, x22 = S or T, x23 = Y or N, x24 = E or Q, x25 = R, N, I or T, x26 = S or N, x27 = R or K, x28 = S or N, x29 = D or E, x30 = V, T, or K, x31 = F or Y, x32 = T or S, x33 = T or A, x34 = V or L.

FIG. 50

VL (Mouse Hybridoma Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
HuC6D4V1	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR
HuC6D4A3	EIVMTQSPATLSVSPGEIVTMSC	KSSQSLLNSRSRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLIS	FGQGTVLEIKR
HuC6D4B7	EIVMTQTPVTLSVSPGERVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQAPRLLIY	WASTRES	DVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSSNLIS	FGQGTVLEIKR
HuC6D4E5	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLNSRSRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR

Final clone for in vivo/in vitro Functional test in IgG format

VL (Mouse Hybridoma Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
C6D4	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLNSRTRKNYLA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLS	FGAGTKLELKR
HuC6D4	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLNSRSRKNYLA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR
C6D4-RGD3	DIVMTQSPSSLAVSAGEKVTMSC	KSSQSLLGRGDLGRLKKNALA	WYQQKPGQSPRLLIY	WASTRES	GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC	KQSYNLLS	FGAGTKLELKR
HuC6D4-RGD3	EIVMTQSPATLSVSPGERVTMSC	KSSQSLLGRGDLGRLKKNALA	WYQQKPGQAPRLLIY	WASTRES	GVPARFSGSGSGTEFTLTISSVQSEDFAVYYC	KQSYNLLS	FGQGTVLEIKR

Consensus sequence of HuC6D4 related clones:

Consensus VL: **x40IVMx41Qx42Px43x44Lx45Vsx46GEx47VTMSC KSSQSLLNSRx48RKNYLA WYQQKPGQx49PRLLIY WASTRES x50VPx51RFx52GSGSGTx53FTLTISSVQx54EDx55AVYYC KOSYNLLS FGx56GTx57LEx58KR**

where x40 = E or D, x41 = T or S, x42 = S or T, x43 = A, S or V, x44 = T, S, x45 = S or A, x46 = P or A, x47 = R, K or I, x48 = S or T, x49 = A or S
x50 = G or D, x51 = A or D, x52 = S or T, x53 = E or D, x54 = S, D or A, x55 = F or L, x56 = Q or A, x57 = V or K, x58 = I or L

RGD3 loop: GRGDLGRLK inside VL CDR1

FIG. 51

F9 Variants and parents Confirmed sequence

VH (Mouse Hybridoma clone Name)	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
4F1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTNYLIE	WVKQRPGQGLEWIG	VINPGTGGTNYNKKFKV	KATLTADKSSSTAYMQLGGLTFDDSAVYFCAR	EGNARYYYAMDY	WGQGTSVTVSS
6B9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
(scFv clone Name from yeast display library)							
6B9.1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A1	QVQLQQSGAELVRPGASVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSVYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A2	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSTAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A8	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
A11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDNLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
B1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLSSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
B3	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSGLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
C4=F10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
C7=D1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSGSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D3=F1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSDDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D10=E5	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
E8	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
F2	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
G4	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVRQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKSSSSAYMQLNSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS

FIG. 52

(Produced Rabbit IgG clone name)							
C4	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
D10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KVTLTADKTSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
(scFv clone from Phage Display library)							
4F1E1	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1G3	QVQLQQSGAELVRPGTSVRVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTANKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1B5	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1G11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1A9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1B9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1F9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1H9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1D10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1E10	QVQLQQSGAELVRPGTSVKVPCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1F10	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1H12	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLI*	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYLQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4F1E9	QVQL*QSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4FA11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	RATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
4FH11	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIE	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS
Final clone for in vitro Functional test in IgG format							
F9	QVQLQQSGAELVRPGTSVKVSCKASGY	AFTDYLIQ	WVKQRPGQGLEWIG	VINPETGGTNYNAKFRG	KATLTADKSSSSAYMQLSSLTSGDSAVYFCAR	EAGNYIYAMDY	WGQGTSVTVSS

FIG. 52 (Cont.)

F9 Variants and parents Confirmed sequence

VH	Framework 1	CDR1	Framework 2	CDR2	Framework 3	CDR3	Framework 4
(Mouse Hybridoma clone Name)							
4F1	DIQMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
6B9	DIEMTQTPASLSASVGETVTITC	RASENIYSYLV	WYQQKQGKSPQVLVY	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHNGTPYT	FGGGTKLEIKA
(scFv clone Name from yeast display library)							
6B9.1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKA
A1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
A2	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
A8	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSVQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
A11	HIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
B1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDVGSYYC	QHHHGTPYT	FGGGTKLEIKR
B3	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAA	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
C4=F10	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
C7=D1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
D3=F1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
D10=E5	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
E8	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTRFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
F2	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKISSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
G4	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR

FIG. 53

(Produced Rabbit IgG clone name)								
C4	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
D10	DIEMTQTPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR
(scFv clone from Phage Display library)								
4F1E1	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1G3	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1B5	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1G11	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1A9	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1B9	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1F9	DIVMTQSPAFLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1H9	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSXTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1D10	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1E10	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1F10	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1H12	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4F1E9	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4FA11	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
4FH11	DIVMTQSPASLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIK
Final clone for in vitro Functional test in IgG format								
F9	DIVMTQSPAFLSASVGETVTITC	RASVNIYSYLV	WYQQKQGKSPQLLVH	NAKTLAE	GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC	QHHHGTPYT	FGGGTKLEIKR

FIG. 53 (Cont.)

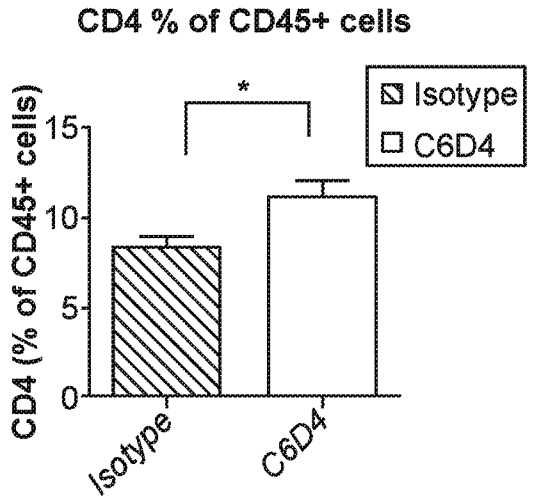


FIG. 54A

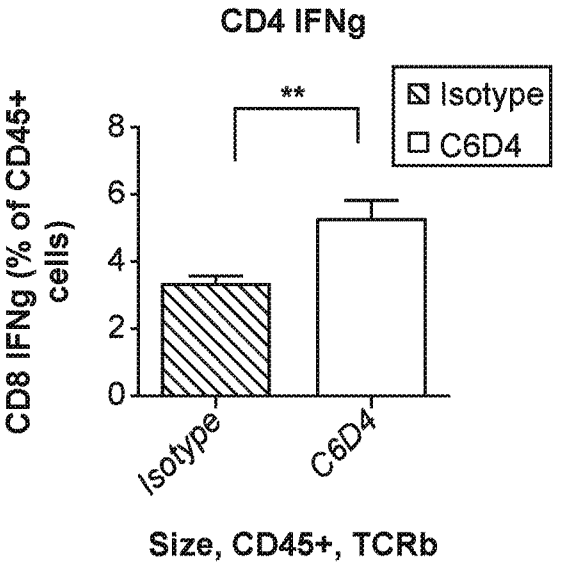


FIG. 54B

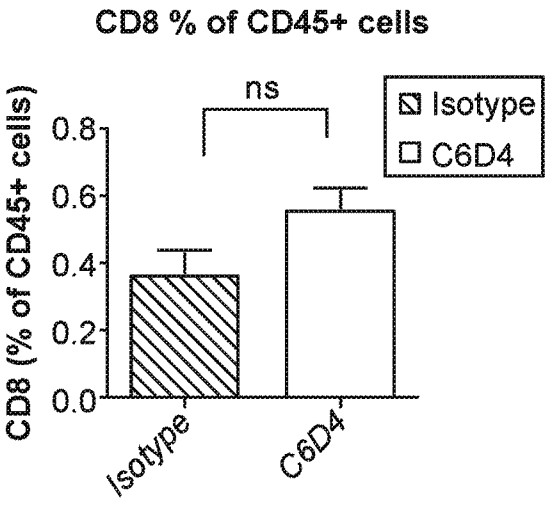


FIG. 54C

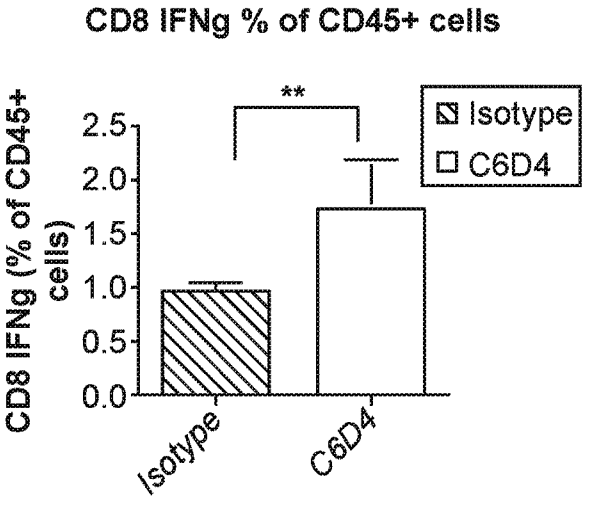


FIG. 54D

Date Reçue/Date Received 2023-12-19