range of 1μg/ml. US20090004198 (Nakajima *et al*) discloses a high affine antibody for the gB AD-1 domain, with apparent pM binding affinity, and 80% hCMV neutralising activity on fibroblasts, if used at concentrations of 1μg/ml and higher (10μg/ml and 100μg/ml). Two recent applications WO 10/114105 A1 and WO 10/114106 A1, both from Evec Inc., describe antibodies that bind to AD-2 and a discontinuous epitope in AD-1, respectively.

As disclosed in the present invention, we have developed hCMV neutralising human antibodies, which bind with high affinity to the gB protein of hCMV. In addition, these antibodies display similar high potency (IC_{50}s below 0.5μg/ml) in hCMV neutralisation using a broad range of hCMV susceptible cell types (fibroblasts, endothelial, epithelial and dendritic cells) and high potency not only on laboratory strain AD-169, but also on all clinical isolates tested so far. In addition, the antibodies disclosed herein recognise and define a novel neutralising epitope of the gB protein that has not been described previously. Owing to their high affinity and potency, and their novel epitope binding characteristics determined by functional studies as described herein, the binding members of the invention are particularly suitable for use in the therapeutic treatment, prophylaxis and/or diagnosis of hCMV infections in human patients. The binding members are useful for treating various disorders associated with CMV infection, as described in detail elsewhere herein.

Summary ~~of Invention~~

Several, highly potent, gB specific and hCMV neutralising human antibodies are described herein, which also recognise a completely new hCMV neutralising epitope and therefore act by a different therapeutic principle in comparison to all other

known antibodies specific for hCMV. Their discovery and functional characterization are disclosed further below. As described in more detail in the Examples, 50 fully human, hCMV neutralising antibodies have been identified. They have been isolated from EBV transformed human peripheral blood derived B cells derived from hCMV-infected donors. CDR sequences of the antibodies 1 to 50 are as detailed in Tables 19 and 20. V_H domain and V_L domain combinations for a panel of antibodies 1 to 46 are as detailed in Table 7. All sequences referred to in Tables 7 and 19 are also shown in the appended sequence listing that forms part of the present disclosure.

As described in more detail below, binding members according to the ~~invention~~disclosure have been shown to neutralise hCMV infection of target cells at therapeutically relevant concentrations, i.e. with IC_{50} below 1μg/ml. The most active binding members neutralise hCMV even at IC_{50}s below 0.5μg/ml. The neutralising capacity has also been observed with different clinical isolates (e.g. Towne and Altu; Table 16), representing different gB genotypes. Binding members of the ~~invention~~disclosure may neutralise one or more activities of hCMV. For example, the inhibited biological activity may be prevention of infection of fibroblasts, endothelial cells, epithelial cells, retinal cells and/or dendritic cells. The prevention of infection of fibroblasts has been demonstrated in an *in vitro* neutralisation assay utilising a recombinant strain of hCMV, AD169 that expresses the reporter gene luciferase. Upon infection with this genetically modified hCMV strain, target cells become positive for luciferase enzyme expression, which can be detected by appropriate substrate-conversion in a standard luminometer. The binding members described in this ~~invention~~disclosure were shown to neutralise the infection of hCMV strain AD169 when first incubated with the recombinant,

luciferase positive virus strain and then seeded onto monolayers of primary human foreskin fibroblasts (HFFs). Following further incubation, luminescence was detected using a luminometer and the relative light units (RLU) detected. The percentage neutralisation was then calculated, wherein the neutralising titre is indicated as the concentration of binding member (µg/ml) that gives a 50% or 100% reduction of hCMV infection of target cells. Binding members may give a 50% reduction of hCMV infection at concentrations of 0.1 to 5.0µg/ml, preferably 0.1 to 2.0µg/ml, more preferably from 0.3 to 1.3µg/ml or more preferably from 0.1 to 0.6µg/ml. The binding members have been shown to result in a 50% reduction of hCMV infection at therapeutically relevant concentrations of 0.1, 0.5, 1.0, 1.1, 1.2, 1.3, 1.5 or 2.0µg/ml.

Other methods that may be used for determining the neutralisation of infectivity of hCMV include ELISA, FACS, Western blotting, immunoprecipitation, and visual inspection based on plaque forming and counting.

The binding members described herein were shown to neutralise human hCMV not only in fibroblasts, but with similar efficacy also in endothelial, epithelial and dendritic cells (as shown in an assay using primary foreskin fibroblasts, Example 4 and in an assay using human umbilical vein endothelial cells (HUVEC), human ARPE-19 retinal pigment epithelial cells and primary dendritic cells, as shown in Example 7).

The ~~invention~~disclosure discloses high affinity binding members for hCMV and specific for the hCMV gB protein. Binding members of the ~~invention~~disclosure may bind hCMV gB protein with a K_D of not more than 50nM, e.g. not more than 25nM, 15nM, 10nM, 5nM, 3nM, 1.5nM, 1nM, 0.5nM, 0.1nM, 75pM or 57pM. Preferably the

binding member has a K_D of 1nM or less, preferably less than 0.5nM, preferably less than 0.1nM and more preferably less than 75pM. The K_D may be determined by surface plasmon resonance, e.g. Biacore®. Biacore® measurements of affinity are described herein in Example 5.

As described elsewhere herein, surface plasmon resonance involves passing an analyte in fluid phase over a ligand attached to a solid support, and determining association rates (k_a) and dissociation rates (k_d) between analyte and ligand. Surface plasmon resonance may for example be performed whereby a binding member is passed in fluid phase over gB protein attached to a support. Surface plasmon resonance data may be fitted to a monovalent analyte data model. The affinity may be expressed as the dissociation constant, K_D, which is calculated from the ratio of the dissociation and the association rate constants k_d/k_a as determined by surface plasmon resonance using a monovalent analyte data model.

The binding members described herein are shown to bind to a specific region of hCMV gB protein. Known epitopes of hCMV gB protein lie within the antigenic domain 1 (AD-1; between amino acids 552-635) and/or antigenic domain 2 (AD-2; between amino acids 67-86) of gB strain AD169, SEQ ID No: 239. In the present ~~invention~~disclosure we describe binding members that bind to two new antigenic domains of hCMV gB protein, antigenic domain 4 (AD-4; a discontinuous region between amino acids 121-132 and 344-438 of gB strain AD169; SEQ ID No: 239) and antigenic domain 5 (AD-5; between amino acids 133 to 343 of gB strain AD169; SEQ ID No: 239). In initial experiments, the ability of six of the binding members described herein, monoclonal, recombinant antibodies Ab-04, Ab-11, Ab-14, Ab-

19, Ab-28 and Ab-42, to bind to specific regions of hCMV gB protein was investigated. In particular, the epitope binding specificity of these six binding members was first investigated in a Biacore® competition assay with a selection of anti-hCMV antibodies known in the art, which bind either to the AD-1 or to the AD-2 epitope of gB protein. As the binding members of the present ~~invention~~disclosure specifically bound to gB protein with high affinity, but could not compete for gB binding with AD-1 and AD-2 specific antibodies, it was clear that the binding members of the present ~~invention~~disclosure recognise a novel neutralising epitope of the gB protein. Further support for this finding was obtained by expressing a truncated version of gB protein comprising amino acid residues 100 to 447 (gB strain AD169; SEQ ID No: 239), which upon expression in COS cells was recognised by binding members of the ~~invention~~disclosure.

Following the generation of a molecular model of HCMV gB (strain AD169; SEQ ID No: 239), surface exposed protein domains were identified and a discontinuous amino acid sequence between amino acid residues 121-132 and 344-438 was predicted to be a likely epitope, to which binding members of the ~~invention~~disclosure could bind. When this predicted epitope was expressed as amino acids 116 to 132 and 344 to 440 (gB strain AD169; SEQ ID No: 239), which were coupled by a synthetic amino acid linker, it was found that this recombinant protein was specifically recognised by binding members Ab-11, Ab-14 or Ab-28 of the ~~invention~~disclosure. This new epitope has been termed AD-4. Therefore the binding members of the ~~invention~~disclosure do not bind to the region AD-1 of hCMV gB protein. Also, the binding members of the ~~invention~~disclosure do not bind to the region AD-2 of hCMV gB protein. In contrast, binding members Ab-01 to Ab-46 of the ~~invention~~disclosure bind to a new conformational epitope termed

AD-4 (also termed Domain II (Dom II)), between amino acid residues 100 to 447,and preferably between amino acid residues 121 to 438. More preferably, binding members of the ~~invention~~disclosure bind to discontinuous amino acid stretches 116-132 and 344-440 of gB strain AD169 (SEQ ID No: 239) and most preferably stretches 121-132 and 344-438 of gB strain AD169 (SEQ ID No: 239). In this regard it has to be understood in accordance with the ~~invention~~disclosure that the discontinuous epitope generated by amino acids stretches 121-132 and 344-438 of gB strain AD169 (SEQ ID No: 239) constitutes the same epitope as the discontinuous epitope generated by amino acids stretches 116-132 and 344-440 of gB strain AD169 (SEQ ID No: 239).

Since Antibodies Ab-01 to Ab-46 all have structurally related CDRs (in particular HCDR3 of identical length and related sequence), and are derived from a single donor, these antibody molecules are most likely somatic mutants of an original gB-reactive clones, and are therefore expected to bind the same or very similar overlapping epitope on the hCMV gB protein. Accordingly, the epitope characterisation results obtained with recombinant antibodies Ab-11, Ab-14 or Ab-28 are also expected to be representative for all of the antibodies Ab-01 to Ab-46 disclosed herein. The present ~~invention~~disclosure therefore relates to a binding member, preferably an antibody, that binds to a conformational epitope of the gB protein recognised by antibodies Ab-11, Ab-14 or Ab-28 and also to a binding member that competes with any of antibodies Ab-11, Ab-14 or Ab-28 for binding to a conformational epitope of the gB protein recognised by these antibodies.

Therefore in a first embodiment, a binding member of the ~~invention~~disclosure may bind hCMV gB protein at a region comprising amino acids 116 to 132 or amino acids 121 to 132 as predicted

from the structural model (Example 9). A binding member of the ~~invention~~disclosure may also bind hCMV gB protein at a region comprising amino acids 344 to 440 or amino acids 344 to 438 as predicted from the structural model (Example 9). Optionally a binding member may bind flanking residues or structurally neighbouring residues in the hCMV gB amino acid sequence, in addition to binding amino acids 116 to 132 and/or amino acids 344 to 440. By convention, residue numbering corresponds to hCMV gB strain AD169 (SEQ ID No: 239).

In further experiments, the ability of four of the binding members described herein, monoclonal, recombinant antibodies Ab-47, Ab-48, Ab-49, Ab-50, to bind to specific regions of hCMV gB protein was also investigated. In particular, the epitope binding specificity of these four binding members was first investigated in an ELISA competition assay (Example 8.3) and then using a capture ELISA (Example 10.2). It was clear that these four binding members recognise a further novel neutralising epitope of the gB protein.

Following the generation of a molecular model of HCMV gB (strain AD169; SEQ ID No: 239), surface exposed protein domains were identified and an amino acid sequence between amino acid residues 133 and 343 was predicted to be a likely epitope, to which binding members of the ~~invention~~disclosure could bind. This predicted epitope was subdivided and expressed as two subdomains: Subdomain 1 (amino acids 133-144 and 251-343) and Subdomain 2 (amino acids 140 to 255) (gB strain AD169; SEQ ID No: 239). When tested in a capture ELISA, Subdomain 1 was recognised by binding members Ab-47, Ab-49 or Ab-50 of the ~~invention~~disclosure. The new epitope region of amino acids 134 to 344 (gB strain AD169; SEQ ID No: 239) has been termed AD-5.

Therefore binding members Ab-47, Ab-48, Ab-49 or Ab-50 of the ~~invention~~disclosure do not bind to the region AD-1 of hCMV gB protein. Also, the binding members of the ~~invention~~disclosure do not bind to the region AD-2 of hCMV gB protein. In contrast, binding members Ab-47 to Ab-50 of the ~~invention~~disclosure bind to a new conformational epitope termed AD-5 (also termed Domain I (Dom I)), between amino acid residues 133 to 343 of gB strain AD169 (SEQ ID No: 239).

The present ~~invention~~disclosure therefore relates to a binding member, preferably an antibody, that binds to an epitope of the gB protein recognised by antibodies Ab-47, Ab-48, Ab-49 or Ab-50 and also to a binding member that competes with any of these four antibodies for binding to a conformational epitope of the gB protein recognised by these antibodies.

Therefore in a second embodiment, a binding member of the ~~invention~~disclosure may bind hCMV gB protein at a region comprising amino acids 133 to 343, as predicted from the structural model (Example 9). Optionally a binding member may bind flanking residues or structurally neighbouring residues in the hCMV gB amino acid sequence, in addition to binding amino acids 133 to 343. By convention, residue numbering corresponds to hCMV gB strain AD169 (SEQ ID No: 239).

A binding member of the ~~invention~~disclosure may comprise an antibody molecule, e.g. an antibody molecule with fully human amino acid sequence. The binding member normally comprises an antibody V_H and/or V_L domain. V_H and V_L domains of binding members are also disclosed as part of the ~~invention~~disclosure. Each of the V_H and V_L domains comprises complementarity determining regions, (CDRs), and framework regions, (FRs). An antibody V_H domain comprises three HCDR regions, designated HCDR1, HCDR2,

and HCDR3. An antibody V_L domain comprises three LCDR regions, designated LCDR1, LCDR2, and LCDR3. A V_H or V_L domain framework comprises four framework regions, FWR1, FWR2, FWR3 and FWR4, interspersed with CDRs in the following structure: FWR1 - CDR1 - FWR2 - CDR2 - FWR3 - CDR3 - FWR4.

Examples of antibody V_H and V_L domains and CDRs according to the present ~~invention~~disclosure are as listed in the appended sequence listing that forms part of the present disclosure. Further CDRs are disclosed below and in Table 19. All V_H and V_L sequences, CDR sequences, sets of CDRs and sets of HCDRs and sets of LCDRs disclosed herein represent aspects and embodiments of the ~~invention~~disclosure. As described herein, a 'set of CDRs' comprises CDR1, CDR2 and CDR3. Thus, a set of heavy chain CDRs refers to HCDR1, HCDR2 and HCDR3, and a set of light chain CDRs refers to LCDR1, LCDR2 and LCDR3. Unless otherwise stated, a 'set of CDRs' includes HCDRs and LCDRs.

Typically, binding members of the ~~invention~~disclosure are monoclonal antibodies.

A binding member of the ~~invention~~disclosure may comprise an antigen-binding site within a non-antibody molecule, normally provided by one or more CDRs e.g. a set of CDRs in a non-antibody protein scaffold, as discussed further below.

Binding members Ab-01 to Ab-46, according to the ~~invention~~disclosure, were initially isolated from an hCMV infected donor and were isolated from EBV immortalised B cell lines, referred to as SM1, SM3, SM4, SM5, SM6, SM7, SM9, SM10 or SM11. From these nine cell lines 37 different V_H and 62 different V_L coding sequences of human antibodies could be identified (Table 6). The combination of all identified V_H and V_L coding sequences

from each cell line as IgH and IgL chains can theoretically generate 295 different antibodies. Of these, 46 different recombinant antibodies have been identified, which were hCMV neutralising in a first-line biological screening assay using luciferase-expressing, hCMV laboratory-strain AD-169 and primary human foreskin fibroblasts. Six of these recombinant antibodies were found to neutralise hCMV with high potency (IC_{50}s below 1μg/ml) and to bind gB protein with high affinity of K_D of 15nM or less (Tables 13 & 15 below).

The structures and locations of binding member variable domains may be determined by reference to Kabat *et al.*, (1991) and updates thereof. Described herein is a panel of binding members each comprising the set of CDRs as specified in Tables 19 and 20, in which HCDR1 has Kabat residues 31-35; HCDR2 has Kabat residues 50-65; HCDR3 has Kabat residues 95-102. LCDR1 has Kabat residues 24-34; LCDR2 has Kabat residues 50-56 and LCDR3 has Kabat residues 89-97. The Kabat numbering was determined using the website: http://www.bioinf.org.uk/abs/abnum/

A binding member of a first embodiment of the ~~invention~~disclosure may comprise one or more CDRs as described herein, e.g. a CDR3, and optionally also a CDR1 and CDR2 to form a set of CDRs. The CDR or set of CDRs may be a CDR or set of CDRs of any of antibodies Ab-01 to Ab-46, or may be a variant thereof as described herein.

A binding member may comprise a set of H and/or L CDRs of any of antibodies Ab-01 to Ab-46 with one or more amino acid mutations within the disclosed set of H and/or L CDRs. Amino acid mutations are substitutions, deletions or insertions of one amino acid. Based on the examples provided and the

disclosed sequences, there may be, e.g., up to 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 mutations e.g. substitutions, within the set of H and/or L CDRs. Furthermore, there may be up to 9, 8, 7, 6, 5, 4, 3, 2 or 1 mutations, in HCDR3 and/or there may be up to 6, 5, 4, 3, 2 or 1 mutations, in HCDR2 and/or there may be up to 3, 2 or 1 mutations in HCDR1 and/or there maybe up to 6, 5, 4, 3, 2 or 1 mutations in LCDR3 and/or there maybe 1 mutation in LCDR2 and/or LCRD1. The mutation may be a substitution or the H and/or L CDRs may optionally contain an insertion or deletion of one amino acid as compared with the disclosed set of H and/or L CDRs.

Substitutions, insertions or deletions may be made at any point in the CDRs. For example, in HCDR1 substitutions may be of any of Kabat residues 31-35, e.g. any of Kabat residues 31, 32, 34 and/or 35, in HCDR2 substitutions may be of any of Kabat residues 50-65, e.g. any of Kabat residues 50, 53, 54, 58, 60,and/or 64 and in HCDR3 substitutions may be of any of Kabat residues 99-102, e.g. any of Kabat residues 99-100C, 100E, 100F and/or 100K-102. For example, in LCDR1 a substitution may be of any of Kabat residues 24-34 e.g. Kabat residues 26 or 27, in LCDR2 substitutions may be of any of Kabat residues 50-56, e.g. Kabat residue 56 and in LCDR3 substitutions may be of any of Kabat residues 89 to 97, e.g. any of Kabat residues 89 and there may be an insertion at position 95B. Details of specific amino acid mutations compared with the sequence of antibody Ab-28 can be found in Tables 20a and 20b for the HCDRs and LCDRs respectively, e.g. amino acid substitutions or insertions.

For example, the present ~~invention~~disclosure provides an isolated binding member for hCMV, comprising a set of CDRs: HCDR1,

HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein the set of CDRs has 22 or fewer amino acid alterations from a set of CDRs in which:

HCDR1 has amino acid sequence SEQ ID No: 3;

HCDR2 has amino acid sequence SEQ ID No: 4;

HCDR3 has amino acid sequence SEQ ID No: 5;

LCDR1 has amino acid sequence SEQ ID No: 93;

LCDR2 has amino acid sequence SEQ ID No: 94; and

LCDR3 has amino acid sequence SEQ ID No: 95.

Hence, in a first aspect, there is provided an isolated antibody molecule for human cytomegalovirus (hCMV) gB protein, which binds hCMV gB protein at a region within residues 121 to 132 and 344 to 438, the residue numbering being defined according to the full length gB strain AD169 amino acid sequence SEQ ID No: 239,

said isolated antibody molecule comprising a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein the set of CDRs has 22 or fewer amino acid alterations from a set of CDRs in which:

HCDR1 has amino acid sequence SEQ ID No: 3;

HCDR2 has amino acid sequence SEQ ID No: 4;

HCDR3 has amino acid sequence SEQ ID No: 5;

LCDR1 has amino acid sequence SEQ ID No: 93;

LCDR2 has amino acid sequence SEQ ID No: 94; and

LCDR3 has amino acid sequence SEQ ID No: 95,

and wherein the antibody molecule has a K_D of not more than 0.5nM as defined by surface plasmon resonance.

For example a binding member or V_H domain according to the ~~invention~~disclosure may comprise the HCDR1 of antibody Ab-28 with one or more of the following mutations:

Kabat residue Asp 31 replaced by Gly;

Kabat residue His 32 replaced by Phe or Tyr;

Kabat residue Met 34 replaced by Ile or Leu; and
Kabat residue Val 35 replaced by Asn.

A binding member or V_H domain according to the ~~invention~~disclosure may comprise the HCDR2 of antibody Ab-28 with one or more of the following mutations:
Kabat residue Trp 50 replaced by Ser or Cys;
Kabat residue Gln 53 replaced by Asn or His;
Kabat residue Ser 54 replaced by Thr;
Kabat residue Gly 58 replaced by Lys, Asn or His;
Kabat residue Gly 60 replaced by Ala; and
Kabat residue Gln 64 replaced by Arg.

A binding member or V_H domain according to the ~~invention~~disclosure may comprise the HCDR3 of antibody Ab-28 with one or more of the following mutations:
Kabat residue Thr 99 replaced by Ala;
Kabat residue Val 100 replaced by Met;

Kabat residue Ser 100A replaced by Thr;
Kabat residue Asn 100B replaced by Thr;
Kabat residue Ser 100C replaced by Phe;
Kabat residue Leu 100E replaced by Met or Ala;
Kabat residue Ser 100F replaced by Gly;
Kabat residue His 100K replaced by Tyr;
Kabat residue Asn 100L replaced by Ser or Asp;
Kabat residue Arg 100M replaced by Val or Ile;
Kabat residue Leu 100N replaced by Met;
Kabat residue Asp 101 replaced by Gly; and
Kabat residue Ala 102 replaced by Val or Ile.

A binding member or V_L domain according to the ~~invention~~disclosure may comprise the LCDR1 of antibody Ab-28 in which Kabat residue Ser 26 is replaced by Asn or Kabat residue Ser 27 is replaced by Arg.

A binding member or V_L domain according to the ~~invention~~disclosure may comprise the LCDR2 of antibody Ab-28 in which Kabat residue Ser 56 is replaced by Pro.

A binding member or V_L domain according to the ~~invention~~disclosure may comprise the LCDR3 of antibody Ab-28 with one or more of the following mutations:
Kabat residue Gly 89 replaced by Ala;
Kabat residue Pro 91 replaced by Trp;
Kabat residue Arg 93 replaced by Ser;
Kabat residue Ser 94 replaced by Asp;
Kabat residue Ser 95a replaced by Gly or Ala;
Ala inserted at Kabat residue 95b;
Kabat residue Val 96 replaced by Tyr; and
Kabat residue Ile 97 replaced by Val.

Thus a binding member of the ~~invention~~disclosure may comprise a LCDR3 wherein Kabat residue 95b is Ala or wherein Kabat residue 95b is absent.

The ~~invention~~disclosure provides binding members comprising an HCDR1, HCDR2 and/or HCDR3 of any of antibodies Ab-01 to Ab-46, and/or an LCDR1, LCDR2 and/or LCDR3 of any of antibodies 1 to 46 e.g. a set of CDRs of any of antibodies Ab-01 to Ab-46 shown in Table 19 or 20.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 8; HCDR2 is SEQ ID No: 9; HCDR3 is SEQ ID No: 10; LCDR1 is SEQ ID No: 98; LCDR2 is SEQ ID No: 99; and LCDR3 is SEQ ID No: 100, representing the CDRs of antibody Ab-02.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 13; HCDR2 is SEQ ID No: 14; HCDR3 is SEQ ID No: 15; LCDR1 is SEQ ID No: 103; LCDR2 is SEQ ID No: 104; and LCDR3 is SEQ ID No: 105, representing the CDRs of antibody Ab-04.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 18; HCDR2 is SEQ ID No: 19; HCDR3 is SEQ ID No: 20; LCDR1 is SEQ ID No: 108; LCDR2 is SEQ ID No: 109; and LCDR3 is SEQ ID No: 110, representing the CDRs of antibody Ab-11.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3,

wherein: HCDR1 is SEQ ID No: 23; HCDR2 is SEQ ID No: 24; HCDR3 is SEQ ID No: 25; LCDR1 is SEQ ID No: 113; LCDR2 is SEQ ID No: 114; and LCDR3 is SEQ ID No: 115, representing the CDRs of antibody Ab-14.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 3; HCDR2 is SEQ ID No: 4; HCDR3 is SEQ ID No: 5; LCDR1 is SEQ ID No: 93; LCDR2 is SEQ ID No: 94; and LCDR3 is SEQ ID No: 95, representing the CDRs of antibody Ab-28.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 28; HCDR2 is SEQ ID No: 29; HCDR3 is SEQ ID No: 30; LCDR1 is SEQ ID No: 108; LCDR2 is SEQ ID No: 109; and LCDR3 is SEQ ID No: 110, representing the CDRs of antibody Ab-42.

In a second aspect, there is provided an isolated antibody molecule comprising a heavy chain comprising amino acid sequence SEQ ID No: 2 and a light chain comprising amino acid sequence SEQ ID No: 92.

In a third aspect, there is provided an isolated antibody molecule that binds hCMV gB protein, wherein the antibody molecule comprises a V_H domain amino acid sequence at least 90% identical to SEQ ID No: 2 and a V_L domain amino acid sequence at least 90% identical to SEQ ID No: 92.

The binding member may comprise a set of V_H CDRs of one of these antibodies. Optionally it may also comprise a set of V_L CDRs of one of these antibodies, and the V_L CDRs may be from the same or a different antibody as the V_H CDRs.

A V_H domain comprising a set of HCDRs of any of antibodies Ab-01 to Ab-46, and/or a V_L domain comprising a set of LCDRs of any of antibodies Ab-01 to Ab-46 are also provided by the ~~invention~~disclosure.

Typically, a V_H domain is paired with a V_L domain to provide an antibody antigen-binding site, although as discussed further below a V_H or V_L domain alone may be used to bind antigen. The V_H domain of antibody Ab-28 may be paired with

the V_L domain of antibody Ab-28, so that an antibody antigen-binding site is formed comprising both the antibody Ab-28 V_H and V_L domains. Analogous embodiments are provided for the other V_H and V_L domains disclosed herein. In other embodiments, the antibody Ab-28 V_H is paired with a V_L domain other than the antibody V_L. Light-chain promiscuity is well established in the art (Kang *et al.*, 1991). Again, analogous embodiments are provided by the ~~invention~~disclosure for the other V_H and V_L domains disclosed herein.

Thus, an IgH chain containing the V_H of any of antibodies 1 to 46 may be paired with the IgL chain containing V_L of any of antibodies Ab-01 to Ab-46 to generate a gB specific binding member.

A binding member may comprise an antibody molecule having one or more CDRs, e.g. a set of CDRs, within an antibody framework. The framework regions may be of human germline gene segment sequences. Human germline gene segment sequences are known to those skilled in the art and can be accessed for example from the VBase compilation or the IMGT online database (http://imgt.cines.fr).

A binding member of the ~~invention~~disclosure may be an isolated human antibody molecule having a V_H domain comprising a set of HCDRs in a human germline framework, e.g. IGHV1-2. Thus, the VH domain framework regions FWR1, FWR2 and/or FWR3 may comprise framework regions of human germline gene segment IGHV1-2. FWR4 may comprise a framework region of human germline J segments selected from, for example, SEQ ID Nos: 188 to 191. The amino acid sequence of V_H FWR1 may be SEQ ID No: 181. The amino acid sequence of V_H FWR2 may be SEQ ID No: 182. The amino acid sequence of V_H FWR3 may be SEQ ID No: 183 or 184.

An antibody molecule or a V_H domain of the ~~invention~~disclosure may comprise the following set of heavy chain framework regions:

FWR1 SEQ ID No: 181; FWR2 SEQ ID No: 182; FWR3 SEQ ID No: 183 or 184; or may comprise the said set of heavy chain framework regions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 amino acid alterations, such as a substitution, an insertion or a deletion.

Furthermore, an antibody of the ~~invention~~disclosure may include a V_H domain that is encoded by a nucleic acid sequence that is at least 80% homologous to the IGHV1-2 germline gene sequence, Preferably the nucleic acid sequence is at least 90%, 95%, 96%, 97% homologous to the IGHV1-2 germline gene sequence, and more preferably, at least 98%, 99% homologous to the IGHV1-2 germline gene sequence. The V_H domain of an antibody of the ~~invention~~disclosure may be at least 80% homologous to the amino acid sequence of the V_H domain encoded by the IGHV1-2 germline gene sequence. Preferably the amino acid sequence of the V_H domain is at least 90%, 95%, 96%, 97% homologous to the amino acid sequence encoded by the IGHV1-2 germline gene sequence, and more preferably, at least 98%, 99% homologous to the amino acid sequence encoded by IGHV1-2 germline gene sequence.

Normally the binding member also has a V_L domain comprising a set of LCDRs, e.g. in a human germline framework, e.g. IGLV1-51. Thus, the V_L domain framework regions may comprise framework regions FWR1, FWR2 and/or FWR3 of human germline gene segment IGLV1-51. FWR4 may comprise a framework region of human germline J segment IGLJ2 (SEQ ID No: 193). The amino acid sequence of V_L FWR1 may be SEQ ID No: 185. The amino acid

sequence of V_L FWR2 may be SEQ ID No: 186. The amino acid sequence of V_L FWR3 may be SEQ ID No: 187.

An antibody molecule or a V_L domain of the ~~invention~~disclosure may comprise the following set of light chain framework regions: FWR1 SEQ ID No: 185; FWR2 SEQ ID No: 186; FWR3 SEQ ID No: 187; or may comprise the said set of light chain framework regions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 amino acid alterations, such as a substitution, an insertion or a deletion.

Furthermore, an antibody of the ~~invention~~disclosure may include a V_L domain that is encoded by a nucleic acid sequence that is at least 80% homologous to the IGLV1-51 germline gene sequence. Preferably the nucleic acid sequence is at least 90%, 95%, 96%, 97% homologous to the IGLV1-51 germline gene sequence, and more preferably, at least 98%, 99% homologous to the IGLV1-51 germline gene sequence. The V_L domain of an antibody of the ~~invention~~disclosure may be at least 80% homologous to the amino acid sequence of the V_L domain encoded by the IGLV1-51 germline gene sequence. Preferably the amino acid sequence of the V_L domain is at least 90%, 95%, 96%, 97% homologous to the amino acid sequence encoded by the IGLV1-51 germline gene sequence, and more preferably, at least 98%, 99% homologous to the amino acid sequence encoded by IGLV1-51 germline gene sequence.

For example, an antibody molecule of the ~~invention~~disclosure may comprise a set of heavy and light chain framework regions, wherein heavy chain FWR1 is SEQ ID No: 181; heavy chain FWR2 is SEQ ID No: 182; heavy chain FWR3 is SEQ ID No: 183; light chain FWR1 is SEQ ID No: 185; light chain FWR2 is SEQ ID No: 186; light chain FWR3 is SEQ ID No: 187; or may comprise the

said set of heavy and light chain framework regions with 10 or fewer, e.g. five or fewer, amino acid alterations, e.g. substitutions.

Binding members Ab-47 to Ab-50, according to the ~~invention~~disclosure, were initially isolated from three hCMV infected donors and were isolated from EBV immortalised B cell lines, referred to as SM10, SM12, 2C2 or 1G2. From these four cell lines, four different V_H and five different V_L coding sequences of human antibodies could be identified (Table 12). The combination of all identified V_H and V_L coding sequences from each cell line as IgH and IgL chains can theoretically generate 20 different antibodies. Of these, four different recombinant antibodies have been identified, which were hCMV neutralising in a first-line biological screening assay using luciferase-expressing, hCMV laboratory-strain AD-169 and primary human foreskin fibroblasts. All of these recombinant antibodies were found to neutralise hCMV with high potency (IC_{50}s below 0.6μg/ml; Table 14 below).

The structures and locations of binding member variable domains may be determined by reference to Kabat *et al.*, (1991) and updates thereof. Described herein are binding members Ab-46, Ab-47, Ab-48 and Ab-50 each comprising the set of CDRs as specified in Table 19, in which the CDRs were identified by the Kabat numbering system (Kabat & Wu, 1991) and determined using the website: http://www.bioinf.org.uk/abs/abnum/

A binding member of a second embodiment of the ~~invention~~disclosure may comprise one or more CDRs as described herein, e.g. a CDR3, and optionally also a CDR1 and CDR2 to form a set of CDRs. The CDR or set of CDRs may be a CDR or set of CDRs of any of

antibodies Ab-47 to Ab-50, or may be a variant thereof as described herein.

A binding member may comprise a set of H and/or L CDRs of any of antibodies Ab-47 to Ab-50 with one or more amino acid mutations within the disclosed set of H and/or L CDRs. Amino acid mutations are substitutions, deletions or insertions of one amino acid. Based on the examples provided and the disclosed sequences, there may be, e.g., up to 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 mutations within the set of H and/or L CDRs. The mutation may be a substitution or the H and/or L CDRs may optionally contain an insertion or deletion of one amino acid as compared with the disclosed set of H and/or L CDRs. Substitutions, insertions or deletions may be made at any point in the CDRs.

The ~~invention~~disclosure provides binding members comprising an HCDR1, HCDR2 and/or HCDR3 of any of antibodies Ab-47 to Ab-50, and/or an LCDR1, LCDR2 and/or LCDR3 of any of antibodies Ab-47 to Ab-50, e.g. a set of CDRs of any of antibodies Ab-47 to Ab-50 shown in Table 19.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 243; HCDR2 is SEQ ID No: 244; HCDR3 is SEQ ID No: 245; LCDR1 is SEQ ID No: 263; LCDR2 is SEQ ID No: 264; and LCDR3 is SEQ ID No: 265, representing the CDRs of antibody Ab-47.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 248; HCDR2 is SEQ ID No: 249; HCDR3 is SEQ ID No: 250; LCDR1 is SEQ ID No: 268; LCDR2 is

SEQ ID No: 269; and LCDR3 is SEQ ID No: 270, representing the CDRs of antibody Ab-48.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 253; HCDR2 is SEQ ID No: 254; HCDR3 is SEQ ID No: 255; LCDR1 is SEQ ID No: 273; LCDR2 is SEQ ID No: 274; and LCDR3 is SEQ ID No: 275, representing the CDRs of antibody Ab-49.

For example, a binding member of the ~~invention~~disclosure may comprise a set of CDRs: HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3, wherein: HCDR1 is SEQ ID No: 258; HCDR2 is SEQ ID No: 259; HCDR3 is SEQ ID No: 260; LCDR1 is SEQ ID No: 278; LCDR2 is SEQ ID No: 279; and LCDR3 is SEQ ID No: 280, representing the CDRs of antibody Ab-50.

A binding member of the ~~invention~~disclosure may be an isolated human antibody molecule having a V_H domain comprising a set of HCDRs in a human germline framework, e.g. IGHV4-39 or IGHV4-59. Thus, the VH domain framework regions FWR1, FWR2 and/or FWR3 may comprise framework regions of human germline gene segment IGHV4-39 or IGHV4-59. FWR4 may comprise a framework region of human germline J segments selected from any of the six heavy chain J segments (see Ravetch *et al.*, 1981).

The amino acid sequence of Ab-47 or Ab-50 V_H domain may comprise the following set of heavy chain framework regions of IGHV4-39: FWR1 SEQ ID No: 281, FWR2 SEQ ID No: 282; FWR3 SEQ ID No: 283; or may comprise the said set of heavy chain framework regions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 amino acid alterations, such as a substitution, an insertion or a deletion.

The amino acid sequence of Ab-48 or Ab-48 V_H domain may comprise the following set of heavy chain framework regions of IGHV4-59: FWR1 SEQ ID No: 284, FWR2 SEQ ID No: 285; FWR3 SEQ ID No: 286; or may comprise the said set of heavy chain framework regions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 amino acid alterations, such as a substitution, an insertion or a deletion.

Furthermore, an antibody of the ~~invention~~disclosure may include a V_H domain that is encoded by a nucleic acid sequence that is at least 75% homologous to the IGHV4-39 or IGHV4-59 germline gene sequence, Preferably the nucleic acid sequence is at least 80%, 85%, 90%, 95%, 96%, 97% homologous to the IGHV4-39 or IGHV4-59 germline gene sequence, and more preferably, at least 98%, 99% homologous to the IGHV4-39 or IGHV4-59 germline gene sequence. The V_H domain of an antibody of the ~~invention~~disclosure may be at least 75% homologous to the amino acid sequence of the V_H domain encoded by the IGHV4-39 or IGHV4-59 germline gene sequence. Preferably the amino acid sequence of the V_H domain is at least 80%, 85%, 90%, 95%, 96%, 97% homologous to the amino acid sequence encoded by the IGHV4-39 or IGHV4-59 germline gene sequence, and more preferably, at least 98%, 99% homologous to the amino acid sequence encoded by IGHV1-2 germline gene sequence.

A binding member of the ~~invention~~disclosure may also comprise a V_L domain comprising a set of kappa light chain CDRs in a human germline framework, e.g. IGKV2D-28 or IGKV1D-33. Thus, the VL domain framework regions FWR1, FWR2 and/or FWR3 may comprise framework regions of human germline gene segment IGKV2D-28 or IGKV1D-33. FWR4 may comprise a framework region of human

germline J segments selected from any of the five kappa J segments (see Hieter *et al.*, 1982).

The amino acid sequence of Ab-47 or Ab-48 V_L domain may comprise the following set of kappa light chain framework regions of IGKV2D-28: FWR1 SEQ ID No: 287, FWR2 SEQ ID No: 288; FWR3 SEQ ID No: 289; or may comprise the said set of light chain framework regions with 1 or 2 amino acid alterations, such as a substitution, an insertion or a deletion.

The amino acid sequence of Ab-49 V_L domain may comprise the following set of light chain framework regions of IGKV1D-33: FWR1 SEQ ID No: 290, FWR2 SEQ ID No: 291; FWR3 SEQ ID No: 292; or may comprise the said set of light chain framework regions with 1, 2, 3, 4, 5, 6, 7, or 8 amino acid alterations, such as a substitution, an insertion or a deletion.

A binding member of the ~~invention~~disclosure may also comprise a V_L domain comprising a set of lambda light chain CDRs in a human germline framework, e.g. IGLV1-47. Thus, the VL domain framework regions FWR1, FWR2 and/or FWR3 may comprise framework regions of human germline gene segment IGLV1-47. FWR4 may comprise a framework region of human germline J segments selected from any of the four lambda J segments (see Udey & Blomberg 1987; Vasicek & Leder, 1990).

The amino acid sequence of Ab-50 V_L domain may comprise the following set of lambda light chain framework regions of IGLV1-47: FWR1 SEQ ID No: 293, FWR2 SEQ ID No: 294; FWR3 SEQ ID No: 295; or may comprise the said set of light chain

framework regions with 1 or 2 amino acid alterations, such as a substitution, an insertion or a deletion.

Furthermore, an antibody of the ~~invention~~disclosure may include a V_L domain that is encoded by a nucleic acid sequence that is at least 90% homologous to the IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence. Preferably the nucleic acid sequence is at least 95%, 96%, 97% homologous to the IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence, and more preferably, at least 98%, 99% homologous to the IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence. The V_L domain of an antibody of the ~~invention~~disclosure may be at least 90% homologous to the amino acid sequence of the V_L domain encoded by the IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence. Preferably the amino acid sequence of the V_L domain is at least 95%, 96%, 97% homologous to the amino acid sequence encoded by the IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence, and more preferably, at least 98%, 99% homologous to the amino acid sequence encoded by IGKV2D-28, IGKV1D-33 or IGLV1-47 germline gene sequence.

A binding member of the ~~invention~~disclosure may be one which competes for binding to hCMV with any binding member that (i) binds hCMV and (ii) comprises a binding member, V_H and/or V_L domain, CDR e.g. HCDR3, and/or set of CDRs disclosed herein. In a fourth aspect, there is provided an isolated antibody molecule that competes for binding to hCMV gB protein with an isolated antibody molecule as defined herein.

Competition between binding members may be assayed *in vitro*, for example using binding assays, like ELISA, surface plasmon resonance, and/or by tagging a specific reporter molecule to one binding member which can be detected in the presence of one or more other untagged binding members, to enable identification of binding members which bind the same epitope or an overlapping epitope. Such methods are readily known to

one of ordinary skill in the art, and are described in more detail herein (see the Examples). Thus, a further ~~aspect~~ embodiment of the present ~~invention~~disclosure provides a binding member comprising an antibody antigen-binding site that competes with an antibody molecule, for example an antibody molecule comprising a V_H and/or V_L domain, CDR e.g. HCDR3 or set of CDRs of any of antibodies Ab-01 to Ab-50, for binding to hCMV.

In further embodiments~~aspects~~, the ~~invention~~disclosure provides an isolated nucleic acid which comprises a sequence encoding a binding member, comprising a V_H domain and/or V_L domain according to the present ~~invention~~disclosure, and methods of preparing a binding member, comprising a V_H domain and/or a V_L domain of the ~~invention~~disclosure, encoded by said nucleic acid under conditions to bring about production of said binding member, comprising V_H domain and/or V_L domain, and recovering it.

Another embodiment ~~aspect~~ of the present ~~invention~~disclosure provides isolated nucleic acids encoding any of the V_H CDR or V_L CDR sequences disclosed herein. In another aspect, there is provided an isolated V_H domain of an antibody molecule as defined herein. In another aspect, there is provided an isolated V_L domain of an antibody molecule as defined herein. In another aspect, there is provided an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody molecule as defined herein, a V_H domain as defined herein, or a V_L domain as defined herein.

A further embodiment ~~aspect~~ provides a host cell containing or transfected with nucleic acid of the ~~invention~~disclosure. In another aspect, there is provided a host cell *in vitro*

transfected or transduced with a nucleic acid molecule as defined herein.

Further embodiments ~~aspects~~ of the present ~~invention~~disclosure describe compositions containing binding members of the ~~invention~~disclosure, and their use in methods of binding, inhibiting and/or neutralising hCMV infection, including methods of treatment of the human or animal body by therapy. In another aspect, there is provided a composition comprising an isolated antibody molecule as defined herein, and a pharmaceutically acceptable excipient. In another aspect, there is provided a composition comprising an isolated antibody molecule as defined herein, for use in a method of treatment of the human or animal body by therapy. In another aspect, there is provided a composition as defined herein for use in treating a disorder associated with hCMV.

Binding members according to the ~~invention~~disclosure may be used in a method of treatment or diagnosis, such as a method of treatment (which may include prophylactic treatment) of a

disease or disorder in the human or animal body (e.g. in a human patient), which comprises administering to said human or animal body an effective amount of a binding member of the ~~invention~~disclosure or a combination of several binding members of the ~~invention~~disclosure. Conditions treatable in accordance with the present ~~invention~~disclosure include any in which hCMV plays a role, as discussed in detail elsewhere herein.

In another aspect, there is provided a method of producing an antibody molecule or an antibody V_H or V_L domain, comprising culturing a host cell as defined herein under conditions for production of the antibody molecule or antibody V_H or V_L domain.

In another aspect, there is provided a method of neutralising hCMV in a sample, comprising administering to said sample the antibody molecule as defined herein, in an amount sufficient to reduce hCMV infectivity by at least 50% at a concentration of from about 0.1 to about 5.0 μg/ml.

In another aspect, there is provided a composition comprising an isolated antibody molecule as defined herein, for use in neutralising hCMV in a subject, wherein the antibody molecule is present in the composition in an amount sufficient to reduce hCMV infectivity by at least 50% at a concentration of from about 0.1 to about 5.0 μg/ml.

These and other aspects and embodiments of the ~~invention~~disclosure are described in further detail below.

Terminology

It is convenient to point out here that 'and/or' where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example 'A and/or B' is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

hCMV

The full-length amino acid sequence of human cytomegalovirus (hCMV) has GenBank Acc. No. X17403 (Human cytomegalovirus strain AD169 complete genome) and comprises a 229354 base pair sequence (Chee *et al.*, 1990; Bankier *et al.*, 1991).

gB

gB complex is a surface glycoprotein complex of the virion envelope of CMV. There are a number of different strains of gB protein:

gB strain AD169 - SwissProt Acc. No. P06473 (SEQ ID No: 239)

gB strain Towne - SwissProt Acc. No. P13201 (SEQ ID No: 240)

Known neutralising domains of gB include antigenic domain-1 (AD-1; amino acids 552-635 of SEQ ID No: 239 [AD169]) and

3. The isolated antibody molecule according to any of the preceding claims, wherein the antibody molecule ~~binding member~~ does not bind to antigenic domain 1 (AD-1) or antigenic domain 2 (AD-2) of hCMV gB protein.

4. The isolated antibody molecule according to any of the preceding claims, wherein the concentration of antibody molecule required for 50% neutralisation of a clinical isolate of hCMV is 10µg/ml or less in a neutralisation assay for neutralisation of hCMV infection of human foreskin fibroblasts.

5. The isolated antibody molecule according to claim 4, comprising an HCDR1 wherein:
Kabat residue 31 is Asp or Gly;
Kabat residue 32 is His, Phe or Tyr;
Kabat residue 33 is Tyr;
Kabat residue 34 is Met, Ile or Leu; and
Kabat residue 35 is Val or Asn.

6. The isolated antibody molecule according to claim 5, wherein HCDR1 is SEQ ID No: 3.

7. The isolated antibody molecule according to any of claims 4 to 6, comprising an HCDR2 wherein:
Kabat residue 50 is Trp, Ser or Cys;
Kabat residue 53 is Gln, Asn or His;
Kabat residue 54 is Ser or Thr;
Kabat residue 58 is Gly, Lys, Asn or His;
Kabat residue 60 is Gly or Ala; and
Kabat residue 64 is Gln or Arg.

8. The isolated antibody molecule according to claim 7, wherein HCDR2 has amino acid sequence SEQ ID No: 4.

20. An isolated antibody molecule comprising a heavy chain comprising amino acid sequence SEQ ID No: 2 and a light chain comprising amino acid sequence SEQ ID No: 92.

21. An isolated antibody molecule that binds hCMV gB protein, wherein the antibody molecule comprises a V_H domain amino acid sequence at least 90% identical to SEQ ID No: 2 and a V_L domain amino acid sequence at least 90% identical to SEQ ID No: 92.

22. An isolated antibody molecule that competes for binding to hCMV gB protein with an isolated antibody molecule of any of the preceeding claims.

23. The isolated antibody molecule of claim 22, wherein the antibody molecule binds hCMV gB protein at a region within residues 121 to 132 and 344 to 438, the residue numbering being defined according to the full length gB strain AD169 amino acid sequence SEQ ID No: 239.

24. An isolated antibody molecule according to claim 20 or 21, wherein the antibody molecule is an IgG.

25. The isolated antibody molecule according to claim 24, wherein the isolated antibody molecule is an IgG_1.

26. The isolated antibody molecule according to claim 24, wherein the isolated antibody molecule is an IgG_4.

~~25~~27. An isolated V_H domain of an antibody molecule according to any of claims 18 or 20 to 24.

~~26~~28. An isolated V_L domain of an antibody molecule according to any of claims 19 to 24.

~~27~~29. A composition comprising an isolated antibody molecule according to any of claims 1 to ~~24~~26, and a pharmaceutically acceptable excipient.

~~28~~30. A composition comprising an isolated antibody molecule according to any of claims 1 to ~~24~~26, for use in a method of treatment of the human or animal body by therapy.

~~29~~31. The composition according to claim ~~28~~30 for use in treating a disorder associated with hCMV.

~~30. A composition comprising an isolated antibody molecule according to any of claims 1 to 24, for use in the treatment of a disorder associated with hCMV in an individual.~~

~~31~~32. The composition according to claim 31~~29 or the composition for use according to claim 30~~, wherein the disorder is a hCMV infection.

~~32~~33. The composition according to any one of claims ~~28~~30 to ~~31~~32, further comprising an isolated binding member or antibody molecule that binds hCMV gB, gH, gL, UL128, UL130 and/or UL131A protein.

~~33~~34. The composition according to any one of claims ~~28~~30 to ~~32~~33, wherein the individual has a compromised immune system.

~~34~~35. The composition according to claim ~~33~~34, wherein the individual is a pregnant woman, a newborn, a transplant recipient or an individual infected with HIV.

36. The composition according to claim 31, wherein the isolated antibody molecule comprises a heavy chain comprising amino acid sequence SEQ ID No: 2 and a light chain comprising amino acid sequence SEQ ID No: 92.

37. The composition according to claim 31, comprising a dosage amount of the isolated antibody molecule of between 100 µg and 1 g.

~~35~~38. An isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody molecule according to any of claims 1 to ~~24~~26, a V_H domain according to claim ~~25~~27, or a V_L domain according to claim ~~26~~28.

~~36~~39. A host cell *in vitro* transfected or transduced with a nucleic acid molecule according to claim ~~35~~38.

~~37~~40. A method of producing an antibody molecule or an antibody V_H or V_L domain, comprising culturing a host cell according to claim ~~36~~39 under conditions for production of the antibody molecule or antibody V_H or V_L domain.

~~38~~41. The method according to claim ~~37~~40, further comprising isolating and/or purifying the antibody molecule, V_H domain or V_L domain.

~~39~~42. The method according to claim ~~37~~ 40 or claim ~~38~~41, further comprising formulating the antibody molecule, V_H domain or V_L domain into a composition comprising at least one additional component.

~~40~~43. A method of neutralising hCMV in a sample, comprising administering to said sample the antibody molecule according to any of claims 1 to ~~24~~26, in an amount sufficient to reduce hCMV infectivity by at least 50% at a concentration of from about 0.1 to about 5.0 µg/ml.

44. The method according to claim 43, wherein the antibody molecule comprises a heavy chain comprising amino acid sequence SEQ ID No: 2 and a light chain comprising amino acid sequence SEQ ID No: 92.

~~41~~45. A composition comprising an isolated antibody molecule according to any of claims 1 to ~~24~~26, for use in neutralising hCMV in a subject, wherein the antibody molecule is present in the composition in an amount sufficient to reduce hCMV infectivity by at least 50% at a concentration of from about 0.1 to about 5.0 µg/ml.

46. The composition according to claim 45, wherein the antibody molecule comprises a heavy chain comprising amino acid sequence SEQ ID No: 2 and a light chain comprising amino acid sequence SEQ ID No: 92.