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(54) **Title: HIGH AFFINITY HUMAN ANTIBODIES TO HUMAN CYTOMEGALOVIRUS (CMV) GB PROTEIN**

(57) **Abrégé/Abstract:**
Antibodies to human Cytomegalovirus (CMV) gB protein have been isolated from human B cells. The affinities of these antibodies are higher than the best previously reported antibodies. Since high affinity is critical to prevention of virus transfer across the placenta, the invention antibodies are useful as therapeutic and prophylactic agents to prevent or ameliorate effects on the fetus of CMV infection during pregnancy.

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(54) Title: HIGH AFFINITY HUMAN ANTIBODIES TO HUMAN CYTOMEGALOVIRUS (CMV) GB PROTEIN

(57) Abstract: Antibodies to human Cytomegalovirus (CMV) gB protein have been isolated from human B cells. The affinities of these antibodies are higher than the best previously reported antibodies. Since high affinity is critical to prevention of virus transfer across the placenta, the invention antibodies are useful as therapeutic and prophylactic agents to prevent or ameliorate effects on the fetus of CMV infection during pregnancy.

HIGH AFFINITY HUMAN ANTIBODIES TO HUMAN CYTOMEGALOVIRUS (CMV) GB PROTEIN

[0001] <Deleted>

Reference to Sequence Listing

[0002] This description contains a sequence listing in electronic form in ASCII text format. A copy of the sequence listing in electronic form is available from the Canadian Intellectual Property Office.

Technical Field

[0003] The invention relates to human monoclonal antibodies (mAbs) against the gB protein of CMV, for therapeutic and prophylactic use to prevent or ameliorate the effects on the fetus of CMV infection during pregnancy, and to treat CMV infection in immunocompromised patients, including transplant patients.

Background Art

[0004] CMV is a major disease-causing agent in transplant patients, other immunocompromised patients, and newborns. About 40,000 infants are born shedding CMV every year in the US. Of these, 8,000 are born with symptoms and/or severe handicaps and up to 8,000 more will later develop progressive hearing loss. About half of pregnant mothers have adequate immunity naturally. Thus it is known that effective mAbs exist in human blood. This is also shown by successful passive transfer of immunity by intravenously administered gamma globulin (IVIG), which has shown very high efficacy for protecting the fetus. This is in contrast to the limited efficacy observed for IVIG in the transplant setting, for which cellular immunity is apparently more important than humoral immunity.

[0005] A substantial portion of the natural response to CMV is directed towards the gB protein (Park, J. W., *et al., J. Korean Med. Sci.* (2000) 15:133-138). The Towne vaccine is an attenuated live virus vaccine passaged extensively *in vitro*, which induces antibodies that neutralize fibroblast infection, but not endothelial cell infection. This vaccine is known to be safe and has been studied for 20 years (Adler, S. P., *et al., Pediatr. Infect. Dis. J.* (1998) 17:200-206). Blood donors useful for isolating antibodies to gB as described below include seropositive individuals with previous exposure to CMV and seronegative subjects before and after vaccination with the Towne vaccine.

[0006] Antibodies to gB protein of CMV have been prepared (Nozawa N., *et al., J. Clin. Virol.* (2009) [Epub ahead of print], Nakajima, N., *et al.* (US2009/0004198 A1), Lanzavecchia, A, *et al.* (US2009/0004198 A1), Ohlin, M., *et al.* (*J Virol* (1993) 67:703-710). A neutralizing antibody to the AD-2 domain of gB, ITC88, has been reported (Lantto, *Virology* (2003) 305:201-209). However, prior efforts to clone human antibodies against CMV, while successful, are limited in scope and no high affinity (sub-nanomolar) antibodies have been described. High affinity is a key parameter as weak affinity antibodies to CMV actually promote transmission across the human placenta (Nozawa, *supra*), an aspect of the pathology not seen in rodents. Human CMV has a double stranded DNA genome of approximately 236 kb and is a prototypical member of the β-herpesvirus family. The high complexity of the genome means that there are many potential antigens of interest. Efforts to characterize neutralizing antibodies and their associated epitopes resulted in a subunit vaccine based on glycoprotein B (gB) that elicits an effective neutralizing response, but, when tested in a cohort of seronegative women has only 50% efficacy. This appears to be the highest efficacy of any CMV vaccine. Since vaccines typically induce antibodies with a range of affinities, the disappointing efficacy of the tested vaccines to date may be attributable to the requirement for high affinity antibodies, which argues in favor of supplying a high affinity mAb directly as a prophylactic strategy.

[0007] Failure to focus the immune response on the specific neutralizing epitopes has also been postulated as the cause of the poor efficacy (Marshall, B. C., *et al., Viral Immunol.* (2003) 16:491-500. Another suspected technical problem in developing anti-CMV vaccines is that they have only been assessed for their ability to generate antibodies that neutralize fibroblast infection although infection of other cell types has increasingly become a focus for understanding the viral pathology. This bias reflects technical obstacles with regard to growth of the virus *in vitro*. Repeated virus passage on fibroblast cells is believed to have caused many lab strains to lose tropism for endothelial and epithelial cells. During the last few years, this

deficit has been associated with the loss of one or more components of the gH/gL/UL131-UL128 glycoprotein complex on the virus surface.

[0008] Clearly a need exists for a more effective anti-CMV prophylaxis strategy.

Disclosure of the Invention

[0009] Human antibodies that are specifically immunoreactive with the CMV gB protein, with improved affinity compared to prior antibodies (human or murine) and with neutralizing ability have been prepared. The humoral immune system is capable of producing millions of antibody structures with tens of thousands of well differentiated binding capabilities, yet the protective antibodies are only a very small subset of these. The present inventors have employed CellSpot™ technology (Harriman, W. D., *et al.*, *J. Immunol. Methods* (2009) 34:135-145, Collarini, E. J., et al., *J. Immunol.* (2009) 183:6338-6345), and U.S. patent 7,413,868) to generate a panel of mAbs from blood of donors verified as having high titer to CMV.

[009A] The invention disclosed and claimed herein pertains to An isolated monoclonal antibody (mAb) or immunoreactive fragment thereof that neutralizes cytomegalovirus (CMV) strain V1814 or AD169 of CMV wherein: the heavy chain comprises the CDR1, CDR2 and CDR3 regions of the heavy chain variable region of MAB345 (SEQ ID NO:22); and the light chain comprises the CDR1, CDR2 and CDR3 regions of light chain variable region of MAB345 (SEQ ID NO:36).

[009B] Various embodiments of this invention relate to nucleic acid molecules that comprise nucleotide sequences that encode an antibody or fragment thereof of this invention or where the nucleotide sequence is complementary to such a coding nucleotide sequence over its entire length.

[0009C] Various embodiments of this invention relate to recombinant host cells containing expression systems that produce an antibody or fragment thereof of this invention as well as methods to produce the antibody or fragment involving culturing such a host cell and recovering the antibody or fragment.

[0009D] Various embodiments of this invention relate to pharmaceutical compositions that comprise an antibody or fragment thereof of this invention and a pharmaceutically acceptable excipient. In some cases, such an antibody, fragment thereof or composition may be useful to enhance resistance to infection by CMV in a subject or for treating CMV in a subject infected with CMV.

[0010] Thus, in one aspect, the invention is directed to human monoclonal antibodies or immunoreactive fragments thereof that bind an epitope on the gB protein, with a preferred embodiment being binding to a conserved sequence therein. These antibodies display neutralizing

capabilities in standard plaque forming assays for neutralization of CMV and demonstrate EC_{50} in such assays of <500 ng/ml, preferably <200 ng/ml, more preferably <100 ng/ml. The antibodies of the invention also have affinities for the gB protein of CMV strain AD169 of <10 nM or <5 nM or <1 nM.

[0011] For use in the methods of the invention to treat CMV infection or to enhance resistance to CMV, the monoclonal antibodies or fragments of the invention may be immunoreactive with a multiplicity of CMV strains and a single monoclonal antibody may suffice to have the desired effect. Alternatively, the subject to be treated or to be made resistant may be administered more than a single monoclonal antibody, which bind to the same or different CMV proteins.

[0012] The invention also includes pharmaceutical compositions useful for prophylaxis or treatment which contain as an active agent a single antibody or immunoreactive fragment of the invention, or no more than two antibodies or fragments of the invention.

[0013] Other aspects of the invention include methods of using the antibodies to treat CMV in human subjects or to induce resistance to infection in human subjects.

[0013A] Various embodiments of the claimed invention pertain to an isolated monoclonal antibody (mAb) or immunoreactive fragment thereof that neutralizes cytomegalovirus (CMV) strain VR1814 or AD169 of CMV wherein: the heavy chain comprises the CDR1, CDR2 and CDR3 regions of the heavy chain variable region of MAB345 as defined by SEQ ID NO:22; and the light chain comprises the CDR1, CDR2 and CDR3 regions of light chain variable region of MAB345 as defined by SEQ ID NO:36.

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[0014] The monoclonal antibodies of the invention may be produced recombinantly and therefore the invention also includes recombinant materials for such production as well as cell lines or immortalized cells and non-human multicellular organisms or cells thereof, or microbial cells, for the production of these antibodies. In one embodiment, cells obtained from human subjects are produced in "immortalized" form wherein they have been modified to permit secretion of the antibodies for a sufficient time period that they may be characterized and the relevant encoding sequence cloned.

Brief Description of the Drawings

[0015] Figures 1A and 1B show the binding of 4A2 and 19B10 to gB protein and to the conserved region thereof.

[0016] Figures 2A and B show the neutralization of VR1814 by mAbs 4A2, 310, 313, 338, and 345 of HUVEC and HFF cells.

[0017] Figure 3 shows the neutralization of VR1814 by mAbs 4A2, 310, 313, 338, and 345 in HUVECs.

[0018] Figure 4 shows the neutralization of VR1814 by mAbs 4A2, 310, 313, 338, and 345 in HFF cells.

Modes of Carrying Out the Invention

[0019] As used herein, the term "treat" refers to reducing the viral burden in a subject that is already infected with CMV or to ameliorating the symptoms of the disease in such a subject. Such symptoms include retinitis and hepatitis.

[0020] The term "confers resistance to" refers to a prophylactic effect wherein viral infection by RSV upon challenge is at least reduced in severity.

[0021] "Immortalized cells" refers to cells that can survive significantly more passages than unmodified primary isolated cells. As used in the context of the present invention, "immortalized" does not necessarily mean that the cells continue to secrete antibodies over very long periods of time, only that they can survive longer than primary cell cultures. The time over which secretion of antibody occurs need only be sufficient for its identification and recovery of the encoding nucleotide sequence.

[0022] Human antibodies, such as those herein isolated from human cells do not elicit a strong immune response. It is known that human antibodies do elicit a response in 5-10% of humans treated, even for antibodies that are isolated from humans, since there is a certain level of background "noise" in an immune response elicited. The immune response may be humoral

or cellular or both. In particular, elevated levels of cytokines may be found in this percentage of individuals.

[0023] The gB Protein of CMV is synthesized as a precursor protein of 130 kDa, which is cleaved into fragments of 116 kDa (N-terminal) and 58 kDa (C-terminal) that remain covalently linked; the observed molecular weights may vary depending on glycosylation status. The AD-2 antigenic determinant refers to residues 67-82 of gp116. A considerable portion of natural immunity to CMV is accounted for by binding to AD-2 (*i.e.*, can be blocked by a peptide covering this region), Ohlin (*supra*).

[0024] The antibodies of the invention have been recovered from CMV exposed human donors using the proprietary CellSpot™ method which is described in U.S. Patent No. 7,413,868, PCT publications WO 2005/045396 and WO 2008/008858, as set forth in Example 1.

[0025] Production of the human or humanized antibody of the invention is accomplished by conventional recombinant techniques, such as production in Chinese hamster ovary cells or other eukaryotic cell lines, such as insect cells. Alternatively, techniques are also known for producing recombinant materials, including antibodies, in plants and in transgenic animals, for example in the milk of bovines, or in microbial or plant or insect derived single cell systems or in cell free extracts of such cells.

[0026] In addition, since the nucleotide sequences encoding the antibodies are available, the relevant fragments which bind the same epitope, *e.g.*, Fab, $F(ab')_2$ or F_v fragments, may be produced recombinantly (or by proteolytic treatment of the protein itself) and the antibody may be produced in single-chain form. A variety of techniques for manipulation of recombinant antibody production is known in the art.

[0027] Chimeric, humanized and human antibodies are all within the scope of the present invention as are antibody mimics based on other protein scaffolds such as fibronectin, transferrin, or lipocalin. Likewise, multiple technologies now exist for making a single antibody-like molecule that incorporates antigen specificity domains from two separate antibodies (bi-specific antibody). Suitable technologies have been described by Macrogenics (Rockville, MD), Micromet (Bethesda, MD) and Merrimac (Cambridge, MA). (See, *e.g.*, Orcutt KD, Ackerman ME, Cieslewicz M, Quiroz E, Slusarczyk AL, Frangioni JV, Wittrup KD. A modular IgG-scFv bispecific antibody topology. *Protein Eng Des Sel.* (2010) 23:221-228; Fitzgerald J, Lugovskoy A. Rational engineering of antibody therapeutics targeting multiple oncogene pathways. *MAbs.* (2011) 1;3(3); Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. *Cancer Res.* (2009) 69:4941-4944.)

[0028] Thus, a single antibody with very broad strain reactivity can be constructed using the Fab domains of individual antibodies with reactivity to different CMV epitopes, such that for example, the bi-specific antibody has activity against both gB and the gH complex, or alternatively, may be reactive with gB proteins from the same or different strains. High affinity gH antibodies have been described, for example, by Macagno A, Bernasconi NL, Vanzetta F, Dander E, Sarasini A, Revello MG, Gerna G, Sallusto F, Lanzavecchia A. Isolation of human monoclonal antibodies that potently neutralize human cytomegalovirus infection by targeting different epitopes on the gH/gL/UL128-131A complex. *J Virol.* (2010) 84:1005-1013. High affinity antibodies to gH proteins from other strains may also be generated and used.

[0029] For use in therapy, the recombinantly produced antibodies or fragments are formulated into pharmaceutical compositions using suitable excipients and administered according to standard protocols. The pharmaceutical compositions may have as their sole active ingredient a monoclonal antibody or fragment of the invention, especially a monoclonal antibody or fragment that is crossreactive with gB protein of all CMV strains. Alternatively, two monoclonal antibodies may be the sole active ingredients wherein one more strongly reacts with the one strain gB protein and the other more strongly with another strain gB protein. In all of these cases, additional therapeutic agents may be present including those binding to other CMV proteins. Also, the compounds may include nutritional substances such as vitamins, or any other beneficial compound other than an antibody.

[0030] In one embodiment, when the formulations for administration are used in order to increase resistance to infection, complete antibodies, including the complement-containing Fc region are employed. Typically, the antibodies are administered as dosage levels of 0.01-20 mg/kg of human subjects or in amounts in the range of 0.01-5 mg/kg or intermediate amounts within these ranges. In one embodiment, amounts in the range of 0.1-1.0 mg/kg are employed. Repeated administration separated by several days or several weeks or several months may be beneficial.

[0031] In another embodiment, for a therapeutic effect in order to reduce viral load, complete antibodies, containing the complement-containing Fc region are also employed. The amounts administered in such protocols are of the order of .001-50 mg/kg or intermediate values in this range such as 0.01, 1 or 10 mg/kg are employed. Repeated administration may also be used. The therapeutic treatment is administered as soon as possible after diagnosis of infection, although administration within a few days is also within the scope of the invention. Repeated administration may also be employed. In order to reduce the inflammatory response in the lungs, only the immunospecific fragments of the antibodies need be employed. Dosage levels

are similar to those for whole antibodies. Administration of mixtures of immunospecific fragments and entire antibodies is also included within the scope of the invention.

[0032] Administration of the antibody compositions of the invention is typically by injection, generally intravenous injection. Thus, parenteral administration is preferred. However, any workable mode of administration is included, including gene therapy (production of recombinant antibody *in vivo*).

[0033] The formulations are prepared in ways generally known in the art for administering antibody compositions. Suitable formulations may be found in standard formularies, such as Remington's Pharmaceutical Sciences, latest edition, Mack Publishing Co., Easton, PA. The formulations are typically those suitable for parenteral administration including isotonic solutions, which include buffers, antioxidants and the like, as well as emulsions that include delivery vehicles such as liposomes, micelles and nanoparticles.

[0034] The desired protocols and formulations are dependent on the judgment of the attending practitioner as well as the specific condition of the subject. Dosage levels will depend on the age, general health and severity of infection, if appropriate, of the subject.

[0035] The following examples are offered to illustrate but not to limit the invention.

Example 1

Isolation of Human B cells Secreting Antibody to CMV gB

[0036] Peripheral blood mononuclear cells from 50 adults with confirmed titer against CMV were surveyed for human B cells producing anti-viral antibodies. Subjects with the desired antibodies against CMV gB protein were used for cloning of specific mAbs. The result of the survey was that ~10% of the subjects had a frequency of the desired cells greater than 1 in 50,000.

[0037] To accomplish the survey and recovery of rare favorable cells, we used the previously described CellSpot™ technology. The CellSpot™ assay method effectively shrinks an ELISA equivalent assay down to a virtual well of nearly single cell dimensions by capturing secreted IgG from a single cell as a footprint in the vicinity of the cell, so that millions of cells can be readily analyzed. Further, by use of microscopic multiplexing reagents (combinatorially colored fluorescent latex microspheres), each clone's secreted antibody footprint can be characterized in detail for specificity and/or affinity using multiple biochemical probes. The fidelity of the quantitative assay is sufficient to enable rescue of extremely rare favorable cells

from the survey population, with the cloned expression cell showing a phenotype consistent with the original identifying assay.

[0038] The screening criteria were binding to purified gB protein as well as to viral lysate. gB protein was purified from 293 cells infected with AD169 strain of CMV. Affinity rank ordering of clones is accomplished by diluting the antigen on the bead with serum albumin. This reduces the chances for multi-dentate binding to the secreted IgG footprint (an "avidity" effect), thus selecting for higher intrinsic affinity.

[0039] Non-B cells were depleted from PBMCs in plasma of human donors using standard magnetic separation methods. Cells were resuspended in IMDM/20% HI-FCS at 1e6/ml; and immortalized with EBV (direct pelleted from the supernatant of infected B95-8 cells). EBV was added at 1:100 dilution, and the cells incubated 2 hr at 37°C. Excess EBV was washed away, and cells either:

(1) cultured at 2e6/ml in IMDM, 20% HI-FCS, 20% Giant cell tumor conditioned medium, 2 μg/ml CpG (ODN2006), and 10 ng/ml IL-10 for surveying only, or

(2) further selected for surface IgG using magnetic positive selection.

[0040] Cells were cultured at 200-300 cells/well on irradiated human lung cells (MRC-5, 5,000 cells/well) in IMDM, 20% HI-FCS, 20% Giant cell tumor conditioned medium, 2 μg/ml CpG (ODN2006), and 10 ng/ml IL-10. Medium was supplemented every 2-3 days. One half of the contents of the wells were assayed in CellSpot™ at day 6. The remaining cells in the small number of wells positive by the survey assay were then diluted to 10, 5, 1, and 0.5 cells/well with the same feeder cells and culture conditions. After 4-5 days these limiting dilution plates were again assayed by ELISA or CellSpot™.

[0041] CellSpot™ nano-particles were conjugated with viral lysate or purified gB protein to screen for the desired antibodies. Lysate created from cells infected with the CMV AD169 virus was purchased from Virusys (cat # CV046). (The lysate is produced in Normal Human Dermal Fibroblast (NHDF) cell line.) Recombinant CMV gB antigen was produced as His-tagged fusion protein in 293 cells and purified using a nickel chelation column. Purified gB protein was used for ELISA and CellSpot. The preparations of AD169 lysate and gB purified protein were conjugated to nano-particles, respectively, as previously described, cf Harriman et al (*supra*) and Collarini et al (*supra*).

[0042] Contents of positive wells at limiting dilution were then processed using Reverse Transcriptase-PCR to recover the encoding mRNA for the antibody heavy and light chains. Total time from thawing PBMCs to recovery of the encoding mRNA sequence via RT-PCR was 10-12 days.

Example 2

Cloning of Human Antibodies to CMV gB

[0043] Amplification of rearranged Ig Heavy and Ig Light genes from positive ELISA wells was accomplished using semi-nested polymerase chain reaction (PCR). For amplification of a previously unknown V-gene rearrangements, a collection of family-specific V-gene primers was constructed, which recognize nearly all V-gene segments in the human Ig Locus. The 5' primers were used together with primer mixes specific for the Cγ, Cκ and Cλ gene segments. The clonality of the limiting dilution CMV-gB specific B cells was unequivocally determined by sequence comparison of V-gene amplificates from distinct progeny cells, and the amplified full length V-gene rearrangements were cloned into IgG expression vectors.

[0044] In detail, total mRNA from the isolated human B cells was extracted using a commercially available RNA purification kit (RNeasy™; Qiagen (Germany)). Reverse transcription-PCR was done by using total RNA preparations and oligonucleotides as primers. Three PCR reactions were run for each sample: one for light chain kappa (κ) one for light chain lambda (λ), and one for gamma heavy chain (γ). The QIAGEN® OneStep RT-PCR kit was used for amplification, (Qiagen Catalog No. 210212). In the coupled RT-PCR reactions, cDNA is synthesized with unique blend of RT enzymes (Omniscript™ and Sensiscript™) using antisense sequence specific primer corresponded to C-κ, C-λ or to a consensus of the CH1 regions of Cγ genes, RT is preformed at 50°C for 1 hour followed by PCR amplification of the cDNA by HotStarTaq DNA Polymerase for high specificity and sensitivity. Each PCR reaction used a mixture of 5' sense primers. Primer sequences were based on leader sequences of VH, VK and VL. PCR reactions were run at 95°C for 15 minutes, initial hot start followed by 20 cycles of 95°C for 30 seconds (denaturation), 60°C for 45 seconds (annealing) and 72°C for 1 minute (elongation).

[0045] *Nested PCR for detection and cloning of the variable Ig fragments into expression vectors.* In the second round, an aliquot of 5 μl of the first amplification reaction was applied. The primers used carry the 5'BglII and 3' XbaI restriction sites. Thirty PCR cycles were performed. Identical conditions were used for the first and second rounds of amplification. Five microliters of each reaction were loaded and separated on a 1% agarose gel and then stained with ethidium bromide. The V-C PCR product is predicted to amplify rearranged fragments of VH and VL, 500 and 450 bp respectively. PCR bands with a molecular size of approximately 500 bp indicated a positive result. PCR products were purified (Qiagen gel purification kit catalog number 28704) and the extracted PCR products were directly sequenced

using specific constant region primers. The sequences of the cloned fragments were confirmed by sequencing plasmids prepared for recombinant production.

[0046] The PCR fragments described above were digested and cloned into individual expression vectors carrying the constant region of human gamma 1, or of human kappa or lambda, for *in vitro* antibody production in mammalian cells. The expression vectors coding for heavy and light chains were co-transfected into the 293 (human kidney) cell line (Invitrogen). The expression plasmids were introduced with the use of a cationic lipid-based transfection reagent (293fectin™; Invitrogen). For each transfection reaction, 20 µg of purified plasmids and 40 µL of the 293fectin™ were mixed with 1 mL of Opti-MEM® (Invitrogen) and incubated for 5 min at room temperature before being combined and allowed to form complexes for 20 min at room temperature. The DNA-293fectin complexes were added to 3×10^6 cells seeded in 90 mm petri plates and incubated at 37°C, 8% CO2. In the final procedure, the supernatant was harvested 72 hrs post-transfection by centrifugation (3,000 *g*, 15 min at 4°C), to recover the secreted antibodies.

[0047] From ~2 million lymphocytes, 45 clones were isolated which bound the AD169 lysate. Of these, the majority also bound the recombinant gB protein.

[0048] Two of the mAbs that bound both AD169 and gB (4A2 and 19B10) had neutralizing capability. One of these (4A2) binds the AD-2 peptide, which is a conserved site on the gB protein. An additional mAb (5C5) binds AD-2 but does not neutralize the virus.

[0049] The amino acid sequences of the heavy and light chains of 4A2 and 19B10, including variable region, the D and J joining regions, the framework (FR) and complementarity determining (CDR) regions, are shown below. The secretion signal sequence on the heavy chain is italicized, and CDRs 1-3 are underlined.

4A2 HC, VH3-30 nucleic acid (SEQ ID NO:1) and amino acid (SEQ ID NO:2)

```
atggaattggggctgagctgggttttcgtcgttgctcttttaagaggtgtccagtgtcaa
 M  E  L  G  L  S  W  V  F  V  V  A  L  L  R  G  V  Q  C  Q
gtgttgttggaggagtctgggggaggcgtggtccagcctgggaggtctctgagactctcc
 V  L  L  E  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L  S
tgtgcaggctctggattcaccttcaataggcatggaattcactgggtccgccaggctcca
 C  A  G  S  G  F  T  F  N  R  H  G  I  H  W  V  R  Q  A  P
ggcaaggggctggagtgggtgactgttatatcatctgatggagcaaatcaacagtatgca
 G  K  G  L  E  W  V  T  V  I  S  S  D  G  A  N  Q  Q  Y  A
gagtccgtgaagggccgattcatcatctccagagacaattccaagaacacggtatatcta
 E  S  V  K  G  R  F  I  I  S  R  D  N  S  K  N  T  V  Y  L
gaaatgaatagcctgaggaatgacgacacgggtgtgtatttctgcgcgagagacggtcgt
 E  M  N  S  L  R  N  D  D  T  G  V  Y  F  C  A  R  D  G  R
tgtgaaggcgagaggtgctactccggtgtcacggacttctggggccagggaacactggtc
 C  E  G  E  R  C  Y  S  G  V  T  D  F  W  G  Q  G  T  L  V
```

4A2 LC L6, IgKV3-11 nucleic acid (SEQ ID NO:3) and amino acid (SEQ ID NO:4)

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atggaagccccagcgcagcttctcttcctcctgctactctggctcccagataccaccgga
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gaaattgtattgacacagtctccagccaccctgtctttgtctccaggggagagagccacc
 E  I  V  L  T  Q  S  P  A  T  L  S  L  S  P  G  E  R  A  T
ctctcctgcagggccagtcagaatattggcggctacttggcctggttccaacaaaaagct
 L  S  C  R  A  S  Q  N  I  G  G  Y  L  A  W  F  Q  Q  K  A
ggccaggctcccaggctcctcatctatgatgcatccatcagggccactggcatcccagcc
 G  Q  A  P  R  L  L  I  Y  D  A  S  I  R  A  T  G  I  P  A
aggttcagtggcagtgggtctgggacagacttcactctcaccatcagcagcctagagcct
 R  F  S  G  S  G  S  G  T  D  F  T  L  T  I  S  S  L  E  P
gaagattttgcagtttattactgtcagcagcgtaacagttggcctccactcactttcggc
 E  D  F  A  V  Y  Y  C  Q  Q  R  N  S  W  P  P  L  T  F  G
```

19B10 HC VH4-31, D2, J6 nucleic acid (SEQ ID NO:5) and amino acid (SEQ ID NO:6)

```
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gtgcagctgcagcagtcgggcccaggactggtgaagccttcacagaccctgtccctcacc
 V  Q  L  Q  Q  S  G  P  G  L  V  K  P  S  Q  T  L  S  L  T
tgcactgtctctggtggctccatcagtagcggtgattttgctggaattggatccgccag
 C  T  V  S  G  G  S  I  S  S  G  D  F  C  W  N  W  I  R  Q
cccccagggaagggcctggagtggattgggtacatctgttacaccggggacacctactac
 P  P  G  K  G  L  E  W  I  G  Y  I  C  Y  T  G  D  T  Y  Y
aacccgccccttaacagtcgagttaccatatcagtcgacaggtccaggaaccaaatctcc
 N  P  P  L  N  S  R  V  T  I  S  V  D  R  S  R  N  Q  I  S
ctgaggctgagttctgtgactgccgcagacacggccgtgtattattgtgccagagaggat
 L  R  L  S  S  V  T  A  A  D  T  A  V  Y  Y  C  A  R  E  D
aggagacaactacactctcgcccctacttctactacggtttggacgtctggggccgaggg
 R  R  Q  L  H  S  R  P  Y  F  Y  Y  G  L  D  V  W  G  R  G
accaaggtcaccgtctcctcagcttccaccaagggcccatcggtcttcccccctggtaccc
 T  K  V  T  V  S  S  A  S  T  K  G  P  S  V  F  P  L  V  P
tctagc
 S  S
```

19B10 LC, A3, IgKV2 nucleic acid (SEQ ID NO:7) and amino acid (SEQ ID NO:8)

```
atgaggctccctgctcagcttctggggctgctaatgctctgggtctctggatccagtggg
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gagattgtgatgactcagtctccgctctccctgcccgtcacccctggagagacggcctcc
 E  I  V  M  T  Q  S  P  L  S  L  P  V  T  P  G  E  T  A  S
atctcctgcaggtctagtcagagcctcctgcatagtaatggacacaactatttggattgg
 I  S  C  R  S  S  Q  S  L  L  H  S  N  G  H  N  Y  L  D  W
tatctgcagaagccagggcagtctccacacctcctgatctatttgggttctattcgggcc
 Y  L  Q  K  P  G  Q  S  P  H  L  L  I  Y  L  G  S  I  R  A
tccggggtccctgacaggttcagtggcagtggaacaggcacagattttacactgaaaatc
 S  G  V  P  D  R  F  S  G  S  G  T  G  T  D  F  T  L  K  I
agcagagtggaggctgaggatgttggggtttattactgcatgcaagctctacaaactcct
 S  R  V  E  A  E  D  V  G  V  Y  Y  C  M  Q  A  L  Q  T  P
aacacttttggccaggggaccaagctggagatcagacgaactgtggctgcaccatctgtc
 N  T  F  G  Q  G  T  K  L  E  I  R  R  T  V  A  A  P  S  V
```

[0050] High affinity antibodies were generated by preparing CellSpot probes coated with full length gB protein or with the Ad-2 peptide at either high or low density on the fluorescent bead. Without being constrained by theory, since low density reduces the multi-dentate avidity effect, the search is biased in favor oa antibodies with high intrinsic affinity. Multiple high affinity antibodies were isolated and sequenced. The sequences of other monoclonal antibodies that are reactive to CMV were determined, and are shown as SEQ ID NOs:9-36, and 38-66. The nucleotide sequence of the human IgG1 heavy chain constant region is shown in SEQ ID NO:37.

[0051] In antibodies of the invention, the heavy chain can have a CDR1 of GFTFNRHG (SEQ ID NO:67) or GSISSEDFC (SEQ ID NO:68); and/or a CDR2 region of SSDGANQ (SEQ ID NO:69) or ICYTGD (SEQ ID NO:70); and/or a CDR3 region of ARDGRCEGERCYSGVTDF (SEQ ID NO:71) or AREDRRQLHSRPYFYYGLDV (SEQ ID NO:72). In other embodiments, the light chain has a CDR1 region of QNIGGY (SEQ ID NO:73) or QSLLHSNGHNY (SEQ ID NO:74); and/or a CDR2 region of DAS (SEQ ID NO:75) or LG (SEQ ID NO:76); and/or a CDR3 region of QQRNSWPPLT (SEQ ID NO:77) or QALQTPNT (SEQ ID NO:78).

Example 3

Affinity Determination

[0052] The affinity of the invention antibodies was determined by FortéBio® (Menlo Park, CA) biosensor analysis. In this method, the carboxylic acid groups on Amine Reactive Biosensors were activated with EDC/NHS. Antibody, diluted in MES buffer at pH 5, was attached to the activated surface of the probe and the remaining active carboxylated groups were blocked with ethanolamine. The gB protein was incubated with the Ab-coated probe and rates of association to and dissociation from the Ab-coated probe were determined by the FortéBio® instrument.

[0053] In one experiment, 4A2 was found to have an affinity of 168 pM and 19B10 an affinity of 697 pM, as shown as corresponding IC_{50} in μg/ml in Table 1. These affinity constants are substantially better than for published monoclonal antibodies to gB.

Table 1

Comparison of neutralizing potency of mAbs.

mAb (target)	*IC50 (μg/mL)*	*citation*	*source*
4A2 (gB)	0.02	———	human
19B10 (gB)	0.04	———	human
CH177 (gB)	0.23	Nozawa, N, *et al.* (2009) *supra*	murine
G3D (gB)	0.50	Nakajima, N., *et al.* (2009) *supra*	human
10C6 (gB)	0.30	Lanzavecchia, A., *et al.* (2009)*supra*	human

[0054] The binding affinity of mAbs 310, 313, 345, and 4A2 to the AD-2 epitope of gB was determined. The gB binding kinetics are shown in Table 2. The mAbs 310, 313, and 338 have about 10x higher potency than mAb 4A2. The mAbs 323, 316, and 338 also have higher potency than mAb 4A2 (data not shown). The binding affinities of the remaining mAbs are also tested and also better than for published monoclonal antibodies to gB.

Table 2

gB binding kinetics

mAb	ka ($x10^4$) (1/Ms)	kd ($x10^{-5}$) (1/s)	KD nM
4A2	58	9.5	16
310	1.6	1.2	0.8
313	1.7	1.2	0.7
345	1.4	3.3	2.3

Example 4

Elisa Binding Assay and Epitope Mapping

[0055] The mAbs 4A2 and 19B10 were assessed for binding to purified gB protein and to a conserved peptide designated AD-2: NETIYNTTLKYGDV (SEQ ID NO:79). As shown in Figure 1, 4A2 binds well to both full length protein and peptide AD-2, whereas 19B10 only binds the protein.

Example 5

Virus Neutralization Assay

[0056] The mAbs 4A2 and 19B10 neutralized the AD169 strain of CMV in MRC5 primary fibroblasts. Serial dilutions of the antibodies were mixed with an equal volume of AD169 (10^8/ml stock diluted to give 2000 infected cells per well) and incubated for 1 h at room temperature before addition to target cell monolayers in 96-well microplates. After 24 h, cells were fixed, permeabilized, and stained with monoclonal antibody against IE1 (Intermediate Early protein 1, also known as UL123, a marker of replicating virus) conjugated to HRP. The infected cells were detected following deposition of HRP substrate. The number of infected cells was plotted against the concentration of the antibody.

[0057] Virus neutralization was also assessed using the VR1814 strain (Revello, *et al.*, *J. Gen. Virol.* (2001) 82:1429-1438). The mAbs 4A2, 310, 313, 338, and 345 neutralized the VR1814 strain in both human umbilical vein endothelial cells (HUVEC) and human foreskin fibroblast (HFF) cells. Figures 2A and 2B show the IC50 and IC90 values for each of mAbs 4A2, 310, 313, 338, and 345. Figures 3 and 4 show the neutralization of HUVEC and HFF cells, respectively, by each of the mAbs 4A2, 310, 313, 338, and 345. The results were tested in duplicate.

[0058] Other mAbs are also tested, which neutralize the AD169 and VR1814 strains.

SEQUENCE TABLE

4A2 HC, VH3-30 nucleic acid (SEQ ID NO:1) and amino acid (SEQ ID NO:2)

```
atggaattggggctgagctgggttttcgtcgttgctcttttaagaggtgtccagtgtcaa
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gtgttgttggaggagtctgggggaggcgtggtccagcctgggaggtctctgagactctcc
 V  L  L  E  E  S  G  G  G  V  V  Q  P  G  R  S  L  R  L  S
tgtgcaggctctggattcaccttcaataggcatggaattcactgggtccgccaggctcca
 C  A  G  S  G  F  T  F  N  R  H  G  I  H  W  V  R  Q  A  P
ggcaaggggctggagtgggtgactgttatatcatctgatggagcaaatcaacagtatgca
 G  K  G  L  E  W  V  T  V  I  S  S  D  G  A  N  Q  Q  Y  A
gagtccgtgaagggccgattcatcatctccagagacaattccaagaacacggtatatcta
 E  S  V  K  G  R  F  I  I  S  R  D  N  S  K  N  T  V  Y  L
gaaatgaatagcctgaggaatgacgacacgggtgtgtatttctgcgcgagagacggtcgt
 E  M  N  S  L  R  N  D  D  T  G  V  Y  F  C  A  R  D  G  R
tgtgaaggcgagaggtgctactccggtgtcacggacttctggggccagggaacactggtc
 C  E  G  E  R  C  Y  S  G  V  T  D  F  W  G  Q  G  T  L  V
```

4A2 LC L6, IgKV3-11 nucleic acid (SEQ ID NO:3) and amino acid (SEQ ID NO:4)

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atggaagccccagcgcagcttctcttcctcctgctactctggctcccagataccaccgga
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 E  I  V  L  T  Q  S  P  A  T  L  S  L  S  P  G  E  R  A  T
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 L  S  C  R  A  S  Q  N  I  G  G  Y  L  A  W  F  Q  Q  K  A
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 E  D  F  A  V  Y  Y  C  Q  Q  R  N  S  W  P  P  L  T  F  G
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19B10 HC VH4-31, D2, J6 nucleic acid (SEQ ID NO:5) and amino acid (SEQ ID NO:6)

```
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 V  Q  L  Q  Q  S  G  P  G  L  V  K  P  S  Q  T  L  S  L  T
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 C  T  V  S  G  G  S  I  S  S  G  D  F  C  W  N  W  I  R  Q
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ctgaggctgagttctgtgactgccgcagacacggccgtgtattattgtgccagagaggat
 L  R  L  S  S  V  T  A  A  D  T  A  V  Y  Y  C  A  R  E  D
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 R  R  Q  L  H  S  R  P  Y  F  Y  Y  G  L  D  V  W  G  R  G
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 T  K  V  T  V  S  S  A  S  T  K  G  P  S  V  F  P  L  V  P
tctagc
 S  S
```

19B10 LC, A3, IgKV2 nucleic acid (SEQ ID NO:7) and amino acid (SEQ ID NO:8)

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Human IgG1 HC amino acid sequence of constant region (SEQ ID NO:9)

ASTKGPSVFPLVPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

MAB297 HC variable domain amino acid sequence (SEQ ID NO:10)

QVQLVQSGGGVVQPGRSLRLSCSASGFTFSNYNMHWVRQAPGKGPEWVAVISKDGNE
KHYAESAKGRFTISRDNSKNTLYMEMHSLTPEDTAMYYCTRDGRTDGTGYSGILDIW
GQGTKVIVS

MAB309 and 318 HC variable domain amino acid sequence (SEQ ID NO:11)

QVQLVQSGGGVVQPGTSLRLSCAASGFMFNTYNMHWVRQAPGKGLEWVAVISNDGTY
KHFADSLKGRFSISRDDSKNTLYLHMNSLRPDDTAIYYCARDGRSVGGFSGILDPWG
QGTLVTVSS

MAB310 HC variable domain amino acid sequence (SEQ ID NO:12)

QVQLVQSGGGVVQPGTSLRLSCAASGFMFNTYNMHWVRQAPGKGLEWVAVISNDGTY
KYSADSLKGRFSISRDNSKNTLYLHMNSLRPDDTAVYYCARDGRSVGGFSGILDPWG
QGTLVTVSS

MAB313 HC variable domain amino acid sequence (SEQ ID NO:13)

QVQLVQSGGGVIQPGRSLTLSCAASGFTFSAYSLHWVRQAPGKGLQWVAVISFDGNF
KHFADSLRGRFTISRDNSKNRFYLQMNGLRGEDTAVYYCARDGRAVDGFSGILDFWG
QGTLVSVSS

MAB314 HC variable domain amino acid sequence (SEQ ID NO:14)

QVQLQESGGGLVQPGGSLKLSCAVSGFSFGGSAMHWVRQASGKGLEWIGHIRSGANN
FETAYAPSLDGRFTISRDDSKNTAYLHMNSLKTDDTAMYFCTTGLIASGDANFDYWG
QGTQVTVSS

MAB316 HC variable domain amino acid sequence (SEQ ID NO:15)

QVQLVQSGGGVVQPGRSLTLSCAASGFTFSGFSLHWVRQAPGKGLQWVAVISFDGNH
KHFADSLKGRFTISRDNSKNTLYLQINDLRGEDTAVYYCARDGRAVDGFSGILDFWG
QGTLVSVSS

MAB319 HC variable domain amino acid sequence (SEQ ID NO:16)

QVQLVESGGGVVQPGRSLRLSCSASGFTFSDYNLHWVRQAPGKGLEWVAVISIDGSD
KHHADSVKGRFTVSRDNSKNTVSLQMDSLRPEDTAVYYCARDGRSVGGYSGILDPWG
QGTLVTVSS

MAB321 HC variable domain amino acid sequence (SEQ ID NO:17)

EVQLVESGAEVKKPGESLKISCQGSGYRFTNYWIAWVRQMPGKGLEWMGIIYPGDSD
TRYHPSFQGQVTISSDKSLNTAYLQWSSLKPSDTAVYYCARHHCLSTNCQTAVAGYN
DYWGQGNPGRRLLS

MAB322 HC variable domain amino acid sequence (SEQ ID NO:18)

QVQLVQSGGGVVQPGRSLRLSCSASGFTFTNYNMHWVRQAPGKGLEWVAVTSKDGNE
KHFADSVKGRFTISRDNSKNTLYLEMNTLTAEDTAIYYCTRDGRTDGTGYSGILDIW
GQGTKVTVSS

MAB323 HC variable domain amino acid sequence (SEQ ID NO:19)

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSNFAMHWVRQAPGKGLEWVAVISNAGRE
THYADSVKGRFTVSRDNSKNMLSLQMNSLRGEDTAVYYCARDGRTDGSGYSGVLDIW
AQGTLVTVSS

MAB338 HC variable domain amino acid sequence (SEQ ID NO:20)

QVQLVESGGGVVQPGRSLRLSCSGSGFTFSDYNLHWVRQAPGKGLEWVAVISIDGTN
KHHADSVKGRFTISRDNSKNTVNLEMSRLKAEDTAVYYCVRDGRSIGGYSGIFDPWG
QGTLVTVSS

MAB343 HC variable domain amino acid sequence (SEQ ID NO:21)

QVQLQESGGGVVQPGRSLRLSCAASGFTFNTYNMHWVRQAPGKGLEWVAVISNDGTY
KYSADSVKGRFSISRGNSKNTLYLQMNSLRPDDTAVYYCARDGRSVGGFSGILDPWG
QGTLATVSS

MAB345 HC variable domain amino acid sequence (SEQ ID NO:22)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYNMHWVRQAPGKGLEWVAVISIDGTY
KYSADSVAGRFSLSRDNSKNTLYLQMNSLRPDDTAIYYCARDGRSVGGFSGILDPWG
QGTLVTVSS

Human LC amino acid sequence of constant kappa region (SEQ ID NO:23)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

MAB297 and MAB322 LC variable domain amino acid sequence (SEQ ID NO:24)

EIVMTQSPATLSLSPGERATLSCRASQSVGGYLAWYQQKPDQAPRLLIYDVSNRAAG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNTWPPLTFGGGTKVEIKR

MAB309 LC variable domain amino acid sequence (SEQ ID NO:25)

EIVLTQSPATLSLSPGDRATLSCRASQTVGRYLAWYQQKPGQAPRLLIYDASDRATG
ISARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSSWPPLTFGGGTKVEIKR

MAB310 LC variable domain amino acid sequence (SEQ ID NO:26)

EIVLTQSPATLSLSPGDRATLSCRASQTVGRYLAWYQQKPGQAPRLLIYDASDRATG
ISARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIKR

MAB313 LC variable domain amino acid sequence (SEQ ID NO:27)

EIVMTQSPATLSLSPGERATLSCRASQSVGRYLTWFQQKPGQAPRLLIYDASERATG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRANWPPLTFGGGTKVEIK

MAB314 LC variable domain amino acid sequence (SEQ ID NO:28)

EIVMTQSPGTLSLFPGERATLSCRASQTVRNGYLAWYQQKPGQAPRLLIYGASIRAT
GIPDRFSGSGSETDFTLSITRVEPEDFAVYYCQQYGRLSSTFGQGTKLDLK

MAB316 LC variable domain amino acid sequence (SEQ ID NO:29)

EIVMTQSPATLSLSPGERATLSCRASQSVGRYLTWFQQKPGQAPRLLIYDASERATG
VPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIK

MAB318 LC variable domain amino acid sequence (SEQ ID NO:30)

EVVLTQSPATLSLSPGDRATLSCRASQTVGRYLAWYQQKPGQAPRLLIYDASDRATG
ISARFSGSGSCTDFTLTIGSLEPEDFAVYYCQQRSSWPPLTFGGGTKVEIK

MAB319 LC variable domain amino acid sequence (SEQ ID NO:31)

EIVLTQSPATLSLSPGERATLSCRASQSVGSYLAWYQQKPGQAPRLLIYDASERATG
IPARFSGSGSGTDFTLTISSLEPEDVAVYYCQQRNNWPPLTFGGGTKVEIK

MAB321 LC variable domain amino acid sequence (SEQ ID NO:32)

EIVMTQSPDSLAVSLGERATINCKSSQSILFSSKNQNHLAWYQQKPGQPPKLLIYWA
STRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYNIPHTFGGGTKVEIK

MAB323 LC variable domain amino acid sequence (SEQ ID NO:33)

EIVLTQSPATLSLSPGERATLSCRASQSVNRYLAWFQHRPGQPPRLLIYDASKRATG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK

MAB338 LC variable domain amino acid sequence (SEQ ID NO:34)

EIVLTQSPATLSLSPGERATLSCRASQSVDRYLAWYQQKPGQAPRLLIYDASQRATG
IPARFSGSGSGTDFTLAISSLEPEDVAVYYCQQRSNWPPLTFGGGTKIEIK

MAB343 LC variable domain amino acid sequence (SEQ ID NO:35)

EIVMTQSPATLSLSPGDRATLSCRASQSVGSYLAWYQQKPGQAPRLLIYDASDRATG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIK

MAB345 LC variable domain amino acid sequence (SEQ ID NO:36)

EIVMTQSPATLSLSPGDRATLSCRASQSVGSYLAWYQQKPGQAPRLLMYDSSVRATG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNNWPPLTFGGGTKVEIK

Human IgG1 HC nucleotide sequence of constant region (introns are underlined) (SEQ ID NO:37)

GCCTCCACCAAGGGCCCATCAGTCTTCCCCCTGGCACCCTCTACCAAGAGCACCTCT
GGGGGCACAACGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG
GGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
AAGAGAGTTGGTGAGAGGCCAGCACAGGGAGGGAGGGTGTCTGCTGGAAGCCAGGCT
CAGCGCTCCTGCCTGGACGCATCCCGGCTATGCAGTCCCAGTCCAGGGCAGCAAGGC
AGGCCCCGTCTGCCTCTTCACCCGGAGGCCTCTGCCCGCCCCACTCATGCTCAGGGA
GAGGGTCTTCTGGCTTTTTCCCCAGGCTCTGGGCAGGCACAGGCTAGGTGCCCCTAA
CCCAGGCCCTGCACACAAAGGGGCAGGTGCTGGGCTCAGACCTGCCAAGAGCCATAT
CCGGGAGGACCCTGCCCCTGACCTAAGCCCACCCCAAAGGCCAAACTCTCCACTCCC
TCAGCTCGGACACCTTCTCTCCTCCCAGATTCCAGTAACTCCCAATCTTCTCTCTGC
AGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGGTAAGCCAGC
CCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTAGCCTGCATCCA
GGGACAGGCCCCAGCCGGGTGCTGACACGTCCACCTCCATCTCTTCCTCAGCACCTG
AACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCA
TGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA
AGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCC
TGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC
TCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGTGGGACCCGTGGGGTGC
GAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCCTGAGAGTGACCGCT
GTACCAACCTCTGTCCCTACAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCC
CCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
TACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG
CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGTAAA
TGA

MAB297 HC variable domain nucleotide sequence (SEQ ID NO:38)

CAGGTGCAACTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTCTCCTGTTCAGCCTCTGGATTCACCTTCAGCAACTATAATATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCCGGAGTGGGTGGCAGTTATATCAAAAGATGGAAACGAA
AAACACTATGCAGAGTCTGCGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAG
AACACGCTGTATATGGAAATGCACAGCCTGACACCTGAGGACACGGCTATGTATTAC
TGTACGAGAGATGGGCGAACCGATGGTACTGGGTACTCCGGTATTCTTGATATCTGG
GGCCAAGGGACAAAGGTCATCGTCTCT

MAB309 and 318 HC variable domain nucleotide sequence (SEQ ID NO:39)

CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGACGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCATGTTCAATACCTATAATATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCAAATGATGGAACCTAT
AAGCATTTCGCTGACTCCCTGAAGGGCCGATTCAGCATCTCCAGAGACGATTCCAAG
AACACGCTGTATCTGCACATGAACAGCCTGAGACCTGACGACACGGCTATATATTAC
TGTGCGAGAGATGGCCGTAGTGTTGGCGGGTTTAGTGGGATCCTCGACCCCTGGGGC
CAGGGAACCCTGGTCACCGTCTCCTCAG

MAB310 HC variable domain nucleotide sequence (SEQ ID NO:40)

CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGACGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCATGTTCAATACCTACAATATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCAAATGATGGAACCTAT
AAGTACTCCGCTGACTCCCTGAAGGGCCGATTCAGCATCTCCAGAGACAATTCCAAG
AACACGTTGTATCTGCACATGAACAGCCTGAGACCTGACGACACGGCTGTATATTAC
TGTGCGAGAGATGGCCGTAGTGTTGGCGGGTTTAGTGGGATCCTCGACCCCTGGGGC
CAGGGAACCCTGGTCACCGTCTCCTCAG

MAB313 HC variable domain nucleotide sequence (SEQ ID NO:41)

CAGGTGCACCTGGTGCAGTCTGGGGGAGGCGTGATCCAGCCTGGGAGGTCCCTGACA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGCCTATTCTCTACACTGGGTCCGC
CAGGCTCCAGGCAAAGGGCTACAGTGGGTGGCGGTTATCTCATTTGATGGGAATTTT
AAACACTTCGCAGACTCCCTGAGGGGCCGATTCACCATCTCCAGAGACAATTCCAAG
AACAGATTCTATTTGCAAATGAATGGCCTGAGAGGTGAGGACACGGCTGTATATTAC
TGTGCGAGAGATGGACGTGCTGTTGACGGGTTTAGTGGGATCCTCGACTTCTGGGGC
CAGGGAACCCTAGTCAGCGTCTCCTCAG

MAB314 HC variable domain nucleotide sequence (SEQ ID NO:42)

CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAAA
CTCTCCTGTGCAGTCTCTGGATTCTCCTTCGGTGGCTCTGCAATGCACTGGGTCCGC
CAGGCTTCCGGGAAAGGGCTGGAGTGGATTGGCCATATTAGAAGCGGAGCTAATAAT
TTCGAGACAGCATATGCTCCGTCGCTGGATGGCAGGTTCACCATCTCCAGAGACGAT
TCAAAGAACACGGCGTATCTGCACATGAACAGCCTGAAAACCGATGACACGGCCATG
TATTTCTGCACTACCGGACTTATAGCGTCAGGTGATGCAAATTTTGACTACTGGGGC
CAGGGAACCCAGGTCACCGTCTCCTCGG

MAB316 HC variable domain nucleotide sequence (SEQ ID NO:43)

CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGACA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGGCTTTTCTCTACACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTACAGTGGGTGGCGGTTATCTCATTTGATGGGAACCAT
AAACACTTCGCAGACTCCCTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAG
AACACATTGTATTTGCAAATTAATGACCTGAGAGGTGAGGACACGGCTGTATATTAC

TGTGCGAGAGATGGACGTGCTGTTGACGGGTTTAGTGGGATTCTCGACTTCTGGGGC
CAGGGAACCCTGGTCAGCGTCTCCTCAG

MAB319 HC variable domain nucleotide sequence (SEQ ID NO:44)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTCTCCTGTTCAGCCTCAGGATTCACCTTCAGTGACTATAATCTACACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTCATCTCAATTGATGGAAGCGAT
AAACACCACGCAGACTCCGTGAAGGGCCGATTCACCGTCTCCAGAGACAATTCCAAG
AACACAGTGAGTCTACAAATGGACAGCCTGAGACCTGAAGACACGGCTGTATATTAC
TGTGCGAGAGATGGCCGTAGTGTGGGCGGCTACAGTGGGATCCTCGACCCCTGGGGC
CAGGGAACCCTGGTCACCGTCTCCTCAG

MAB321 HC variable domain nucleotide sequence (SEQ ID NO:45)

GAGGTGCAGCTGGTGGAGTCCGGAGCAGAGGTGAAAAAGCCCGGGGAGTCTCTGAAG
ATCTCCTGTCAGGGTTCTGGATACAGGTTTACCAATTACTGGATCGCCTGGGTGCGC
CAGATGCCCGGGAAAGGCCTGGAGTGGATGGGGATCATCTATCCTGGTGACTCTGAT
ACCAGATATCACCCGTCCTTCCAAGGCCAGGTCACCATCTCATCCGACAAATCCCTC
AACACCGCCTACCTGCAGTGGAGCAGCCTGAAGCCCTCGGACACCGCCGTGTATTAC
TGTGCGAGACACCACTGCCTTAGTACCAACTGCCAAACCGCAGTGGCTGGATATAAT
GACTACTGGGGCCAGGGAAACCCTGGTCGCCGTCTCCTCAG

MAB322 HC variable domain nucleotide sequence (SEQ ID NO:46)

CAGGTGCAGCTGGTGGAGTCCGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTTTCCTGTTCAGCCTCTGGATTCACCTTCACCAACTATAACATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTACGTCAAAAGATGGAAACGAA
AAACACTTTGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAG
AACACGCTGTATCTGGAAATGAACACCCTGACAGCTGAGGACACGGCGATATATTAC
TGTACGAGAGATGGGCGAACCGATGGTACTGGGTACTCCGGTATTCTTGATATCTGG
GGCCAAGGGACAAAGGTCACCGTCTCCTCA

MAB323 HC variable domain nucleotide sequence (SEQ ID NO:47)

CAGGTGCAGCTGGTGCAGTCTGGGGGAGGGGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAACTTTGCTATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCAAATGCTGGAAGGGAA
ACACACTACGCAGACTCCGTGAAGGGCCGATTCACCGTCTCCAGAGACAATTCCAAG
AATATGTTGTCTCTGCAAATGAACAGCCTGAGAGGTGAGGACACGGCTGTGTATTAC
TGTGCGAGAGATGGGCGAACCGATGGTAGTGGCTATTCCGGTGTTCTTGATATCTGG
GCCCAAGGGACACTGGTCACTGTCTCCTCA

MAB338 HC variable domain nucleotide sequence (SEQ ID NO:48)

CAGGTGCAGCTGGTGGAGTCCGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGA
GACTCTCCTGTTCAGGCTCTGGATTCACCTTCAGTGACTATAATCTACACTGGGTCC
GCCAGGCTCCAGGCAAGGGGCTGGAATGGGTGGCAGTCATTTCAATTGATGGAACT
AATAAACACCACGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACTC
CAAGAATACAGTGAATCTGGAAATGAGTCGGCTGAAAGCAGAAGACACGGCTGTA
TATTACTGTGTGAGAGATGGGCGAAGTATTGGCGGCTACAGTGGAATCTTCGACCC
CTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

MAB343 HC variable domain nucleotide sequence (SEQ ID NO:49)

CAGGTGCAGCTGCAGGAGTCAGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAATACCTACAATATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCAAATGATGGAACCTAT
AAATACTCCGCTGACTCCGTGAAGGGCCGATTCAGCATCTCCAGAGGCAATTCCAAG
AACACGTTGTATCTGCAGATGAACAGCCTGAGACCTGACGACACGGCTGTATATTAC
TGTGCGAGAGATGGGCGTAGTGTTGGCGGGTTTAGTGGGATCCTCGACCCCTGGGGC
CAGGGAACCCTGGCCACCGTCTCCTCA

MAB345 HC variable domain nucleotide sequence (SEQ ID NO:50)

CAGGTGCAGCTGGTGGAGTCCGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACAATATGCACTGGGTCCGC
CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATTTCAATTGATGGAACGTAT
AAATACTCCGCTGACTCCGTGGCGGGCCGATTCAGTCTCTCCAGAGACAATTCCAAG
AACACGTTGTATTTGCAGATGAATAGTCTGAGACCTGACGACACGGCTATATATTAT
TGCGCGAGAGATGGGCGTAGTGTTGGCGGGTTTAGTGGGATCCTCGACCCCTGGGGC
CAGGGAACCCTGGTCACCGTCTCCTCAG

Human LC nucleotide sequence of constant kappa region (SEQ ID NO:51)

ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCA
GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCG
CCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

MAB297 and MAB322 LC variable domain nucleotide sequence (SEQ ID NO:52)

GAAATTGTAATGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCGGCTACTTAGCCTGGTACCAACAG
AAACCTGACCAGGCTCCCAGGCTCCTCATCTATGATGTTTCCAATAGGGCCGCTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC
AGCCTGGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGGAACACCTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

MAB309 LC variable domain nucleotide sequence (SEQ ID NO:53)

GAAATTGTGTTGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGATAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGACTGTTGGCAGGTACTTAGCCTGGTACCAACAA
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGACAGGGCCACTGGC
ATCTCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGGAGCCTGAAGATTTTGCAGTCTATTACTGTCAGCAGCGGAGCAGCTGGCCG
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

MAB310 LC variable domain nucleotide sequence (SEQ ID NO:54)

GAAATTGTGTTGACTCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGATAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGACTGTTGGCAGGTACTTAGCCTGGTACCAACAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGACAGGGCCACTGGC
ATCTCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTCTATTACTGTCAGCAGCGGAGCAACTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

MAB313 LC variable domain nucleotide sequence (SEQ ID NO:55)

GAAATTGTGATGACTCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGATACTTAACTTGGTTCCAGCAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGAGAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGCGTGCTAACTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA

MAB314 LC variable domain nucleotide sequence (SEQ ID NO:56)

GAAATTGTGATGACCCAGTCTCCAGGCACCCTGTCCTTGTTTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGACTGTTAGGAACGGCTACTTAGCCTGGTACCAG
CAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCTTCCATCAGGGCCACT
GGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGAGACAGACTTCACCCTCAGCATC
ACCAGAGTGGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGTATGGAAGGTTA
TCGTCCACTTTTGGCCAGGGGACCAAGCTGGACCTCAAACGA

MAB316 LC variable domain nucleotide sequence (SEQ ID NO:57)

GAAATTGTGATGACCCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGATACTTAACTTGGTTCCAGCAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGAGAGGGCCACTGGC
GTCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGCGTAGTAACTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC

MAB318 LC variable domain nucleotide sequence (SEQ ID NO:58)

GAAGTTGTGCTGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGATAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGACTGTTGGCAGGTACTTAGCCTGGTACCAACAA
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGACAGGGCCACTGGC
ATCTCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCGGC
AGCCTGGAGCCTGAAGATTTTGCAGTCTATTACTGTCAGCAGCGGAGCAGCTGGCCG
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC

MAB319 LC variable domain nucleotide sequence (SEQ ID NO:59)

GAAATTGTGTTGACGCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGGGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGCTACTTAGCCTGGTATCAACAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCATCCGAGAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATGTTGCAGTTTATTACTGTCAGCAGCGTAACAACTGGCCT
CCGCTCACCTTCGGCGGAGGGACCAAGGTGGAGATCAAAC

MAB321 LC variable domain nucleotide sequence (SEQ ID NO:60)

GAAATTGTGATGACCCAGTCTCCAGACTCCCTTGCTGTGTCTCTGGGCGAGAGGGCC
ACCATCAACTGCAAGTCCAGTCAGAGTATTTTATTCAGCTCCAAGAATCAGAACCAC
TTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGCTGCTGATTTACTGGGCA
TCTACCCGGGAATCCGGGGTCCCCGACCGATTCAGTGGCAGCGGGTCTGGGACAGAT
TTCACTCTCACCATCAGCAGCCTCCAGGCTGAAGATGTGGCAGTTTATTACTGTCAG
CAATATTATAATATTCCTCACACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

MAB323 LC variable domain nucleotide sequence (SEQ ID NO:61)

GAAATTGTGTTGACTCAGTCTCCAGCCACCTTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCCGGGCCAGTCAGAGTGTTAACCGCTACTTAGCCTGGTTCCAACAC
AGACCTGGCCAGCCTCCCAGGCTCCTCATCTATGATGCGTCCAAGAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCG
CTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAG

MAB338 LC variable domain nucleotide sequence (SEQ ID NO:62)

GAAATTGTGTTGACCCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGACAGGTACTTAGCCTGGTACCAACAG
AAACCTGGCCAGGCTCCCAGACTCCTCATCTATGATGCATCCCAGAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCCGGGACAGACTTCACTCTCGCCATCAGC
AGCCTGGAGCCTGAAGATGTTGCAGTTTATTACTGTCAGCAGCGTAGTAACTGGCCT
CCGCTCACCTTCGGCGGAGGGACCAAAATAGAGATCAAA

MAB343 LC variable domain nucleotide sequence (SEQ ID NO:63)

GAAATCGTGATGACCCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGATAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGCTACTTAGCCTGGTACCAACAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCTTCCGACAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC

MAB345 LC variable domain nucleotide sequence (SEQ ID NO:64)

GAAATTGTGATGACCCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGATAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGGCAGCTACTTAGCCTGGTACCAACAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATGTATGATTCTTCCGTCAGGGCCACTGGC
ATCCCAGCCAGGTTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAACAACTGGCCT
CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

Human LC nucleotide sequence of constant kappa region (SEQ ID NO:65)

ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAG
CAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCA
GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCG
CCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

Human LC nucleotide sequence of constant lambda region (SEQ ID NO:66)

GGTCAGCCCAAGGCTGCCCCCTCTGTCACTCTGTTCCCGCCCTCTAGCGAGGAGCTT
CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTG
ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACA
CCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCT
GAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACC
GTGGAGAAGACAGTGGTCCCTGCAGAATGCTCT

Claims

1. An isolated monoclonal antibody (mAb) or immunoreactive fragment thereof that neutralizes cytomegalovirus (CMV) strain VR1814 or AD169 of CMV wherein:

the heavy chain comprises the CDR1, CDR2 and CDR3 regions of the heavy chain variable region of MAB345 as defined by SEQ ID NO:22; and

the light chain comprises the CDR1, CDR2 and CDR3 regions of light chain variable region of MAB345 as defined by SEQ ID NO:36.

2. The mAb or immunoreactive fragment thereof of claim 1, wherein

the heavy chain variable region comprises that of MAB345 as defined by SEQ ID NO: 22; and

the light chain variable region comprises that of MAB345 as defined by SEQ ID NO:36.

3. The mAb or immunoreactive fragment thereof of claim 1 or 2 that is in the form of a complete antibody.

4. The mAb or immunoreactive fragment thereof of claim 1 or 2 that is a bi-specific antibody.

5. One or more nucleic acid molecules that comprise nucleotide sequence(s) that encode(s) the mAb or immunoreactive fragment thereof of any one of claims 1 to 4.

6. One or more nucleic acid molecule(s) that comprise(s) nucleotide sequence(s) complementary to nucleotide sequence(s) that encode(s) the mAb or immunoreactive fragment thereof of any one of claims 1 to 4 over its (their) entire length.

7. Recombinant host cells comprising an expression system comprising nucleotide sequence(s) that encode(s) the mAb or immunoreactive fragment thereof of any one of claims 1 to 4, wherein the recombinant host cells are mammalian cells, microbial cells, insect cells or plant cells.

Date Reçue/Date Received 2022-07-29

8. A method to produce the mAb or immunoreactive fragment thereof of any one of claims 1 to 4, which method comprises culturing the recombinant cells of claim 7 and recovering said mAb or immunoreactive fragment.

9. A pharmaceutical composition that comprises the mAb or immunoreactive fragment thereof of any one of claims 1 to 4, along with a pharmaceutically acceptable excipient.

10. The pharmaceutical composition of claim 9 that further contains an additional pharmaceutical agent, along with a pharmaceutically acceptable excipient.

11. The mAb or immunoreactive fragment of any one of claims 1 to 4, or the composition as defined in claim 9 or 10, for use to treat a human subject infected with CMV strain VR1814 or CMV strain AD169.

12. The mAb or immunoreactive fragment thereof of any one of claims 1 to 4, or the composition as defined in claim 9 or 10, for use to enhance immune resistance to infection by CMV strain VR1814 or CMV strain AD169 in a human subject.

13. The mAb or immunoreactive fragment for use of claim 11 or 12, wherein the subject is immunocompromised.

14. The mAb or immunoreactive fragment for use of claim 13, wherein the subject is a pregnant woman.

15. Use of the mAb or immunoreactive fragment thereof of any one of claims 1 to 4 for treating a subject infected with a CMV strain reactive with the antibody of any one of claims 1 to 4.

16. Use of the mAb or immunoreactive fragment thereof of any one of claims 1 to 4 in the preparation of a medicament for treating a subject infected with a CMV strain neutralized by the antibody of any one of claims 1 to 4.

Date Reçue/Date Received 2022-07-29

17. Use of the mAb or immunoreactive fragment thereof of any one of claims 1 to 4 to enhance resistance to infection by a CMV strain neutralized by the antibody of any one of claims 1 to 4 in a subject.

18. Use of the mAb or immunoreactive fragment thereof of any one of claims 1 to 4 in the preparation of a medicament to enhance resistance to infection by a CMV strain neutralized by the antibody of any one of claims 1 to 4 in a subject.

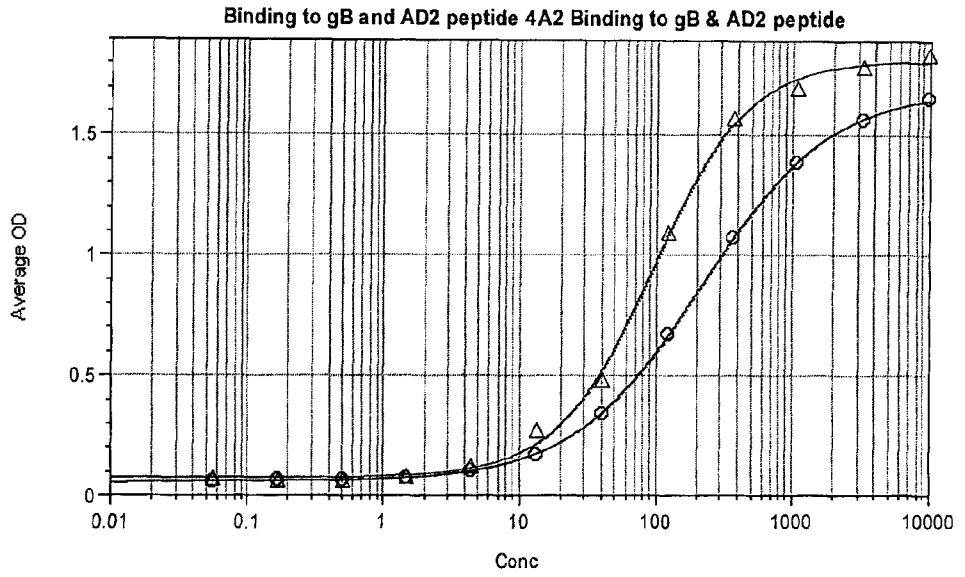
19. The use of any one of claims 15 to 18, wherein the subject is immunocompromised.

20. The use of any one of claims 15 to 19, wherein the subject is human.

21. The use of claim 20, wherein the subject is a pregnant woman.

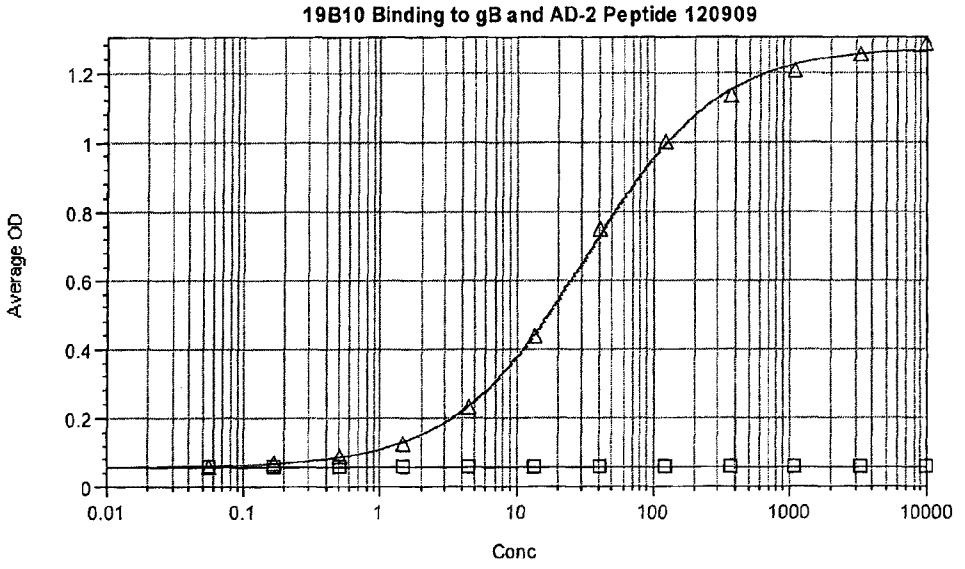
Date Reçue/Date Received 2022-07-29

A



△ 4A2 Binding to peptide AD2
○ 4A2 Binding to gB

B



□ 19B10 & gB-AD-2
△ 19B10 & gB

Figure 1

A

Virus strain VR1814: IC50 (μg/ml)

	HUVEC	HFF
4A2	~ 1.0	1.32
310	0.30	0.53
313	0.37	0.37
338	0.24	0.63
345	0.13	0.18

B

Virus strain VR1814: IC90 (μg/ml)

	HUVEC	HF
4A2	6.81	7.09
310	3.59	5.28
313	4.30	1.51
338	2.62	>10
345	0.97	0.89

Figure 2

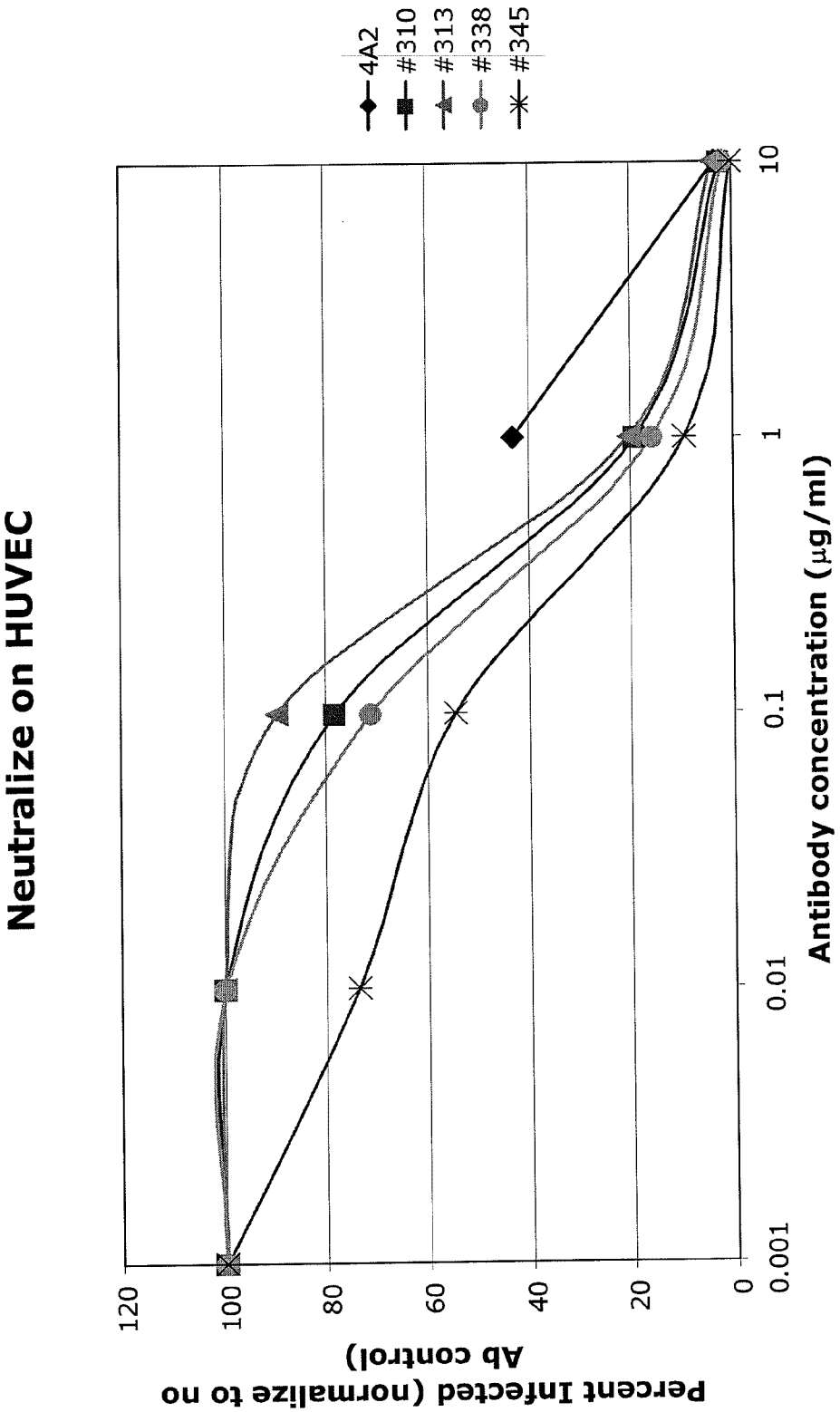

Neutralize on HUVEC
4A2
#310
#313
#338
#345
Percent Infected (normalize to no Ab control)
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
Antibody concentration (μg/ml)

Figure 3

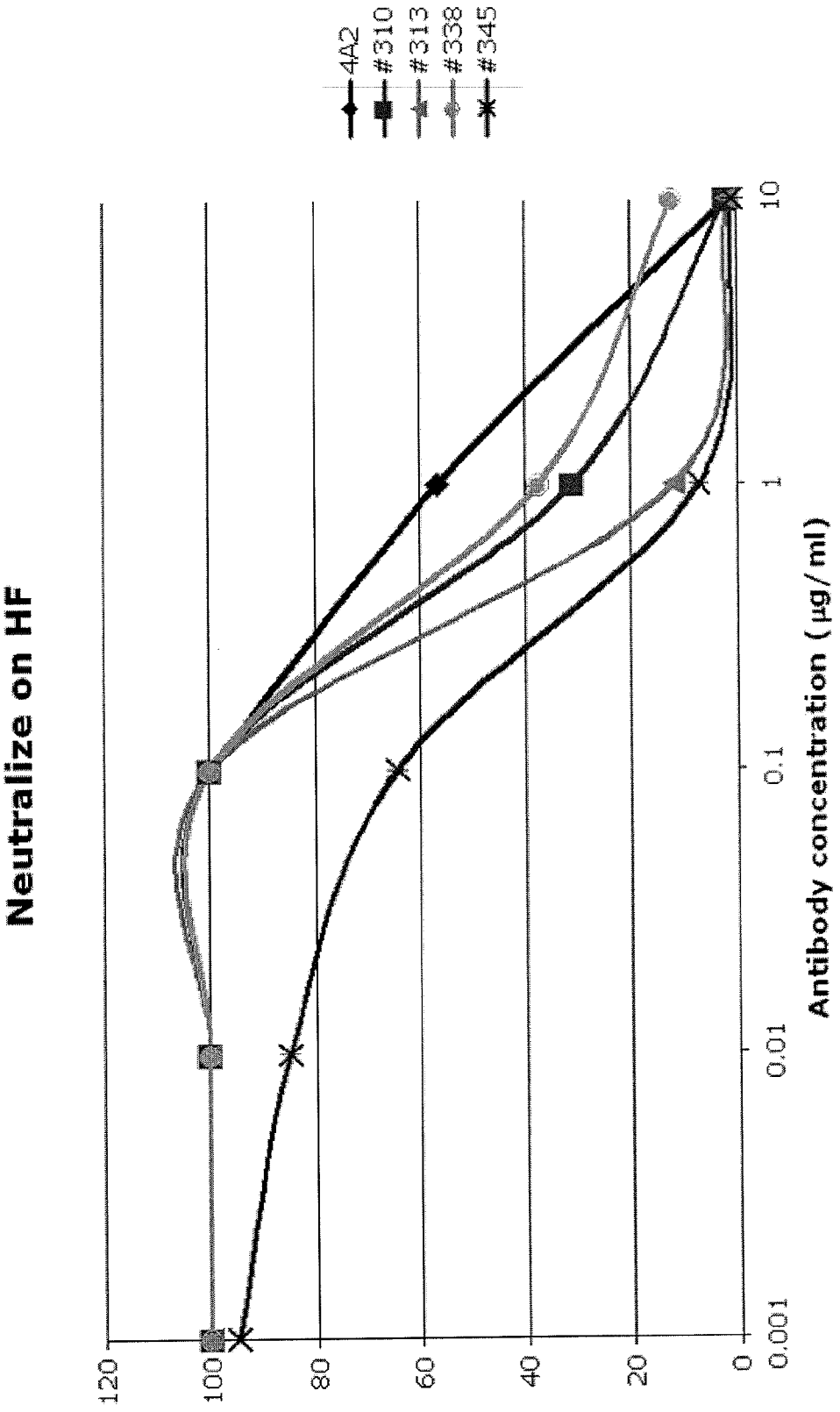

4A2
#310
#313
#338
#345
Neutralize on HF
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
Antibody concentration (µg/ml)

Figure 4