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(71) **Applicants**: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US). **CAMBRIDGE UNIVERSITY** [GB/GB]; The Old Schools, Trinity Lane, Cambridge CB1 7PN (GB). **CARDIFF UNIVERSITY** [GB/GB]; Park Place, Cardiff CF10 3AT (GB).

(72) **Inventors**: **WEEKES, Michael, P.**; 54 Harvard Street, Apt. 3, Boston, MA 02445 (US). **GYGI, Steven, P.**; 4 Stockbridge Road, Foxborough, MA 02035 (US). **LEHNER, Paul, J.**; 20 Queen Ediths Way, Cambridge CB1 7PN (GB). **WILKINSON, Gavin, W.**; 7 Bronwydd Close, Cardiff CF23 5RA (GB). **TOMASEC, Peter**; 31 Aberbran Road, Cardiff CF14 2SN (GB). **STANTON, Richard, J.**; 2 Plasturton Avenue, Cardiff CF11 9HH (GB).

(74) **Agents**: **SMITH, DeAnn, F.** et al.; Patent Group, FOLEY HOAG LLP, 155 Seaport Blvd., Boston, MA 02210-2600 (US).

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(54) **Title**: METHODS AND COMPOSITIONS FOR THE TREATMENT OF HCMV

(57) **Abstract**: Provided herein are compositions and methods for the treatment of HCMV infection in a subject.

METHODS AND COMPOSITIONS FOR THE TREATMENT OF HCMV

RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent Application serial number 61/904,646, filed November 15, 2013,which is hereby incorporated by reference in its entirety.

GOVERNMENT INTEREST

This invention was made with Government support under National Institutes of Health Grants GM067945 and HG006673. The Government has certain rights in the invention.

BACKGROUND

Human Cytomegalovirus (HCMV, also known as human herpesvirus-5) is a nearly ubiquitous herpes virus that infects between 60% and 90% of individuals. Following primary infection, HCMV typically establishes a persistent infection that is kept under control by a healthy immune system. HCMV employs a multitude of immune-modulatory strategies to evade the host immune response. Examples of such strategies include inhibition of interferon (IFN) and IFN-stimulated genes, degradation of HLA to prevent antigen presentation to cytotoxic T cells and modulation of activating and inhibitory ligands to prevent natural killer (NK) cell function.

Though HCMV infection typically goes unnoticed in healthy individuals, reactivation from viral latency in immunocompromised individuals (*e.g.,* HIV-infected persons, organ transplant recipients), or acquisition of primary infection in such individuals (*e.g.,* during transplantation) can lead to serious disease. For example, HCMV is one of the major causes of graft failure and mortality in transplant recipients who require prolonged immunosuppression, and HCMV infection during pregnancy can lead to congenital abnormalities. HCMV infection has also been linked with mucoepidermoid carcinoma, even in immunocompetent individuals.

HCMV infection in immunocompromised individuals is currently treated using purified plasma immunoglobulin (CMV-IGIV) and antiviral drugs, such as Ganciclovir (Cytovene) and Valganciclovir (Valcyte). Because CMV-IVIG is derived from donated human plasma, it is difficult to produce in large quantity and its use carries the risk of the transmission of infectious disease. Drug-resistant HCMV strains have become increasingly common, often rendering current therapies ineffective. Recent attempts to develop an

HCMV vaccine have proven unsuccessful. Thus, there is a great need for new and improved methods and compositions for the treatment of HCMV.

SUMMARY

Provided herein are compositions and methods for the treatment of HCMV infection in a subject.

In certain aspects, provided herein are methods of treating HCMV infection that include the step of administering to a subject an agent that specifically binds to a target protein expressed on the plasma membrane of HCMV infected cells. In some embodiments, the target protein is an HCMV protein, such as the proteins encoded by the genes listed in Table 1 and/or Table 2. In some embodiments, the target protein is an endogenous protein that has upregulated plasma membrane expression following HCMV infection, such as the proteins encoded by the genes listed in Table 3 and/or Table 4. In some embodiments, the agent binds to an epitope listed in Table 5.

In some embodiments of the methods provided herein, the agent is an antibody (*e.g.,* a full-length antibody or an antigen binding fragment thereof). In some embodiments, the antibody is a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody is a chimeric antibody, a humanized antibody or a fully human antibody. In some embodiments, the antibody is a full length immunoglobulin molecule, an scFv, a Fab fragment, an Fab' fragment, a F(ab')2 fragment, an Fv, a NANOBODY® or a disulfide linked Fv. In some embodiments, the antibody binds to the target protein with a dissociation constant of no greater than about 10^{-7} M, 10^{-8} M or 10^{-9}M. In some embodiments, the antibody binds to an extracellular epitope of the target protein. In some embodiments, the antibody binds to an epitope listed in Table 5.

In some embodiments of the methods provided herein, the antibody is part of an antibody-drug conjugate. In some embodiments, the antibody is linked to a cytotoxic agent (*e.g.,* MMAE, DM-1, a maytansinoid, a doxorubicin derivative, a auristatin, a calcheamicin, CC-1065, aduocarmycin or a anthracycline). In some embodiments, the antibody is linked to an antiviral agent (*e.g.,* ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X).

In certain aspects, provided herein are antibodies that specifically bind to an extracellular epitope of a protein expressed on the plasma membrane of HCMV infected cells (*e.g.,* an epitope listed in Table 5). In some embodiments, the target protein is an HCMV protein, such as the proteins encoded by the genes listed in Table 1 and/or Table 2.

In some embodiments, the target protein is an endogenous protein that has upregulated plasma membrane expression following HCMV infection, such as the proteins encoded by the genes listed in Table 3 and/or Table 4

In some embodiments of the antibodies provided herein, the antibody is a monoclonal antibody or a polyclonal antibody. In some embodiments, the antibody is a chimeric antibody, a humanized antibody or a fully human antibody. In some embodiments, the antibody is a full length immunoglobulin molecule, an scFv, a Fab fragment, an Fab' fragment, a F(ab')2 fragment, an Fv, a NANOBODY® or a disulfide linked Fv. In some embodiments, the antibody binds to the target protein with a dissociation constant of no greater than about 10^{-7} M, 10^{-8} M or 10^{-9}M. In some embodiments, the antibody binds to an extracellular epitope of the target protein. In some embodiments, the epitope is an epitope listed in Table 5.

In some embodiments of the antibodies provided herein, the antibody is part of an antibody-drug conjugate. In some embodiments, the antibody is linked to a cytotoxic agent (*e.g.,* MMAE, DM-1, a maytansinoid, a doxorubicin derivative, an auristatin, a calcheamicin, CC-1065, an aduocarmycin or an anthracycline). In some embodiments, the antibody is linked to an antiviral agent (*e.g.,* ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X).

In certain aspects, provided herein are methods of treating HCMV infection that include the step of administering to a subject a cytotoxic agent to which a transport protein provides cellular resistance, wherein plasma membrane expression of the transport protein is downregulated following HCMV infection. In some embodiments, the transport protein is encoded by ABCC3, SLC38A4 or SLC2A10. In some embodiments the agent is Etoposide.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the workflow of experiments PM1, PM2, WCL1 and WCL2 of the Exemplification. PM1 and PM2 refer to independent experiments in which quantitative temporal viromics were used to examine protein expression at the plasma membrane of HCMV infected cells. WCL1 and WCL2 refer to independent experiments in which the protein expression in whole cell lysates of HCMV infected cells was examined.

Figure 2 shows the relative abundance of ABC transporters in mock infected cells and in infected cells at 24, 48 and 72 hours after HCMV infection.

Figure 3 shows the relative abundance of HCMV proteins in mock infected cells and in infected cells at 24, 48 and 72 hours after HCMV infection. gB, gO, gH and gL are virion glycoproteins expressed late in infection.

Figure 4 shows a principal component analysis of quantified proteins from experiments PM1 and WCL1.

Figure 5 is a table listing endogenous proteins that have upregulated plasma membrane expression following HCMV infection.

Figure 6 shows the temporal modulation of cell surface immunoreceptors. 6A and 6B show temporal profiles of NK ligands (A) or T-cell ligands (B). C shows temporal profiles of γ-protocadherins.

Figure 7 is a table listing proteins quantified in either experiment PM1 or PM2 that have an Interpro annotation of butyrophylin, c-type lectin, immunoglobulin, Ig, MHC or TNF and that exhibit a greater than 4-fold modulation in plasma membrane expression following HCMV infection.

Figure 8 is a table listing functional protein categories that were enriched among the proteins that were highly downregulated at the plasma membrane following HCMV infection.

Figure 9 shows temporal classes of HCMV gene expression. In 9A, the k-means method was used to cluster all quantified HCMV proteins into 4 or 5 classes. Shown are the average temporal profiles of each class. With 4 classes, proteins grouped into the classical cascade of a, b, g1, g2 gene expression. With 5 classes, a distinct temporal profile appeared, with maximal expression at 48h but little expression before or after this time. 9B depicts the number of temporal classes of HCMV gene expression. The summed distance of each protein from its cluster centroid was calculated for 1-14 classes and plotted. The point of inflexion fell between 5-7 classes. In 9C, temporal profiles of proteins in each k-means class were subjected to hierarchical clustering by Euclidian distance. 9D depicts temporal profiles of the central protein of each cluster (upper panels), and all new ORFs quantified by QTV (lower panels).

Figure 10 shows the changes in plasma membrane expression of canonical HCMV proteins following HCMV infection.

Figure 11 is a table listing the origin of g1b proteins quantified. "Genetic Region" refers to the region of the viral genome from which the specified gene originates, listed in

kb. The listed "Start" and "Stop" positions are with reference to the Merlin strain HCMV genome nucleic acid sequence provided at NCBI Reference number NC_006273.2.

Figure 12 shows the relationship between four novel ORFs and the associated canonical HCMV counterparts, with temporal profiles.

Figure 13 is a table listing 9 new ORFs quantified. It was not possible to distinguish between ORFL184C.iORF3 and ORFL185C, or between ORFL294W.iORF1 and ORFL294W on the basis of the identified peptides. The listed "Start" and "Stop" positions are with reference to the Merlin strain HCMV genome nucleic acid sequence provided at NCBI Reference number NC_006273.2.

Figure 14 is a table listing 67 HCMV proteins detected at the cell surface in experiments PM1 or PM2. A peptide ratio cutoff for 'high confidence' PM viral proteins was determined (bold line between UL141 and UL14). The temporal class of protein expression is shown.

Figure 15 shows data related to the HCMV proteins quantified at the surface of infected fibroblasts. 15A is a histogram of peptide ratios for all GO-annotated proteins quantified in experiments PM1 or PM2. The proteins indicated as "PM Only" were not detected in experiments WCL1 or WCL2. 15B depicts temporal profiles of all 'high confidence' PM proteins. Virion envelope glycoproteins were generally detected significantly earlier in whole cell lysates than in plasma membrane samples.

Figure 16 shows temporal profiles of 'high confidence' PM proteins detected in experiment PM1. Known virion envelope glycoproteins (starred) were generally detected significantly earlier in whole cell lysates than in plasma membrane samples. Values shown are averages of two biological replicates, +/- range.

Figure 17 shows temporal profiles and normalized abundance of selected PM proteins. The top panels depict the relative abundance of the selected PM proteins as determined in an 8-plex TMT experiment in biological duplicate at 4 time points of HCMV infection. The middle panels depict the relative abundance of the selected PM proteins as determined in a 10-plex TMT, 8-time-point analysis. The bottom panel depicts the normalized spectral abundance of the selected PM proteins, as well as the relative abundance of known cell surface / virion glycoproteins gM, gB and gN.

Figure 18 shows that serum from HCMV seropositive individuals induces antibody-dependent cellular cytotoxicity. Fibroblasts were infected with HCMV strain Merlin. After 48 or 72 hours, serum from HCMV seropositive (sero+) or seronegative (sero-) donors was

added to the culture along with NK cells, and the level of NK degranulation assessed via a CD107a assay.

DETAILED DESCRIPTION

General

Disclosed herein are novel compositions and methods for the treatment of HCMV infection.

As described herein, a new proteomic approach was used to study temporal changes in plasma membrane expression of viral and endogenous proteins following HCMV infection. Accurate multiplexed quantitative measurement of protein abundance using triple-stage mass spectrometry (MS3) to measure ten isobaric chemical reporters (tandem mass tags, TMT). The TMT-based process was combined with plasma membrane profiling (PMP), a method for isolation of highly purified plasma membrane proteins for proteomic analysis. In total, 1,184 cell surface receptors were quantified over eight time points during productive infection of primary human fibroblasts with HCMV. Through simultaneous analysis of lysates of infected cells, expression of 7,491 host proteins and 80% of all canonical viral proteins was quantified, providing a near-complete view of the host proteome and HCMV virome over time following HCMV infection.

Using the above approach, proteins for which plasma membrane expression was rapidly upregulated following HCMV expression were identified (*e.g.,* the proteins encoded by the genes listed in Tables 1-4). Therapeutic agents that selectively bind to such proteins (*e.g.,* therapeutic antibodies) can be used to selectively target virus infected cells for the treatment of HCMV infection.

As described herein, HCMV infection induces the downregulation of the plasma membrane expression of numerous endogenous proteins, including many involved in the host immune response (including natural killer cell ligands and T-cell costimulatory molecules). HCMV proteins present on the plasma membrane (*e.g.,* the proteins encoded by the genes listed in Tables 1 and 2) may facilitate this process by binding to and internalizing the endogenous proteins (*e.g.,* via the endosome network). Indeed, a vast majority of the plasma membrane expressed HCMV proteins disclosed herein contain amino acid sequences that correspond to sorting signals known to facilitate protein movement through the endosome network. Internalization of an agent (*e.g.,* an anti-viral or a cytotoxic agent) by an HCMV infected cell can therefore be facilitated by linking the agent to an antibody that binds to an extracellular epitope of a plasma membrane expressed HCMV protein (*e.g.,*

a protein encoded by a gene listed in Tables 1 and 2), which would then shuttle the antibody and agent into the cell as it would its endogenous protein target.

Thus, in certain embodiments, provided herein are methods and compositions for treating HCMV infection by targeting a protein selectively expressed on the plasma membrane of HCMV infected cells (*e.g.,* the proteins encoded by the genes listed in Tables 1-4). In some embodiments, provided herein are antibodies that specifically bind to an extracellular epitope of a protein selectively expressed on the plasma membrane of HCMV infected cells (*e.g.,* an extracellular epitope of proteins encoded by the genes listed in Tables 1-4, such as the epitopes listed in Table 5). In some embodiments, provided here are methods of treating HCMV infection by administering a cytotoxic agent for which cellular resistance is conveyed by a protein that is rapidly downregulated on the plasma membrane of HCMV infected cells.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The articles "*a*" and "*an*" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

As used herein, the term "*administering*" means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering. Such an agent can contain, for example, an antibody or antigen binding fragment thereof described herein.

The term "*agent*" is used herein to denote a chemical compound, a small molecule, a mixture of chemical compounds and/or a biological macromolecule (such as a nucleic acid, an antibody, an antibody fragment, a protein or a peptide). Agents may be identified as having a particular activity by screening assays described herein below. The activity of such agents may render them suitable as a "therapeutic agent" which is a biologically, physiologically, or pharmacologically active substance (or substances) that acts locally or systemically in a subject.

The term "*amino acid*" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino

acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing.

As used herein, the term "*antibody*" may refer to both an intact antibody and an antigen binding fragment thereof. Intact antibodies are glycoproteins that include at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain includes a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. Each light chain includes a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.,* effector cells) and the first component (Clq) of the classical complement system. The term "antibody" includes, for example, monoclonal antibodies, polyclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, multispecific antibodies (*e.g.,* bispecific antibodies), single-chain antibodies and antigen-binding antibody fragments.

The terms "*antigen binding fragment*" and "*antigen-binding portion*" of an antibody, as used herein, refers to one or more fragments of an antibody that retain the ability to bind to an antigen. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include Fab, Fab', $F(ab')_2$, Fv, scFv, disulfide linked Fv, Fd, diabodies, single-chain antibodies, NANOBODIES®, isolated CDRH3, and other antibody fragments that retain at least a portion of the variable region of an intact antibody. These antibody fragments can be obtained using conventional recombinant and/or enzymatic techniques and can be screened for antigen binding in the same manner as intact antibodies.

The term "*binding*" or "*interacting*" refers to an association, which may be a stable association, between two molecules, *e.g.*, between a polypeptide and a binding partner or agent, *e.g.,* small molecule, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

The terms "*CDR*", and its plural "*CDRs*", refer to a complementarity determining region (CDR) of an antibody or antibody fragment, which determine the binding character of an antibody or antibody fragment. In most instances, three CDRs are present in a light chain variable region (CDRL1, CDRL2 and CDRL3) and three CDRs are present in a heavy chain variable region (CDRH1, CDRH2 and CDRH3). CDRs contribute to the functional activity of an antibody molecule and are separated by amino acid sequences that comprise scaffolding or framework regions. Among the various CDRs, the CDR3 sequences, and particularly CDRH3, are the most diverse and therefore have the strongest contribution to antibody specificity. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (*i.e.,* Kabat et al., Sequences of Proteins of Immunological Interest (National Institute of Health, Bethesda, Md. (1987), incorporated by reference in its entirety); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Chothia et al., Nature, 342:877 (1989), incorporated by reference in its entirety).

The term "*epitope*" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains. Certain epitopes can be defined by a particular sequence of amino acids to which an antibody is capable of binding. The term "*extracellular epitope*" refers to an epitope that is located on the outside of a cell's plasma membrane. Exemplary extracellular epitopes of plasma membrane expressed HCMV proteins are listed in Table 5.

As used herein, the term "*humanized antibody*" refers to an antibody that has at least one CDR derived from a mammal other than a human, and a FR region and the constant region of a human antibody.

As used herein, the term "*monoclonal antibody*" refers to an antibody obtained from a population of substantially homogeneous antibodies that specifically bind to the same epitope, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

The terms "*polynucleotide*", and "*nucleic acid*" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or

ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. A polynucleotide may be further modified, such as by conjugation with a labeling component. In all nucleic acid sequences provided herein, U nucleotides are interchangeable with T nucleotides.

As used herein, "*specific binding*" refers to the ability of an antibody to bind to a predetermined antigen or the ability of a polypeptide to bind to its predetermined binding partner. Typically, an antibody or polypeptide specifically binds to its predetermined antigen or binding partner with an affinity corresponding to a K_D of about 10^{-7} M or less, and binds to the predetermined antigen/binding partner with an affinity (as expressed by K_D) that is at least 10 fold less, at least 100 fold less or at least 1000 fold less than its affinity for binding to a non-specific and unrelated antigen/binding partner (*e.g.,* BSA, casein).

As used herein, the term "*subject*" means a human or non-human animal selected for treatment or therapy.

The phrases "*therapeutically-effective amount*" and "*effective amount*" as used herein means the amount of an agent which is effective for producing the desired therapeutic effect in at least a sub-population of cells in a subject at a reasonable benefit/risk ratio applicable to any medical treatment.

"*Treating*" a disease in a subject or "*treating*" a subject having a disease refers to subjecting the subject to a pharmaceutical treatment, *e.g.*, the administration of a drug, such that at least one symptom of the disease is decreased or prevented from worsening.

Target Proteins

In certain embodiments, provided herein are methods of treating HCMV infection by administering an agent (*e.g.,* a therapeutic antibody) that specifically binds to an HCMV protein that is expressed on the plasma membrane of HCMV infected cells. In some

embodiments the plasma membrane expressed HCMV protein is selected from among the proteins encoded by the genes listed in Table 1. In some embodiments, the agent binds to an extracellular epitope of a protein encoded by a gene listed in Table 1. The protein and gene reference numbers provided in Table 1 and elsewhere herein are merely exemplary and refer to the Merlin strain of HCMV. These protein and gene reference numbers are not meant to be limiting. The methods and compositions provided herein can be applied to any strain of HCMV. The corresponding gene and protein sequences of the genes listed in Table 1 in non-Merlin strains of HCMV are known in the art and/or readily determined without need for undue experimentation.

Table 1. Genes encoding selected HCMV proteins expressed on the plasma membrane of HCMV infected cells.

Gene	Uniprot	GI Number	Description
UL142	D2K3T4	395455117	Membrane glycoprotein UL142
UL9	F5H9T4	384952364	Membrane glycoprotein UL9
UL1	Q6SWC8	82013985	Glycoprotein UL1
UL5	F5HHY9	82013982	Protein UL5
UL41A	F5HFG3	395455127	Protein UL41A
RL12	Q6SWD0	82013987	Uncharacterized protein RL12
UL33	Q6SW98	82055331	G-protein coupled receptor homolog UL33
UL119	F5HC14	391359343	Viral Fc-gamma receptor-like protein UL119
UL16	F5HG68	395455121	Protein UL16
RL10	F5HI32	395406822	Protein IRL10
UL100	Q6SW43	82013927	Envelope glycoprotein M
UL40	Q6SW92	82013961	Protein UL40
US6	Q6SW00	82013896	Unique short US6 glycoprotein
UL144	F5HAM0	363805602	Membrane glycoprotein UL144
US28	Q80KM9	82058001	Envelope protein US28
US27	F5HDK1	380875404	Envelope glycoprotein US27
RL11	Q6SWD1	82013988	Membrane glycoprotein RL11
US9	F5HC33	384951451	Membrane glycoprotein US9
UL148D	D2K3U5	77543601	Protein UL148D

Gene	Uniprot	GI Number	Description
US20	F5HGH8	395455141	Membrane protein US20
UL78	B8YEA3	395455130	Protein UL78
UL136	F5HF35	391359344	Protein UL136
US14	F5HD92	384951455	Membrane protein US14
UL73	F5HHQ0	380876918	Envelope glycoprotein N
UL132	D2K3S7	395455115	Envelope glycoprotein UL132
UL141	Q6RJQ3	82013863	Protein UL141
UL14	Q6SWB7	82013974	Uncharacterized protein UL14
UL22A	F5HF90	384952467	Glycoprotein UL22A
US12	F5HE44	395455137	Uncharacterized protein US12
UL103	F5HA10	395455111	Tegument protein UL103
UL133	Q6SW10	82013903	Protein UL133
US8	F5HB52	384951444	Membrane glycoprotein US8
UL50	Q6SW81	82013953	Nuclear egress membrane protein
UL94	F5HAC7	391359347	Capsid-binding protein UL94
UL13	F5HGX4	82013975	Protein UL13
UL148	F5H8Q3	395455119	Membrane protein UL148
UL99	F5HI87	395455101	Tegument protein UL99
UL135	F5HAQ7	384952459	Protein UL135
UL146	F5HBX1	395406771	Chemokine vCXCL1
IRS1	Q6SW04	82013899	Protein IRS1
UL44	A9YU18	270355806	DNA polymerase processivity factor
UL83	Q6SW59	82013937	65 kDa phosphoprotein

In certain embodiments, provided herein are methods of treating HCMV infection by administering an agent (*e.g.,* a therapeutic antibody) that specifically binds to an HCMV protein that is expressed on the plasma membrane early after HCMV infection (*e.g.,* within 24, 48 or 72 hours of HCMV infection). In some embodiments such early plasma membrane expressed HCMV protein is selected from among the proteins encoded by the genes listed in Table 2. In some embodiments, the agent binds to an extracellular epitope of a protein encoded by a gene listed in Table 2. The protein and gene reference numbers provided in Table 2 and elsewhere herein are merely exemplary and refer to the Merlin

strain of HCMV. These protein and gene reference numbers are not meant to be limiting. The methods and compositions provided herein can be applied to any strain of HCMV. The corresponding gene and protein sequences of the genes listed in Table 2 in non-Merlin strains of HCMV are known in the art and/or readily determined without need for undue experimentation.

Table 2. Selected genes encoding selected HCMV proteins expressed on the plasma membrane of HCMV infected cells soon after HCMV infection.

Gene	Uniprot	GI Number	Description
UL9	F5H9T4	384952364	Membrane glycoprotein UL9
UL5	F5HHY9	82013982	Protein UL5
RL12	Q6SWD0	82013987	Uncharacterized protein RL12
UL119	F5HC14	391359343	Viral Fc-gamma receptor-like protein UL119
UL16	F5HG68	395455121	Protein UL16
UL40	Q6SW92	82013961	Protein UL40
US6	Q6SW00	82013896	Unique short US6 glycoprotein
US28	Q80KM9	82058001	Envelope protein US28
RL11	Q6SWD1	82013988	Membrane glycoprotein RL11
US9	F5HC33	384951451	Membrane glycoprotein US9
UL148D	D2K3U5	77543601	Protein UL148D
US20	F5HGH8	395455141	Membrane protein US20
UL78	B8YEA3	395455130	Protein UL78
UL136	F5HF35	391359344	Protein UL136
US14	F5HD92	384951455	Membrane protein US14
UL14	Q6SWB7	82013974	Uncharacterized protein UL14
US12	F5HE44	395455137	Uncharacterized protein US12
UL103	F5HA10	395455111	Tegument protein UL103
UL133	Q6SW10	82013903	Protein UL133
US8	F5HB52	384951444	Membrane glycoprotein US8
UL13	F5HGX4	82013975	Protein UL13
UL135	F5HAQ7	384952459	Protein UL135
IRS1	Q6SW04	82013899	Protein IRS1

In some embodiments, provided herein are methods of treating HCMV infection by administering an agent (*e.g.,* a therapeutic antibody) that specifically binds to an endogenous protein that is upregulated on the plasma membrane after HCMV infection. In some embodiments, the endogenous protein is upregulated at the plasma membrane soon after HCMV infection (*e.g.,* within 24, 48 or 72 hours of HCMV infection). In some embodiments the endogenous protein is selected from among the proteins encoded by the genes listed in Table 3 or Table 4. In some embodiments, the agent binds to an extracellular epitope of a protein encoded by a gene listed in Table 3 or Table 4.

Table 3. Genes encoding selected endogenous proteins upregulated on the plasma membrane of HCMV infected cells after HCMV infection.

Gene Symbol	Uniprot	GI Number	Protein name
CHST11	Q9NPF2	61212137	Carbohydrate sulfotransferase 11
KCNK1	O00180	13124036	Potassium channel subfamily K member 1
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
CDH1	P12830	399166	Cadherin-1
CEACAM1	P13688	399116	Carcinoembryonic antigen-related cell adhesion molecule 1
EPCAM	P16422	160266056	Epithelial cell adhesion molecule
TNFRSF1B	P20333	21264534	Tumor necrosis factor receptor superfamily member 1B
ERBB3	P21860	119534	Receptor tyrosine-protein kinase erbB-3
CNTFR	P26992	1352099	Ciliary neurotrophic factor receptor subunit alpha
PCDH1	Q08174	215273864	Protocadherin-1
BST2	Q10589	1705508	Bone marrow stromal antigen 2
SDK2	Q58EX2	296452966	Protein sidekick-2
RALGPS2	Q86X27	74750518	Ras-specific guanine nucleotide-releasing factor RalGPS2
SLCO4A1	Q96BD0	27734555	Solute carrier organic anion transporter family member 4A1
MEGF10	Q96KG7	74716908	Multiple epidermal growth factor-like domains

Gene Symbol	Uniprot	GI Number	Protein name
			protein 10
SEMA4D	Q92854	8134701	Semaphorin-4D
PCDH1	Q08174	215273864	Protocadherin-1
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
TTC17	Q96AE7	52783467	Tetratricopeptide repeat protein 17
MFSD2A	Q8NA29	74751132	Major facilitator superfamily domain-containing protein 2A
DNAH1	Q9P2D7	327478598	Dynein heavy chain 1, axonemal
GFRA2	O00451	118582303	GDNF family receptor alpha-2
P2RY2	P41231	311033490	P2Y purinoceptor 2
TYRO3	Q06418	1717829	Tyrosine-protein kinase receptor TYRO3
TSPAN18	Q96SJ8	68053316	Tetraspanin-18
SLC38A3	Q99624	52783419	Sodium-coupled neutral amino acid transporter 3
CADM1	Q9BY67	150438862	Cell adhesion molecule 1
RTN4R	Q9BZR6	25453267	Reticulon-4 receptor
SLC39A8	Q9C0K1	74733496	Zinc transporter ZIP8
NPDC1	Q9NQX5	22261810	Neural proliferation differentiation and control protein 1
CACNA2D2	Q9NY47	387912827	Voltage-dependent calcium channel subunit alpha-2/delta-2
PODXL2	Q9NZ53	74734719	Podocalyxin-like protein 2
NPC1L1	Q9UHC9	425906049	Niemann-Pick C1-like protein 1
SLC7A8	Q9UHI5	12643348	Large neutral amino acids transporter small subunit 2
LIFR	P42702	1170784	Leukemia inhibitory factor receptor
NCAM1	P13591	205830665	Neural cell adhesion molecule 1
MMP15	P51511	1705988	Matrix metalloproteinase-15
NGFR	P08138	128156	Tumor necrosis factor receptor superfamily member 16

Gene Symbol	Uniprot	GI Number	Protein name
SCARB1	Q8WTV0	37999904	Scavenger receptor class B member 1
CD55	P08174	60416353	Complement decay-accelerating factor
GPR108	Q9NPR9	296439338	Protein GPR108
HLA-E	P13747	34395942	HLA class I histocompatibility antigen, alpha chain E
F11R	Q9Y624	10720061	Junctional adhesion molecule A
GPR56	Q9Y653	45476992	G-protein coupled receptor 56
ERO1LB	Q86YB8	116241353	ERO1-like protein beta
B3GNT9	Q6UX72	74738184	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 9
ERO1L	Q96HE7	50400608	ERO1-like protein alpha
SREK1	Q8WXA9	37537968	Splicing regulatory glutamine/lysine-rich protein 1
IQGAP2	Q13576	37537968	Ras GTPase-activating-like protein IQGAP2
TSPAN13	O95857	11135162	Tetraspanin-13
PRICKLE2	Q7Z3G6	85701877	Prickle-like protein 2
ABCA3	Q99758	85700402	ATP-binding cassette sub-family A member 3
SLC27A6	Q9Y2P4	74725713	Long-chain fatty acid transport protein 6
LUC7L3	O95232	94730369	Luc7-like protein 3
HSPA9	P38646	21264428	Stress-70 protein, mitochondrial
PTGS2	P35354	3915797	Prostaglandin G/H synthase 2
C19orf10	Q969H8	61221730	UPF0556 protein C19orf10
HSPA5	P11021	14916999	78 kDa glucose-regulated protein
CCDC134	Q9H6E4	74752694	Coiled-coil domain-containing protein 134
ARHGAP31	Q2M1Z3	296452881	Rho GTPase-activating protein 31
CRELD1	Q96HD1	209572751	Isoform 2 of Cysteine-rich with EGF-like domain protein 1
PSAP	P07602	134218	Proactivator polypeptide
CERCAM	Q5T4B2	74744901	Glycosyltransferase 25 family member 3
ARHGAP21	Q5T5U3	74745129	Rho GTPase-activating protein 21

Gene Symbol	Uniprot	GI Number	Protein name
MCFD2	Q8NI22	49036425	Multiple coagulation factor deficiency protein 2
GNB2L1	P63244	54037168	Guanine nucleotide-binding protein subunit beta-2-like 1
DST	Q03001	294862529	Dystonin
HSPA13	P48723	1351125	Heat shock 70 kDa protein 13
B3GNT2	Q9NY97	29840874	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2
VPS13D	Q5THJ4	74756617	Vacuolar protein sorting-associated protein 13D
SLC39A7	Q92504	12643344	Zinc transporter SLC39A7
SRRM1	Q8IYB3	83305833	Serine/arginine repetitive matrix protein 1
HSPA1A	P08107	147744565	Heat shock 70 kDa protein 1A/1B
TOR1B	O14657	13878818	Torsin-1B
GRPEL1	Q9HAV7	18202951	GrpE protein homolog 1, mitochondrial
PRPF4B	Q13523	317373526	Serine/threonine-protein kinase PRP4 homolog
TBCEL	Q5QJ74	215273924	Tubulin-specific chaperone cofactor E-like protein
RSRC2	Q7L4I2	74739167	Arginine/serine-rich coiled-coil protein 2
BAG3	O95817	12643665	BAG family molecular chaperone regulator 3
IFIT2	P09913	124488	Interferon-induced protein with tetratricopeptide repeats 2
BRD4	O60885	20141192	Bromodomain-containing protein 4
HYOU1	Q9Y4L1	10720185	Hypoxia up-regulated protein 1

Table 4. Preferred genes encoding selected endogenous proteins upregulated on the plasma membrane of HCMV infected cells after HCMV infection.

Gene Symbol	Uniprot	GI Number	Protein name
CHST11	Q9NPF2	61212137	Carbohydrate sulfotransferase 11
KCNK1	O00180	13124036	Potassium channel subfamily K member 1

Gene Symbol	Uniprot	GI Number	Protein name
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
CDH1	P12830	399166	Cadherin-1
CEACAM1	P13688	399116	Carcinoembryonic antigen-related cell adhesion molecule 1
EPCAM	P16422	160266056	Epithelial cell adhesion molecule
TNFRSF1B	P20333	21264534	Tumor necrosis factor receptor superfamily member 1B
ERBB3	P21860	119534	Receptor tyrosine-protein kinase erbB-3
CNTFR	P26992	1352099	Ciliary neurotrophic factor receptor subunit alpha
PCDH1	Q08174	215273864	Protocadherin-1
BST2	Q10589	1705508	Bone marrow stromal antigen 2
SDK2	Q58EX2	296452966	Protein sidekick-2
RALGPS2	Q86X27	74750518	Ras-specific guanine nucleotide-releasing factor RalGPS2
SLCO4A1	Q96BD0	27734555	Solute carrier organic anion transporter family member 4A1
MEGF10	Q96KG7	74716908	Multiple epidermal growth factor-like domains protein 10
SEMA4D	Q92854	8134701	Semaphorin-4D
PCDH1	Q08174	215273864	Protocadherin-1
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
TTC17	Q96AE7	52783467	Tetratricopeptide repeat protein 17

Antibodies

In certain embodiments, the compositions and methods provided herein relate to antibodies and antigen binding fragments thereof that bind specifically to a protein expressed on the plasma membrane of an HCMV infected cell (*e.g.,* a protein encoded by a gene listed in Tables 1-4). In some embodiments, the antibodies bind to a particular epitope of one of the target proteins provided herein. In some embodiment the epitope is an extracellular epitope. In some embodiments, the epitope is an epitope listed in Table 5. In

some embodiments, the antibodies can be polyclonal or monoclonal and can be, for example, murine, chimeric, humanized or fully human.

Table 5. Exemplary extracellular epitopes of plasma membrane expressed HCMV proteins.

Gene Symbol	First Amino Acid	Last Amino Acid	Epitope Sequence
UL9	6	16	MTIPCTPTVGY
UL9	18	28	SHNISLHPLNN
UL9	45	52	VTNKLCLY
UL9	87	102	SRNYYFQSFKYLGQGV
UL9	104	143	KPNNLCYNVSVHFTHQTHCHTTTSSLYPPTSVHDSLEISQ
UL9	151	164	THTAVHYAAGNVEA
UL5	23	40	AFTSSVSTRTPSLAIAPP
UL5	50	63	EEELVPWSRLIITK
RL12	13	29	YRQTVYIILTFYIVYRG
RL12	47	56	VSDTSVYSTP
RL12	106	114	TASTLTALS
RL12	157	170	TYSPVTSIAVNCTV
RL12	188	194	GTIRVKS
RL12	214	221	NCPNVVWY
RL12	228	235	THGHHIYP
RL12	240	271	QTPTYQHKILTSHPICHPDVSSPAAYHDLCRS
RL12	290	296	YSRRCYK
RL12	323	332	TTPLCPRYVG
Ul119	25	36	NVSSAVTTTVQT
Ul119	41	47	ASTSVIA
Ul119	52	80	EGHLYTVNCEASYSYDQVSLNATCKVILL
Ul119	86	96	PDILSVTCYAR
Ul119	99	111	CKGPFTQVGYLSA
Ul119	118	125	GKLHLSYN
Ul119	128	135	AQELLISG
Ul119	142	148	TEYTCSF
Ul119	160	171	DLFTYPIYAVYG

Gene Symbol	First Amino Acid	Last Amino Acid	Epitope Sequence
Ul119	179	216	MRVRVLLQEHEHCLLNGSSLYHPNSTVHLHQGDQLIPP
Ul119	229	250	LREFVFYLNGTYTVVRLHVQIA
Ul119	255	264	TTTYVFIKSD
UL16	13	27	SNSTCRLNVTELASI
UL16	35	46	LHGMCISICYYE
UL16	52	58	EIIGVAF
UL16	62	71	HNESVVDLWL
UL16	94	103	KMRTVPVTKL
UL16	113	121	TVGRYDCLR
UL16	129	143	IIERLYVRLGSLYPR
UL16	145	157	PGSGLAKHPSVSA
UL40	10	38	TTAGVTSAHGPLCPLVFQGWAYAVYHQGD
UL40	40	51	VLMTLDVYCCRQ
UL40	53	62	SSNTVVAFSH
UL40	65	72	ADNTLLIE
UL40	80	106	HVDGISCQDHFRAQHQDCPAQTVHVRG
UL40	111	142	AFGLTHLQSCCLNEHSQLSERVAYHLKLRPAT
UL40	149	181	AMYTVGILALGSFSSFYSQIARSLGVLPNDHHY
US6	7	22	PKTLLSLSPRQACVPR
US6	25	31	SHRPVCY
US6	51	58	FAHQCLQA
US6	77	111	GRLTCQRVRRLLPCDLDIHPSHRLLTLMNNCVCDG
US6	113	119	VWNAFRL
RL11	10	20	KKPLKLANYRA
RL11	26	32	TRTLVTR
RL11	34	49	NTSHHSVVWQRYDIYS
RL11	55	62	MPPLCIIT
RL11	82	100	NLTLYNLTVKDTGVYLLQD
RL11	102	121	YTGDVEAFYLIIHPRSFCRA
RL11	123	139	ETRRCFYPGPGRVVVTD
US9	17	26	SSSRICPLSN
US9	28	35	KSVRLPQY

Gene Symbol	First Amino Acid	Last Amino Acid	Epitope Sequence
US9	41	68	DVSGYRVSSSVSECYVQHGVLVAAWLVR
US9	89	95	THFKVGA
US9	108	152	TELPQVDARLSYVMLTVYPCSACNRSVLHCRPASRLPWL PLRVTP
UL78	4	13	VLRGVLQPAS
UL78	21	30	IMDYVELATR
UL78	33	48	LTMRLGILPLFIIAFF
UL78	58	127	DSFDYLVERCQQSCHGHFVRRLVQALKRAMYSVELAVC YFSTSVRDVAEAVKKSSSRCYADATSAAVVVT
UL78	149	164	PGTTIDVSAESSSVLC
UL136	13	29	MLHDLFCGCHYPEKCRR
UL136	62	68	YGSGCRF
UL136	79	85	PAPPALS
UL136	125	142	DAVHVAVQAAVQATVQVS
US14	7	21	MFSYLAKLGTYHHYR
US15	24	32	NGTLSVILN
UL14	4	15	APPVVRSPCLQP
UL14	26	33	GSPQLLPY
UL14	35	45	DRLEVACIFPA
UL14	47	85	DWPEVSIRVHLCYWPEIVRSLVVDARSGQVLHNDASCYI
UL14	97	109	AAQRLSLSFRLIT
UL14	113	120	GTYTCVLG
UL14	130	140	TTALVADVHDL
UL14	143	151	SDRSCDLAF
UL14	156	162	QTRYLWT
UL14	179	195	RHRVVHYIPGTSGLLPS
UL14	201	210	RELCVPFISQ
UL14	228	234	RRYHLRR
UL103	5	14	MIRGVLEVHT
UL103	23	31	IMEPQVLDF
UL103	42	50	TEHGLLVSM
UL103	53	74	YRSELLCTSAFLGYSAVFLLET

Gene Symbol	First Amino Acid	Last Amino Acid	Epitope Sequence
UL103	77	114	AVTQVRLSDLRLKHRCGIVKADNLLHFALCTVISCVEN
UL103	117	134	LTRKCLHDLLQYLDAVNV
UL103	138	158	FGRLLHHSARRLICSALYLLF
UL103	162	177	EPHIVQYVPATFVLFQ
UL103	179	193	TRHTCLQLVARFFFR
UL103	199	206	EAHSFSLK
UL103	214	227	DGWPVGLGLLDVLN
UL103	230	239	YPNLPSPPKL
UL103	230	239	YPNLPSPPKL
US8	22	35	EPNYVAPPARQFRF
US8	37	63	PLNNVSSYQASCVVKDGVLDAVWRVQG
US8	67	74	PEKGIVAR
US8	87	124	RLHAPECLVETTEAVFRLRQWVPTDLDHLTLHLVPCTK
US8	126	138	KPMWCQPRYHIRY
UL13	14	25	QGATYQLSIVRQ
UL13	30	38	AGFQVRAAS
UL13	44	85	NAVDLDRPPLWSGSLPHLPVYDVRSPRPLRPPSSQHHAVSPE
UL13	95	104	QYQELQYLVE
UL13	116	128	IPRPSFPPPDPPS
UL13	148	154	AESTVSH
UL13	177	185	SRDSLLLTR
UL13	218	246	GLRQLRQQLTVRWQLFRLRCHGWTQQVSS
UL13	254	262	ESNVVSQTA
UL13	266	272	RTWFVQR
UL13	289	303	EAQELAIIPPAPTVL
UL13	364	372	EVQEPQVTY
UL13	401	410	NTLTVACPPR
UL13	413	432	PHRALFRLCLGLWVSSYLVR
IRS1	24	37	SGVGSSPPSSCVPM
IRS1	55	62	PGHGVHRV
IRS1	84	96	PERLLLSQIPVER

Gene Symbol	First Amino Acid	Last Amino Acid	Epitope Sequence
IRS1	98	104	ALTELEY
IRS1	110	116	VWRAAFL
IRS1	132	150	AGTLLPLGRPYGFYARVTP
IRS1	169	184	DAWIVLVATVVHEVDP
IRS1	196	220	HPEGLCAQDGLYLALGAGFRVFVYD
IRS1	223	230	NNTLILAA
IRS1	240	252	GAGEVVRLYRCNR
IRS1	259	274	RATLLPQPALRQTLLR
IRS1	291	297	GTTVALQ
IRS1	303	336	LQPMVLLGAWQELAQYEPFASAPHPASLLTAVRR
IRS1	338	362	LNQRLCCGWLALGAVLPARWLGCAA
IRS1	384	404	GDAPCAMAGAVGSAVTIPPQP
IRS1	410	426	GSAICVPNADAHAVVGA
IRS1	428	443	ATAAAAAAAAAPTVMV
IRS1	458	503	PRAMLVVVLDELGAVFGYCPLDGHVYPLAAELSHFLRAG VLGALAL
IRS1	513	520	AARRLLPE
IRS1	531	544	WDALHLHPRAALWA
IRS1	563	571	IHDPVAFRL
IRS1	575	583	RTLGLDLTT
IRS1	589	602	QSQLPEKYIGFYQI
IRS1	625	640	TMPPPLSAQASVSYAL
IRS1	648	655	RPLSTVDD
IRS1	664	670	ESHWVLG
IRS1	695	706	RPMPVVPEECYD
IRS1	712	722	EGHQVIPLCAS
IRS1	749	756	KPPRLCKT
IRS1	759	765	GPPPLPP
IRS1	833	842	RPKKCQTHAP

Polyclonal antibodies can be prepared by immunizing a suitable subject (*e.g.* a mouse) with a polypeptide immunogen (*e.g.,* a protein encoded by a gene listed in Tables 1-

4 or a fragment thereof). In some embodiments, the polypeptide immunogen comprises an extracellular epitope of a target protein provided herein. The polypeptide antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody directed against the antigen can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies using standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci.* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), a human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol. Today* 4:72), a EBV-hybridoma technique (Cole *et al.* (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or a trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally Kenneth, R. H. in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); Lerner, E. A. (1981) *Yale J. Biol. Med.* 54:387-402; Gefter, M. L. *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds to the polypeptide antigen, preferably specifically.

As an alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody that binds to a target protein described herein can be obtained by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library or an antibody yeast display library) with the appropriate polypeptide (*e.g.* a polypeptide comprising an extracellular epitope of a target protein described herein) to thereby isolate immunoglobulin library members that bind the polypeptide.

Additionally, recombinant antibodies specific for a target protein provided herein and/or an extracellular epitope of a target protein provided herein, such as chimeric or humanized monoclonal antibodies, can be made using standard recombinant DNA

techniques. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in US Pat No. 4,816,567; US Pat. No. 5,565,332; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci.* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Biotechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

Human monoclonal antibodies specific for a target protein provided herein and/or an extracellular epitope of a target protein provided herein can be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. For example, "HuMAb mice" which contain a human immunoglobulin gene miniloci that encodes unrearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg, N. *et al.* (1994) Nature 368(6474): 856 859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGκ monoclonal antibodies (Lonberg, N. *et al.* (1994), supra; reviewed in Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49 101; Lonberg, N. and Huszar, D. (1995) Intern. Rev. Immunol. Vol. 13: 65 93, and Harding, F. and Lonberg, N. (1995) Ann. N. Y Acad. Sci 764:536 546). The preparation of HuMAb mice is described in Taylor, L. *et al.* (1992) Nucleic Acids Research 20:6287 6295; Chen, J. *et al.* (1993) International Immunology 5: 647 656; Tuaillon *et al.* (1993) Proc. Natl. Acad. Sci USA 90:3720 3724; Choi *et al.* (1993) Nature Genetics 4:117 123; Chen, J. *et al.* (1993) EMBO J. 12: 821 830; Tuaillon *et al.* (1994) J. Immunol. 152:2912 2920; Lonberg *et al.*, (1994) Nature 368(6474): 856 859; Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49 101; Taylor, L. *et al.* (1994) International Immunology 6: 579 591; Lonberg, N. and Huszar, D. (1995) Intern. Rev. Immunol. Vol. 13: 65 93; Harding, F. and Lonberg, N. (1995) Ann. N.Y. Acad. Sci 764:536 546; Fishwild, D. *et al.* (1996) Nature Biotechnology 14: 845 851. See further,

U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; 5,770,429; and 5,545,807.

In certain embodiments, the antibodies provided herein are able to bind to an epitope of a protein encoded by a gene listed in Tables 1-4 (*e.g.,* an extracellular epitope) with a dissociation constant of no greater than 10^{-6}, 10^{-7}, 10^{-8} or 10^{-9} M. Standard assays to evaluate the binding ability of the antibodies are known in the art, including for example, ELISAs, Western blots and RIAs. The binding kinetics (*e.g.,* binding affinity) of the antibodies also can be assessed by standard assays known in the art, such as by Biacore analysis.

In some embodiments the antibody is part of an antibody-drug conjugate. Antibody-drug conjugates are therapeutic molecules comprising an antibody (*e.g.,* an antibody that binds to a protein encoded by a gene listed in Tables 1-4) linked to a biologically active agent, such as a cytotoxic agent or an antiviral agent. In some embodiments, the biologically active agent is linked to the antibody via a chemical linker. Such linkers can be based on any stable chemical motif, including disulfides, hydrazones, peptides or thioethers. In some embodiments, the linker is a cleavable linker and the biologically active agent is released from the antibody upon antibody binding to the plasma membrane target protein. In some embodiments, the linker is a noncleavable linker.

In some embodiments, the antibody-drug conjugate comprises an antibody linked to a cytotoxic agent. In certain embodiments, any cytotoxic agent able to kill HCMV infected cells can be used. In some embodiments, the cytotoxic agent is MMAE, DM-1, a maytansinoid, a doxorubicin derivative, an auristatin, a calcheamicin, CC-1065, an aduocarmycin or an anthracycline.

In some embodiments, the antibody-drug conjugate comprises an antibody linked to an antiviral agent. In some embodiments, any antiviral agent capable of inhibiting HCMV replication is used. In some embodiments, the antiviral agent is ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

Nucleic Acid Molecules

Provided herein are nucleic acid molecules that encode the antibodies described herein. The nucleic acids may be present, for example, in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

Nucleic acid molecules provided herein can be obtained using standard molecular biology techniques. For example, nucleic acid molecules described herein can be cloned

using standard PCR techniques or chemically synthesized. For nucleic acids encoding antibodies expressed by hybridomas, cDNAs encoding the light and/or heavy chains of the antibody made by the hybridoma can be obtained by standard PCR amplification or cDNA cloning techniques. For antibodies obtained from an immunoglobulin gene library (*e.g.,* using phage or yeast display techniques), nucleic acid encoding the antibody can be recovered from the library.

Once DNA fragments encoding a V_H and V_L segments are obtained, these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a V_L- or V_H-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

The isolated DNA encoding the V_H region can be converted to a full-length heavy chain gene by operatively linking the V_H-encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see *e.g.,* Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region. For a Fab fragment heavy chain gene, the V_H-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the V_L-encoding DNA to another DNA molecule encoding the light chain constant region, C_L. The sequences of human light chain constant region genes are known in the art (see *e.g.,* Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain

constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region.

In certain embodiments, provided herein are vectors that contain the isolated nucleic acid molecules described herein. As used herein, the term "vector," refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.,* bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.,* non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby be replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").

In certain embodiments, provided herein are cells that contain a nucleic acid described herein (*e.g.,* a nucleic acid encoding an antibody, antigen binding fragment thereof or polypeptide described herein). The cell can be, for example, prokaryotic, eukaryotic, mammalian, avian, murine and/or human. In certain embodiments the cell is a hybridoma. In certain embodiments the nucleic acid provided herein is operably linked to a transcription control element such as a promoter. In some embodiments the cell transcribes the nucleic acid provided herein and thereby expresses an antibody, antigen binding fragment thereof or polypeptide described herein. The nucleic acid molecule can be integrated into the genome of the cell or it can be extrachromasomal.

Therapeutic Agents

In certain embodiments, provided herein are methods and compositions for treating HCMV by administering to a subject an agent that binds to a target protein provided herein (*e.g.,* a protein encoded by a gene listed in Tables 1-4). Agents which may be used to for the methods provided herein include antibodies (*e.g.,* an antibody described herein), proteins, peptides and small molecules.

In some embodiments, any agent that binds to a target protein provided herein can be used to practice the methods described herein. Such agents can be those described

herein, those known in the art, or those identified through routine screening assays (*e.g.* the screening assays described herein).

In some embodiments, assays used to identify agents useful in the methods described herein include a reaction between a target protein provided herein or fragment thereof and a test compound (*e.g.* the potential agent). Agents useful in the methods described herein may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Agents may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.,* Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of agents may be presented in solution (*e.g.,* Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al,* 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

Agents useful in the methods provided herein can be identified, for example, using assays for screening candidate or test compounds which are able to bind to a target protein provided herein or a fragment thereof. The basic principle of the assay systems used to identify compounds that bind to a target protein provided herein or fragment thereof

involves preparing a reaction mixture containing the target protein or fragment thereof and a test agent. The formation of any complexes between the target protein or fragment thereof and the test agent is then detected and test compounds that are able to specifically bind to the target protein or fragment thereof are identified as potential therapeutic agents. Such assays can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the target protein or the test compound onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested.

In a heterogeneous assay system, either the target protein or the test agent is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of target protein or test agent and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose.

In related assays, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates can be used. Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above.

A homogeneous assay may also be used to identify agents that bind to a target protein or fragment thereof. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and

immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993 Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.,* Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.,* 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.,* Ausubel *et al* (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.,* Ausubel *et al* (eds.), In: *Current Protocols in Molecular Biology*, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads.

Pharmaceutical Compositions

In certain embodiments provided herein is a composition, e.g., a pharmaceutical composition, containing at least one agent described herein (*e.g.,* an antibody described herein) formulated together with a pharmaceutically acceptable carrier. In one embodiment, the composition includes a combination of multiple (*e.g.,* two or more) agents provided herein.

The pharmaceutical compositions provided herein can be administered in combination therapy, *i.e.,* combined with other agents. For example, the pharmaceutical composition also include an anti-viral drug that inhibits HCMV replication, such as , ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

The pharmaceutical compositions provided herein may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; or (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation.

Methods of preparing these formulations or compositions include the step of bringing into association an agent described herein with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association an agent described herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Pharmaceutical compositions provided herein suitable for parenteral administration comprise one or more agents described herein in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions provided herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper

fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Regardless of the route of administration selected, agents provided herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the provided herein, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Therapeutic Methods

Disclosed herein are novel therapeutic methods of treatment or prevention of HCMV infection. In some embodiments, the methods provided herein comprise administering to a subject, (*e.g.,* a subject in need thereof), an effective amount of an agent (*e.g.,* an antibody) that binds to a target protein provided herein (*e.g.,* a protein encoded by a gene listed in Tables 1-4). The compositions provided herein may be delivered by any suitable route of administration.

In some embodiments, the subject is a subject is susceptible to HCMV infection. In some embodiments, the subject in need thereof is immunocompromised. In some embodiments, the subject is HIV-infected or has AIDS. In some embodiments, the subject is an organ transplant recipient. In some embodiments, the subject is a bone marrow transplant recipient. In some embodiments, the subject is a newborn infant or is pregnant. In some embodiments, the subject has multiple myeloma, chronic lymphoid leukemia. In some embodiments the subject has undergone chemotherapy. In some embodiments, the subject has undergone immunosuppressive therapy.

In some embodiments, the agents provided herein can be administered in combination therapy, *i.e.,* combined with other agents. For example, an agent provided herein can be administered as part of a conjunctive therapy in combination with an anti-viral drug that inhibits HCMV replication, such as , ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

Conjunctive therapy includes sequential, simultaneous and separate, and/or co-administration of the active compounds in a such a way that the therapeutic effects of the first agent administered have not entirely disappeared when the subsequent agent is administered. In certain embodiments, the second agent may be co-formulated with the first agent or be formulated in a separate pharmaceutical composition.

Actual dosage levels of the active ingredients in the pharmaceutical compositions provided herein may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular agent employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could prescribe and/or administer doses of the compounds provided herein employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

EXAMPLES

The invention now being generally described will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

Experimental Procedures

Cells and Viruses

Primary human fetal foreskin fibroblast cells (HFFF) were grown in Dulbecco's modified eagles medium (DMEM) (Life Technologies) supplemented with fetal bovine serum (10% v/v), penicillin/streptomycin and L-glutamine (Gibco) at 37°C in 5% CO2. Cells were verified to be mycoplasma negative.

The HCMV strain Merlin is designated the reference HCMV genome sequence by the National Center for Biotechnology Information and was sequenced after only 3 passages in vitro. A BAC clone containing the complete Merlin genome was constructed to provide a reproducible source of genetically intact, clonal virus for pathogenesis studies (Stanton *et al., J. Clin. Invest.* 120:3191-3208 (2010), hereby incorporated by reference).

Merlin BAC derived clone RCMV1111 used herein contains point mutations in RL13 and UL128, enhancing replication in fibroblasts.

Virus Infection

Twenty-four hours prior to each infection, 1.5 x 10^7 HFFFs were plated in a 150cm^2 flask. Cells were sequentially infected at multiplicity of infection 10 with HCMV strain Merlin. Infections were staggered such that all flasks were harvested simultaneously.

Plasma Membrane Profiling (PMP)

PMP was performed as described in Weekes *et al., J. Proteome. Res.* 11:1475-1480 (2012) and Weekes *et al., J. Biomol. Tech.* 21:108-115 (2010), each of which is incorporated by reference in its entirety, with minor modifications for adherent cells. Briefly, one 150 cm^2 flask of HCMV-infected HFFFs per condition was washed twice with ice-cold PBS. Sialic acid residues were oxidized with sodium meta-periodate (Thermo) then biotinylated with aminooxy-biotin (Biotium). The reaction was quenched, and the biotinylated cells scraped into 1% Triton X-100 lysis buffer. Biotinylated glycoproteins were enriched with high affinity streptavidin agarose beads (Pierce) and washed extensively. Captured protein was denatured with DTT, alkylated with iodoacetamide (IAA, Sigma) and digested on-bead with trypsin (Promega) in 100 mM HEPES pH 8.5 for 3 hours. Tryptic peptides were then collected.

Preparation of Whole Proteome Samples

Cells were washed twice with PBS, and 1 ml lysis buffer added (experiment 1: 8M Urea/100mM HEPES pH8.5, experiment 2: 6M Guanidine/50mM HEPES pH8.5). Cell lifters (Corning) were used to scrape cells in lysis buffer, which was removed to an eppendorf tube, vortexed extensively then sonicated. Cell debris was removed by centrifugation. Dithiothreitol (DTT) was added to a final concentration of 5 mM and samples were incubated for 20 minutes. Cysteines were alkylated by exposure to 15 mM iodoacetamide for 20 minutes in the dark. Excess iodoacetamide was quenched with DTT for 15 minutes. Samples were diluted with 100mM HEPES pH 8.5 to 4M Urea or 1.5M Guanidine followed by digestion at room temperature for 3 hours with LysC protease at a 1:100 protease-to-protein ratio. In some experiments, trypsin was then added at a 1:100 protease-to-protein ratio followed by overnight incubation at 37 °C. The reaction was quenched with 1 % formic acid, subjected to C18 solid-phase extraction (Sep-Pak, Waters) and vacuum-centrifuged to near-dryness.

Peptide Labeling with Tandem Mass Tags (TMT)

In preparation for TMT labeling, desalted peptides were dissolved in 100 mM HEPES pH 8.5. For whole proteome samples, peptide concentration was measured by microBCA (Pierce), and 100µg of peptide labeled with TMT reagent. For plasma membrane samples, 100% of each peptide sample was labeled.

TMT reagents (0.8 mg) were dissolved in 40 µL anhydrous acetonitrile and 10 µL (whole proteome) or 2.5µl (PM samples) added to peptide at a final acetonitrile concentration of 30% (v/v). For experiments PM1 and WCL1 (described below), samples were labeled as follows: mock replicate 1 (TMT 126); mock replicate 2 (TMT 128); 24 hour infection replicate 1 (TMT 127n); 24 hour infection replicate 2 (TMT 127c); 48 hour infection replicate 1 (TMT 129n); 48h infection replicate 2 (TMT 129c); 72h infection replicate 1 (TMT 130); 72 hour infection replicate 2 (TMT 131). Following incubation at room temperature for 1 hour, the reaction was quenched with hydroxylamine to a final concentration of 0.3% (v/v). TMT-labeled samples were combined at a 1:1:1:1:1:1:1:1 ratio (8-plex TMT) or 1:1:1:1:1:1:1:1:1:1 ratio (10-plex TMT). The sample was vacuum-centrifuged to near dryness and subjected to C18 solid-phase extraction (SPE) (Sep-Pak, Waters).

Offline High pH Reversed-Phase (HPRP) Fractionation

TMT-labeled peptide samples were fractionated using an Agilent 300Extend C18 column (5 µm particles, 4.6 mm ID, 220mm length) and an Agilent 1100 quaternary pump equipped with a degasser and a photodiode array detector (220 and 280nm, ThermoFisher, Waltham, MA). Peptides were separated with a gradient of 5% to 35% acetonitrile in 10mM ammonium bicarbonate pH 8 over 60 min. 96 resulting fractions were consolidated into 12, acidified to 1% formic acid and vacuum-centrifuged to near dryness. Each fraction was desalted using a StageTip, dried, and reconstituted in 4% acetonitrile / 5% formic acid prior to LC-MS/MS.

Offline Tip-Based Strong Cation Exchange (SCX) Fractionation

The protocol for solid-phase extraction based SCX peptide fractionation described in Dephoure and Gygi, *Methods* 54:379-386 (2011), incorporated by reference in its entirety, was modified for small peptide amounts. Briefly, 10 mg of PolySulfoethyl A bulk material (Nest Group Inc) was loaded into a fritted 200 ul tip in 100% Methanol using a vacuum manifold. SCX material was conditioned slowly with 1 ml SCX buffer A (7 mM KH_2PO_4, pH 2.65, 30% Acetonitrile), then 0.5 ml SCX buffer B (7 mM KH_2PO_4, pH 2.65, 350 mM KCl, 30% Acetonitrile) then 2 ml SCX buffer A. Dried peptides were resuspended

in 500 µl SCX buffer A and added to the tip at a flow rate of ~150 µl/min, followed by a 150 µl wash with SCX buffer A. Fractions were eluted in 150 ul buffer at increasing K^+ concentrations (10, 24, 40, 60, 90, 150 mM KCl), vacuum-centrifuged to near dryness then desalted using Stage Tips.

Liquid Chromatography and Tandem Mass Spectrometry

Mass spectrometry data was acquired using an Orbitrap Elite mass spectrometer (Thermo Fisher Scientific, San Jose, CA) coupled with a Proxeon EASY-nLC II liquid chromatography (LC) pump (Thermo Fisher Scientific). Peptides were separated on a 100 µm inner diameter microcapillary column packed with 0.5 cm of Magic C4 resin (5 µm, 100 Å, Michrom Bioresources) followed by ~20 cm of Maccel C18 resin (3 µm, 200 Å, Nest Group).

Peptides were separated using a 3 hour gradient of 6% to 30% acetonitrile in 0.125% formic acid at a flow rate of 300 nL/min. Each analysis used an MS3-based TMT method. The scan sequence began with an MS1 spectrum (Orbitrap analysis, resolution 60,000, 300−1500 Th, AGC target 1×10^6, maximum injection time 150 ms). The top ten precursors were then selected for MS2/MS3 analysis. MS2 analysis consisted of CID (quadrupole ion trap analysis, AGC 2×10^3, NCE 35, q-value 0.25, maximum injection time 100 ms). Following acquisition of each MS2 spectrum, we collected an MS3 spectrum using our recently described method in which multiple MS2 fragment ions are captured in the MS3 precursor population using isolation waveforms with multiple frequency notches. MS3 precursors were fragmented by HCD and analyzed using the Orbitrap (NCE 50, max AGC 1.5×10^5, maximum injection time 250 ms, isolation specificity 0.8 Th, resolution was 30,000 at 400 Th).

Data analysis

Mass spectra were processed using a Sequest-based software pipeline. MS spectra were converted to mzXML using a modified version of ReAdW.exe. A combined database was constructed from (a) the human Uniprot database (August 10, 2011), (b) the human cytomegalovirus (strain Merlin) Uniprot database, (c) all additional novel human cytomegalovirus ORFs described in Stern-Ginossar *et al., Science* 338:1088-1093 (2012), hereby incorporated by reference, and (d) common contaminants such as porcine trypsin and endoproteinase LysC. The combined database was concatenated with a reverse database composed of all protein sequences in reversed order. Searches were performed using a 20 ppm precursor ion tolerance. Product ion tolerance was set to 0.03 Th. TMT tags

on lysine residues and peptide N termini (229.162932 Da) and carbamidomethylation of cysteine residues (57.02146 Da) were set as static modifications, while oxidation of methionine residues (15.99492 Da) was set as a variable modification.

Peptide spectral matches (PSMs) were filtered to an initial peptide-level FDR of 1% with subsequent filtering to attain a final protein-level FDR of 1%. PSM filtering was performed using a linear discriminant analysis, considering the following parameters: XCorr, ΔCn, missed cleavages, peptide length, charge state, and precursor mass accuracy. Protein assembly was guided by principles of parsimony to produce the smallest set of proteins necessary to account for all observed peptides. Where all PSMs from a given HCMV protein could be explained either by a canonical gene or novel ORF, the canonical gene was picked in preference.

For TMT-based reporter ion quantitation, we extracted the signal-to-noise (S/N) ratio for each TMT channel and found the closest matching centroid to the expected mass of the TMT reporter ion. Proteins were quantified by summing reporter ion counts across all matching peptide-spectral matches using in-house software. Briefly, a 0.003 Th window around the theoretical m/z of each reporter ion (126, 127n, 127c, 128n, 128c, 129n, 129c, 130n, 130c, 131) was scanned for ions, and the maximum intensity nearest to the theoretical m/z was used. Peptide-spectral matches with poor quality MS3 spectra (more than 9 TMT channels missing and/or a combined S/N of less than 100 across all TMT reporter ions) or no MS3 spectra at all were excluded from quantitation. All MS2 and MS3 spectra from novel ORFs were all manually validated to confirm both identifications and quantifications. Protein quantitation values were exported for further analysis in Excel.

For protein quantitation, reverse and contaminant proteins were removed, then each reporter ion channel was summed across all quantified proteins and normalized assuming equal protein loading across all 8 or 10 samples. Gene Ontology and KEGG terms were added using Perseus version 1.4.1.3. Gene name aliases were added using GeneALaCart (www.genecards.org). The one-way ANOVA test was used to identify proteins differentially expressed over time in experiments PM1 and WCL1, and was corrected using the method of Benjamini-Hochberg to control for multiple testing error (Benjamini and Hochberg, *J. R. Stat. Soc. Ser. B-Methodol.* 57:289-300 (1995), hereby incorporated by reference. A Benjamini-Hochberg-corrected p-value < 0.05 was considered statistically significant. Values were calculated using Mathematica (Wolfram Research). Other statistical analyses including Principal Component analysis and k-means clustering were

performed using XLStat (Addinsoft). Hierarchical centroid clustering based on uncentered Pearson correlation was performed using Cluster 3.0 (Stanford University) and visualized using Java Treeview (http://jtreeview.sourceforge.net) unless otherwise noted. For RNAseq data from Stern-Ginnosar et al, mRNA reads densities from 5, 24 and 72h for each transcript were normalized to 1, and hierarchical clustering based on Euclidian distance was performed using Cluster 3.0.

Example 1. Validation of Quantitative Temporal Viromics (QTV)

Primary human fetal foreskin fibroblasts (HFFF) were infected with the clinical HCMV strain Merlin as described above and plasma membrane profiling (PMP) was used to measure changes in plasma membrane receptor expression. Initially, 8-plex TMT were used to assess in biological duplicate three of the key time points in productive HCMV infection and mock infection (experiment PM1, Figure 1). In total, 927 PM proteins were quantified. Among the proteins quantified, the cell surface expression level of 56% of the proteins changed by more than 2 fold, and 33% by more than 3-fold at 72 hours after infection. Replicate experiments clustered tightly.

HCMV protein UL138 degrades the cell surface ABC transporter Multidrug Resistance-associated Protein-1 (ABCC1) in both productive and latent infection, and ABCC1-specific cytotoxic substrate Vincristine can be used therapeutically to eliminate cells latently infected with HCMV (Weekes *et al., Science* 340:199-202 (2013), hereby incorporated by reference in its entirety).

To validate the PMP procedure, all quantified ABC transporters were examined, and selective ABCC1 downregulation was confirmed (Figure 2). Multidrug Resistance-associated Protein 3 (ABCC3) was downregulated with very similar kinetics, indicating that this drug transporter represents an additional therapeutic target. To identify additional therapeutic targets, changes the cell surface expression of other transporters were also examined. As with ABCC1 and ABCC3, sodium-coupled neutral amino acid transporter 4 (SLC38A4) and solute carrier family 2, facilitated glucose transporter member 10 (SLC2A10) were also downregulated, providing additional therapeutic targets.

The instant methodology was further validated by the detection of the upregulation of all six HCMV proteins previously reported as being present at the plasma membrane of HCMV infected cells (Figure 3).

Temporal analysis of whole cell lysates (WCLs) of HCMV-infected HFFFs enables the study of changes in expression of intracellular proteins during infection and a

comparison of the total abundance of a given protein to its expression at the plasma membrane. Analyzing HFFF infected with PMP samples revealed a high degree of reproducibility amongst biological replicates (WCL1, Figure 4).

Example 2. Cell Surface Receptors Modulated by HCMV

The QTV procedure described above was used to follow the cell surface expression of endogenous proteins following HCMV infection. Data generated using the QTV procedure was analyzed to identify cell-surface proteins that were rapidly upregulated on the surface of HCMV infected cells but not on the surface of mock-infected cells (Figure 5). Due to their early and selective expression on HCMV infected cells, the proteins listed in Figure 5 can be used to selectively identify HCMV infected cells soon after viral infection and are attractive targets for novel HCMV therapeutics.

A number of NK cell ligands were identified as having altered plasma membrane expression following HCMV infection (Figure 6). For example, E-cadherin (CDH1), the ligand for the inhibitory NK receptor KLRG-1 (killer cell lectin-like receptor subfamily G member 1) was dramatically upregulated during infection (Figure 6A). Vascular cell adhesion molecule 1 (VCAM1) and B7H6, ligands for activating NK receptors $\alpha 4\beta 1$ integrin and NKp30 were downregulated during viral infection (Figure 6A).

A similar screen was performed for all known $\alpha\beta$ T-cell costimulatory molecules, and $\gamma\delta$ T-cell ligands. The T-cell costimulators ICOSLG (inducible T-cell co-stimulator ligand) and PD-L2 (PDCD1LG2) were downregulated during infection, as was butyrophilin subfamily 3 member A1 (BTN3A1), which is recognized by $V\gamma 9V\delta 2+$ T-cells. V-domain Ig suppressor of T cell activation (VISTA, C10Orf54), a novel B7 family inhibitory ligand was upregulated late in infection (Figure 6B).

Known NK and T-cell ligands generally belong to a small number of protein families, including Cadherins, C-type lectins, Immunoglobulin, TNF and major histocompatibility complex (MHC)-related molecules. To discover novel ligands, InterPro functional domain annotations were added to data from experiments PM1 and PM2. Analysis of the resulting data identified 74 proteins that had relevant InterPro annotation and at least a 4-fold change in cell surface expression following infection (Figure 7). Eight downregulated proteins were protocadherins, and all six quantified γ-protocadherins were potently downregulated (Figure 6C). The protocadherins therefore represent a major class of immunoreceptors.

There is increasing evidence for a substantial role of plexin-semaphorin signaling in the immune system. For example, secreted class III semapohrins bind plexins A and D1 to regulate migration of dendritic cells to secondary lymphoid organs. Plexin B2 interacts with membrane-bound semaphorin 4D to promote epidermal γδ T-cell activation. HCMV substantially downregulated five of the nine plexins, A1, A3, B1, B2 and D1. Neuropilin 2, a plexin co-receptor was also rapidly downregulated. Semaphorin 4D was dramatically upregulated and 4C downregulated (Figure 7).

DAVID software was used to determine which functional protein categories were enriched within highly downregulated PM proteins. The Interpro categories 'protocadherin gamma' and 'immunoglobulin-like fold' were significantly enriched in addition to Gene Ontology (GO) biological processes 'regulation of leukocyte activation' and 'positive regulation of cell motion'. DAVID analysis also revealed novel families of downregulated proteins, including six rhodopsin-like superfamily G-protein coupled receptors (Figure 8).

Example 3. Temporal Analysis of HCMV Viral Protein Expression

Using the methods described herein above, the changes in the expression of the majority (136/171) of canonical HCMV proteins and 9 novel ORFs was quantified in one experiment (Figures 9, 10).

The k-means method is useful to cluster viral proteins into classes based on the similarity of temporal profiles, and it is possible to specify the number of classes to be considered. With 4 classes, proteins grouped according to the temporal cascade of α, β, γ1, γ2 (Figure 9A). To determine how many true classes of HCMV genes actually exist, k-means clustering was performed with 2 – 14 classes and the summed distance of each protein from its cluster centroid was assessed. The point of inflexion fell between 5-7 classes, suggesting that there are at least 5 distinct profiles of viral protein expression (Figure 9B).

A cluster of 13 early-late proteins referred to herein as γ1b exhibited a distinct profile to other γ1a early-late proteins, (Figures 9C-D), with maximal expression at 48h and low expression at other time points. Members of this cluster predominantly originated from two regions of the viral genome, and four belonged to the RL11 family (Figure 11).

Eight HCMV proteins are expressed earlier in infection than had previously been supposed. UL27, UL29, UL135, UL138, US2, US11, US23 and US24 all exhibited peak expression at between 6-18 hours post infection. UL29 and US24 appeared particularly early, with peak expression at only 6 hours post infection.

The immediate early gene IE2 (UL122, γ2) demonstrated very little protein expression prior to 48h. UL122 and UL123 are encoded by alternative splicing of a single major immediate-early transcript. Exons 1,2,3 and 4 encode UL123 and exons 1,2,3 and 5 encode UL122 and additional transcripts have also been detected from the region of exon 5. Each peptide quantified from every exon was identified (Figure 10). The expression of all peptides from exon 4 peaked at 18-24h, corresponding to the predicted expression of UL123 protein. Ten exon 5 peptides corresponding to the internal ORF, ORFL265C.iORF1 were maximally expressed at 96h, whereas a single peptide N-terminal to this ORF had a distinct profile with earlier expression. This indicates the existence of at least two proteins arising wholly or in part from exon 5, and corresponds to the known late expression of ORFL265C.iORF1 transcript.

Nine novel ORFs belonging to α, β, γ1b or γ2 classes were identified (Figure 9C). Four ORFs related to canonical HCMV proteins (N-terminal extension, internal ORF, C-terminal extension) and demonstrated similar temporal profiles to their canonical counterparts (Figure 12). Five ORFs were non-canonical, encoded either in different reading frames, or on the opposite strand to canonical genes (Figure 13).

Example 4. HCMV Proteins Present at the Cell Surface

Viral proteins identified herein as present at the surface of infected cells are therapeutic targets. The majority of studies that have examined cell surface location of HCMV proteins have employed transduction of single viral genes, as opposed to productive infection. Only 6 HCMV proteins have been demonstrated at the PM of infected fibroblasts, all appearing late in infection, results that we confirmed (Figure 3). A total of 67 viral proteins were detected in experiments PM1 and PM2. Subcellular localization of these proteins is poorly annotated, making it difficult to determine which may be non-PM contaminants, for example abundant viral tegument and nuclear proteins. A filtering strategy was used to screen out such contaminants: for every human Gene Ontology (GO)-annotated protein quantified in experiment PM1 or PM2, the ratio of peptides (PM1+PM2)/(WCL1+WCL2) was calculated. More than 90% of proteins without a PM GO annotation had a ratio of <1.4 (Figure 15A). Applying this filter, 29 high confidence viral PM proteins were defined, which included the majority of viral proteins previously identified at the surface of either infected or transduced cells, and excluded all proteins unlikely to be present at the cell surface based on their known function (Figure 14).

The high confidence viral PM proteins were assessed based on the following characteristics: (a) presence early in infection; (b) presence throughout the course of infection; and (c) sufficient abundance to distinguish infected from uninfected cells. Among the high confidence viral PM proteins, UL141, US9, US28, UL16, US6, UL78, US20, UL40 and UL136 best fit this criteria (Figure 17).

In general, a striking correlation between the PM2 and WCL2 temporal profiles of all 29 high confidence proteins was observed. For the subset of known virion envelope glycoproteins, protein appearance at the PM was significantly delayed compared to the WCL, confirmed by analysis of the same proteins from experiments PM1 and WCL1 (Figures 15B, 16). PM appearance of UL119 and RL10 was also delayed (Figure 15B).

Example 5. HCMV Seropositive Serum Induces Antibody-Dependent Cytotoxicity

It was investigated whether serum from HCMV seropositive individuals induced antibody-dependent cytotoxicity (antibody-mediated lysis of virally-infected targets by NK cells). Fibroblasts were infected with HCMV strain Merlin. After 48 or 72 hours, NK cells and serum from HCMV seropositive or seronegative donors was added to the infected fibroblasts and the level of NK degranulation assessed in a CD107a assay. As seen in Figure 18, NK cells showed approximately double the response to infected cells in the presence of seropositive serum, compared to seronegative serum, at both 48 and 72 hours post-infection. NK cells showed equal responses to Mock infected cells in the presence of both serums. This data indicates that the addition of serum from HCMV seropositive individuals (but not serum from seronegative individuals) induces antibody-dependent cellular cytotoxicity, supporting the use of therapeutic antibodies for the treatment of HCMV infection.

All publications, patents, patent applications and sequence accession numbers mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method of treating HCMV in a subject comprising administering to the subject an agent that specifically binds to a protein encoded by a gene selected from the genes listed in Table 1.

2. The method of claim 1, wherein the protein is encoded by a gene selected from the genes listed in Table 2.

3. The method of claim 1 or 2, wherein the agent is an antibody.

4. The method of claim 3, wherein the antibody is monoclonal.

5. The method of claim 3, wherein the antibody is chimeric, humanized or fully human.

6. The method of claim 3, wherein the antibody is selected from the group consisting of:

a full length immunoglobulin molecule;

an scFv;

a Fab fragment;

an Fab' fragment;

an F(ab')2;

an Fv;

a NANOBODY®; and

a disulfide linked Fv.

7. The method of claim 3, wherein the antibody binds to the protein with a dissociation constant of no greater than about 10^{-7} M.

8. The method of claim 3, wherein the antibody binds to an extracellular epitope of the protein.

9. The method of claim 8, wherein the epitope is selected from the epitopes listed in Table 5.

10. The method of claim 3, wherein the antibody is linked to a cytotoxic agent.

11. The method of claim 10, wherein the cytotoxic agent is selected from the group consisting of MMAE, DM-1, maytansinoids, doxorubicin derivatives, auristatins, calcheamicin, CC-1065, duocarmycins and anthracyclines.

12. The method of claim 3, wherein the antibody is linked to an antiviral agent.

13. The method of claim 12, wherein the antiviral agent is ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

14. An antibody that specifically binds to an extracellular epitope of a protein encoded by a gene selected from the genes listed in Table 1.

15. The antibody of claim 14, wherein the protein is encoded by a gene selected from the genes listed in Table 2

16. The antibody of claim 14, wherein the epitope is selected from the epitopes listed in Table 5.

17. The antibody of claim 14, 15 or 16, wherein the antibody is monoclonal.

18. The antibody of claim 14, 15 or 16, wherein the antibody is chimeric, humanized or fully human.

19. The antibody of claim 14, 15 or 16, wherein the antibody is selected from the group consisting of:

a full length immunoglobulin molecule;

an scFv;

a Fab fragment;

an Fab' fragment;

an F(ab')2;

an Fv;

a NANOBODY®; and

a disulfide linked Fv.

20. The antibody of claim 14, 15 or 16, wherein the antibody binds to the target protein with a dissociation constant of no greater than about 10^{-7} M.

21. The antibody claim 14, 15 or 16, wherein the antibody is linked to a cytotoxic agent.

22. The antibody claim 21, wherein the cytotoxic agent is selected from the group consisting of MMAE, DM-1, maytansinoids, doxorubicin derivatives, auristatins, calcheamicin, CC-1065, duocarmycins and anthracyclines.

23. The antibody 14, 15 or 16, wherein the antibody is linked to an antiviral agent.

24. The antibody of claim 23, wherein the antiviral agent is ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

25. A method of treating HCMV in a subject comprising administering to the subject an agent that specifically binds to a protein encoded by a group consisting of the genes listed in Table 3.

26. The method of claim 25, wherein the protein is encoded by a gene selected from the group consisting of CHST11, KCNK1, SPINT1, CDH1, CEACAM1, EPCAM, TNFRSF1B, ERBB3, CNTFR, PCDH1, BST2, SDK2, RALGPS2, SLCO4A1, MEGF10, SEMA4D, PCDH1, SPINT1 and TTC17.

27. The method of claim 24 or 25, wherein the agent is an antibody.

28. The method of claim 27, wherein the antibody is monoclonal.

29. The method of claim 27, wherein the antibody is chimeric, humanized or fully human.

30. The method of claim 27, wherein the antibody is selected from the group consisting of:

a full length immunoglobulin molecule;

an scFv;

a Fab fragment;

an Fab' fragment;

an F(ab')2;

an Fv;

a NANOBODY®; and

a disulfide linked Fv.

31. The method of claim 27, wherein the antibody binds to the protein with a dissociation constant of no greater than about 10^{-7} M.

32. The method of claim 27, wherein the antibody binds to an extracellular epitope of the protein.

33. The method of claim 27, wherein the antibody is linked to a cytotoxic agent.

34. The method of claim 33, wherein the cytotoxic agent is selected from the group consisting of MMAE, DM-1, maytansinoids, doxorubicin derivatives, auristatins, calcheamicin, CC-1065, duocarmycins and anthracyclines.

35. The method of claim 27, wherein the antibody is linked to an antiviral agent.

36. The method of claim 35, wherein the antiviral agent is ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

37. An antibody that specifically binds to an extracellular epitope of a protein encoded by a group consisting of the genes listed in Table 3.

38. The antibody of claim 37, wherein the protein is encoded by a gene selected from the group consisting of CHST11, KCNK1, SPINT1, CDH1, CEACAM1, EPCAM, TNFRSF1B, ERBB3, CNTFR, PCDH1, BST2, SDK2, RALGPS2, SLCO4A1, MEGF10, SEMA4D, PCDH1, SPINT1 and TTC17.

39. The antibody of claim 37 or 38, wherein the antibody is monoclonal.

40. The antibody of claim 39, wherein the antibody is chimeric, humanized or fully human.

41. The antibody of claim 39, wherein the antibody is selected from the group consisting of:

a full length immunoglobulin molecule;

an scFv;

a Fab fragment;

an Fab' fragment;

an F(ab')2;

an Fv;

a NANOBODY®; and

a disulfide linked Fv.

42. The antibody of claim 39, wherein the antibody binds to the target protein with a dissociation constant of no greater than about 10^{-7} M.

43. The antibody claim 39, wherein the antibody is linked to a cytotoxic agent.

44. The antibody claim 43, wherein the cytotoxic agent is selected from the group consisting of MMAE, DM-1, maytansinoids, doxorubicin derivatives, auristatins, calcheamicin, CC-1065, duocarmycins and anthracyclines.

45. The antibody 39, wherein the antibody is linked to an antiviral agent.

46. The antibody of claim 45, wherein the antiviral agent is ganciclovir, valganciclovir, foscarnet, cidofovir, acyclovir, formivirsen, maribavir, BAY 38-4766 or GW275175X.

47. A method of treating HCMV in a subject comprising administering to the subject a cytotoxic agent to which a protein encoded by ABCC3, SLC38A4 or SLC2A10 provides cellular resistance.

48. The method of claim 47, wherein the protein is encoded by ABCC3.

49. The method of claim 48, wherein the cytotoxic agent is Etoposide.

50. The method of claim 47, wherein the protein is encoded by SLC38A4.

51. The method of claim 47, wherein the protein is encoded by SLC2A10.

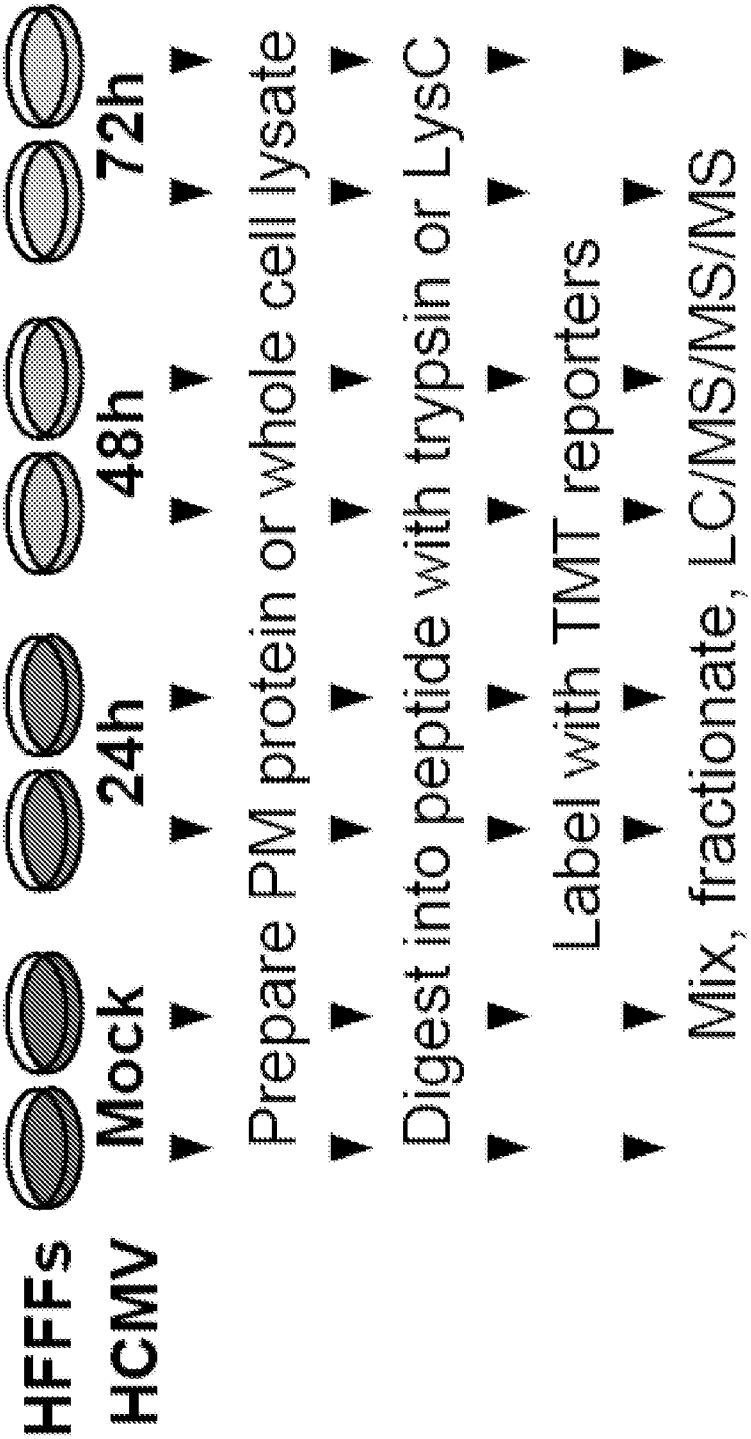

HFFFs
HCMV
Mock
24h
48h
72h
Prepare PM protein or whole cell lysate
Digest into peptide with trypsin or LysC
Label with TMT reporters
Mix, fractionate, LC/MS/MS

Figure 1

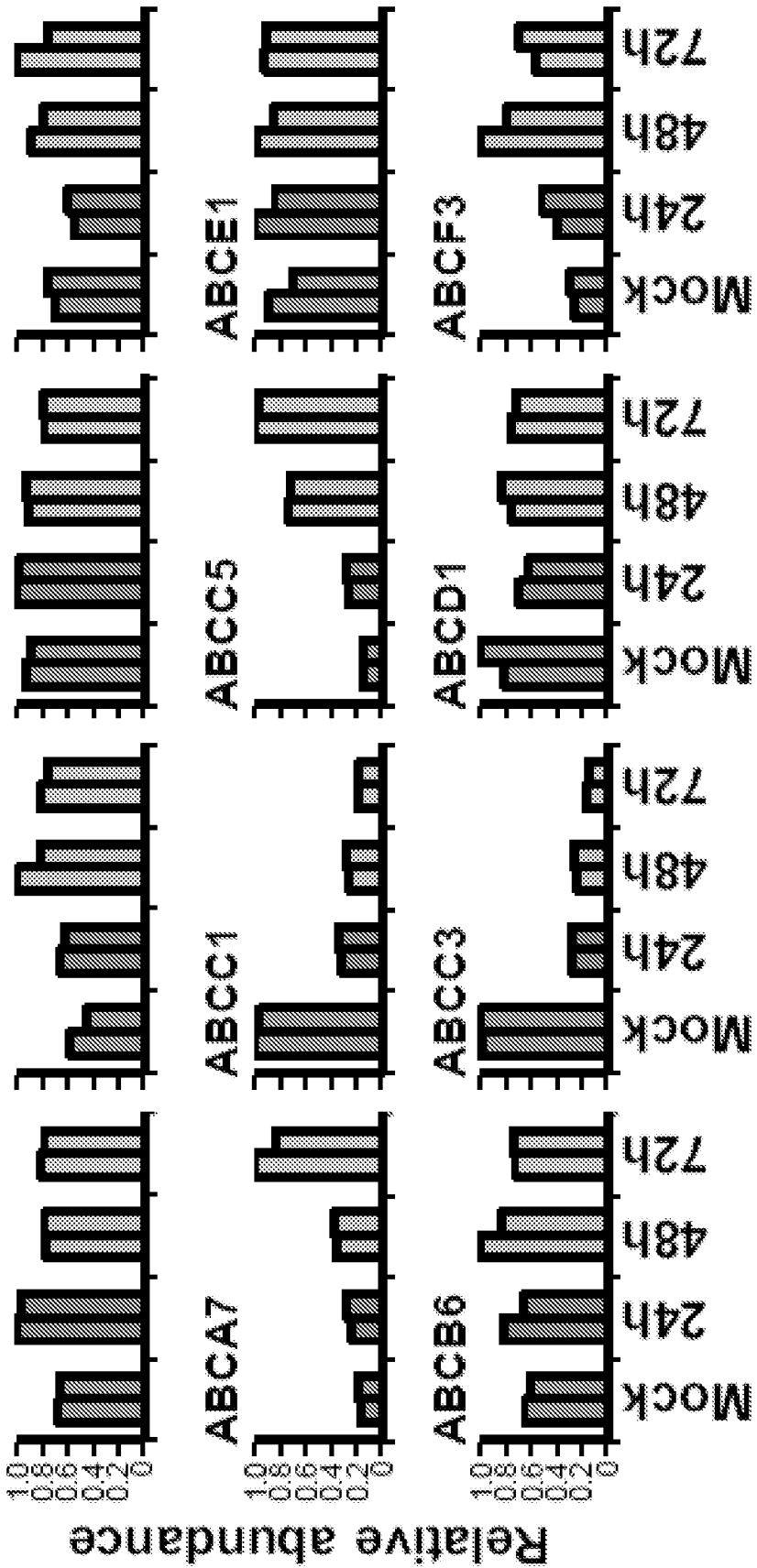

Relative abundance
ABCA1
ABCB7
ABCC4
ABCD3
ABCA7
ABCC1
ABCC5
ABCE1
ABCB6
ABCC3
ABCD1
ABCF3
Mock
24h
48h
72h

Figure 2


Relative abundance
100000
80000
60000
40000
20000
0
UL55 (gB)**
UL74 (gO)**
UL75 (gH)**
UL115 (gL)*
UL132**
UL11**
Mock
24h
48h
72h

Figure 3

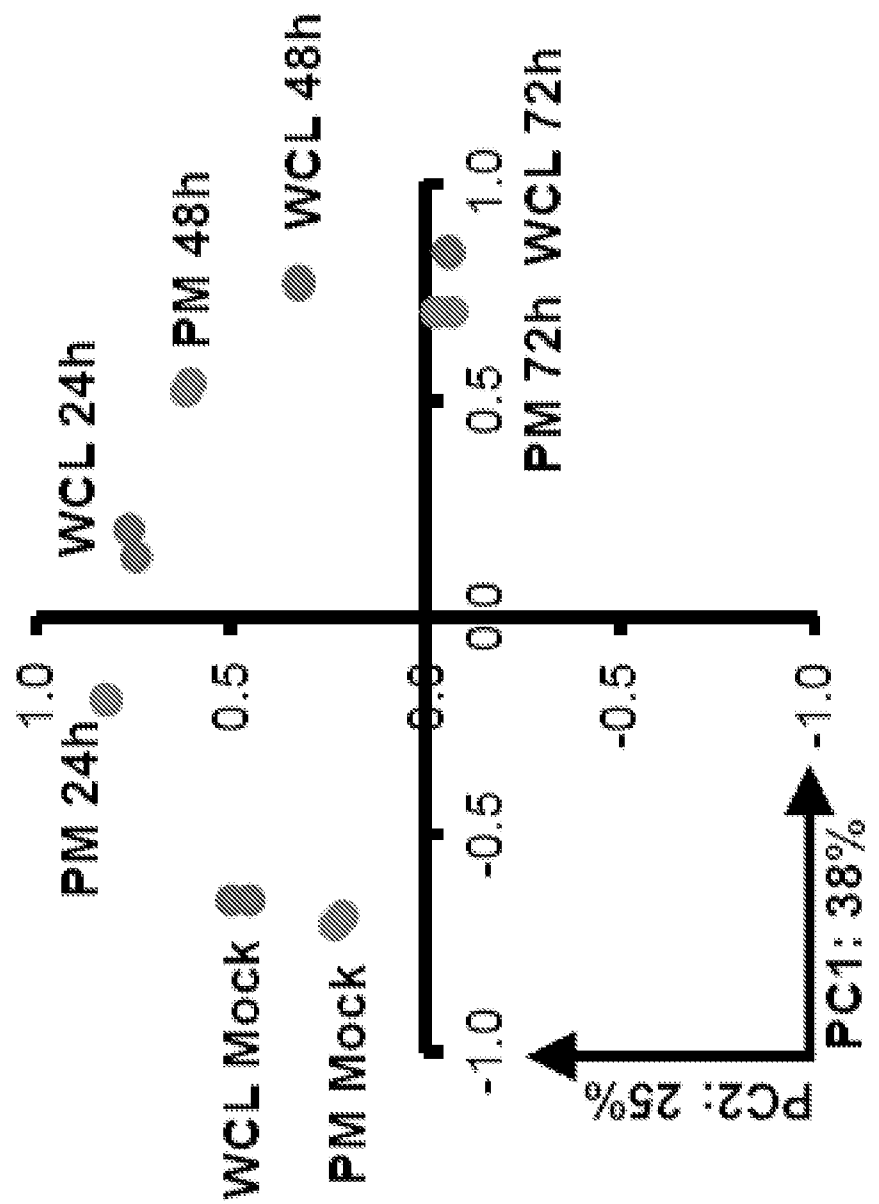

WCL 24h
PM 48h
WCL 48h
PM 72h
WCL 72h
PM 24h
WCL Mock
PM Mock
1.0
0.5
0.0
-0.5
-1.0
PC1: 38%
PC2: 25%

Figure 4

Figure 5

Gene Symbol	Uniprot	GI Number	Protein name
CHST11	Q9NPF2	61212137	Carbohydrate sulfotransferase 11
KCNK1	O00180	13124036	Potassium channel subfamily K member 1
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
CDH1	P12830	399166	Cadherin-1
CEACAM1	P13688	399116	Carcinoembryonic antigen-related cell adhesion molecule 1
EPCAM	P16422	160266056	Epithelial cell adhesion molecule
TNFRSF1B	P20333	21264534	Tumor necrosis factor receptor superfamily member 1B
ERBB3	P21860	119534	Receptor tyrosine-protein kinase erbB-3
CNTFR	P26992	1352099	Ciliary neurotrophic factor receptor subunit alpha
PCDH1	Q08174	215273864	Protocadherin-1
BST2	Q10589	1705508	Bone marrow stromal antigen 2
SDK2	Q58EX2	296452966	Protein sidekick-2
RALGPS2	Q86X27	74750518	Ras-specific guanine nucleotide-releasing factor RalGPS2
SLCO4A1	Q96BD0	27734555	Solute carrier organic anion transporter family member 4A1
MEGF10	Q96KG7	74716908	Multiple epidermal growth factor-like domains protein 10
SEMA4D	Q92854	8134701	Semaphorin-4D
PCDH1	Q08174	215273864	Protocadherin-1
SPINT1	O43278	61252335	Kunitz-type protease inhibitor 1
TTC17	Q96AE7	52783467	Tetratricopeptide repeat protein 17
MFSD2A	Q8NA29	74751132	Major facilitator superfamily domain-containing protein 2A
DNAH1	Q9P2D7	327478598	Dynein heavy chain 1, axonemal
GFRA2	O00451	118582303	GDNF family receptor alpha-2
P2RY2	P41231	311033490	P2Y purinoceptor 2

Figure 5 (Continued)

Gene Symbol	Uniprot	GI Number	Protein name
TYRO3	Q06418	1717829	Tyrosine-protein kinase receptor TYRO3
TSPAN18	Q96SJ8	68053316	Tetraspanin-18
SLC38A3	Q99624	52783419	Sodium-coupled neutral amino acid transporter 3
CADM1	Q9BY67	150438862	Cell adhesion molecule 1
RTN4R	Q9BZR6	25453267	Reticulon-4 receptor
SLC39A8	Q9C0K1	74733496	Zinc transporter ZIP8
NPDC1	Q9NQX5	22261810	Neural proliferation differentiation and control protein 1
CACNA2D2	Q9NY47	387912827	Voltage-dependent calcium channel subunit alpha-2/delta-2
PODXL2	Q9NZ53	74734719	Podocalyxin-like protein 2
NPC1L1	Q9UHC9	425906049	Niemann-Pick C1-like protein 1
SLC7A8	Q9UHI5	12643348	Large neutral amino acids transporter small subunit 2
LIFR	P42702	1170784	Leukemia inhibitory factor receptor
NCAM1	P13591	205830665	Neural cell adhesion molecule 1
MMP15	P51511	1705988	Matrix metalloproteinase-15
NGFR	P08138	128156	Tumor necrosis factor receptor superfamily member 16
SCARB1	Q8WTV0	37999904	Scavenger receptor class B member 1
CD55	P08174	60416353	Complement decay-accelerating factor
GPR108	Q9NPR9	296439338	Protein GPR108
HLA-E	P13747	34395942	HLA class I histocompatibility antigen, alpha chain E
F11R	Q9Y624	10720061	Junctional adhesion molecule A
GPR56	Q9Y653	45476992	G-protein coupled receptor 56
ERO1LB	Q86YB8	116241353	ERO1-like protein beta
B3GNT9	Q6UX72	74738184	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 9
ERO1L	Q96HE7	50400608	ERO1-like protein alpha
SREK1	Q8WXA9	37537968	Splicing regulatory glutamine/lysine-rich protein 1

Figure 5 (Continued)

Gene Symbol	Uniprot	GI Number	Protein name
IQGAP2	Q13576	37537968	Ras GTPase-activating-like protein IQGAP2
TSPAN13	O95857	11135162	Tetraspanin-13
PRICKLE2	Q7Z3G6	85701877	Prickle-like protein 2
ABCA3	Q99758	85700402	ATP-binding cassette sub-family A member 3
SLC27A6	Q9Y2P4	74725713	Long-chain fatty acid transport protein 6
LUC7L3	O95232	94730369	Luc7-like protein 3
HSPA9	P38646	21264428	Stress-70 protein, mitochondrial
PTGS2	P35354	3915797	Prostaglandin G/H synthase 2
C19orf10	Q969H8	61221730	UPF0556 protein C19orf10
HSPA5	P11021	14916999	78 kDa glucose-regulated protein
CCDC134	Q9H6E4	74752694	Coiled-coil domain-containing protein 134
ARHGAP31	Q2M1Z3	296452881	Rho GTPase-activating protein 31
CRELD1	Q96HD1	209572751	Isoform 2 of Cysteine-rich with EGF-like domain protein 1
PSAP	P07602	134218	Proactivator polypeptide
CERCAM	Q5T4B2	74744901	Glycosyltransferase 25 family member 3
ARHGAP21	Q5T5U3	74745129	Rho GTPase-activating protein 21
MCFD2	Q8NI22	49036425	Multiple coagulation factor deficiency protein 2
GNB2L1	P63244	54037168	Guanine nucleotide-binding protein subunit beta-2-like 1
DST	Q03001	294862529	Dystonin
HSPA13	P48723	1351125	Heat shock 70 kDa protein 13
B3GNT2	Q9NY97	29840874	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2
VPS13D	Q5THJ4	74756617	Vacuolar protein sorting-associated protein 13D
SLC39A7	Q92504	12643344	Zinc transporter SLC39A7
SRRM1	Q8IYB3	83305833	Serine/arginine repetitive matrix protein 1
HSPA1A	P08107	147744565	Heat shock 70 kDa protein 1A/1B
TOR1B	O14657	13878818	Torsin-1B

Figure 5 (Continued)

Gene Symbol	Uniprot	GI Number	Protein name
GRPEL1	Q9HAV7	18202951	GrpE protein homolog 1, mitochondrial
PRPF4B	Q13523	317373526	Serine/threonine-protein kinase PRP4 homolog
TBCEL	Q5QJ74	215273924	Tubulin-specific chaperone cofactor E-like protein
RSRC2	Q7L4I2	74739167	Arginine/serine-rich coiled-coil protein 2
BAG3	O95817	12643665	BAG family molecular chaperone regulator 3
IFIT2	P09913	124488	Interferon-induced protein with tetratricopeptide repeats 2
BRD4	O60885	20141192	Bromodomain-containing protein 4
HYOU1	Q9Y4L1	10720185	Hypoxia up-regulated protein 1

Figure 6

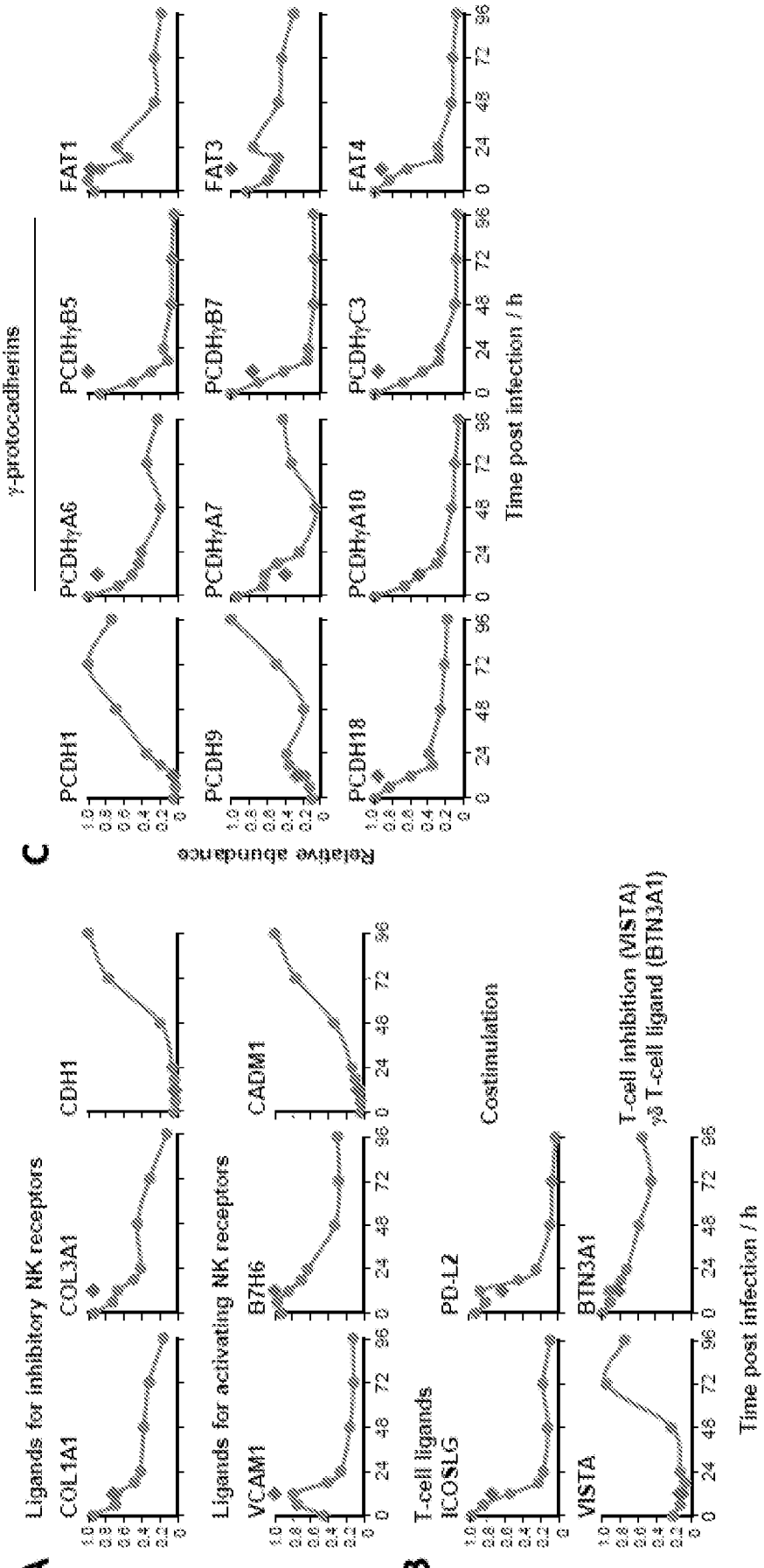

A
Ligands for inhibitory NK receptors
COL1A1
COL3A1
CDH1
Ligands for activating NK receptors
VCAM1
B7H6
CADM1
B
T-cell ligands
ICOSLG
PD-L2
Costimulation
VISTA
BTN3A1
T-cell inhibition (VISTA)
γδ T-cell ligand (BTN3A1)
Relative abundance
Time post infection / h
C
γ-protocadherins
PCDH1
PCDHγA6
PCDHγB5
FAT1
PCDH9
PCDHγA7
PCDHγB7
FAT3
PCDH18
PCDHγA10
PCDHγC3
FAT4
Relative abundance
Time post infection / h

Figure 7

Domain	Gene name	Protein name	Maximum fold change
Butyrophylin	BTN2A1	Butyrophilin subfamily 2 member A1	-4.5
Cadherin	PCDH1	Isoform 3 of Protocadherin-1	29.4
Cadherin	PCDHGA6	Protocadherin gamma-A6	-7.0
Cadherin	PCDHGA10	Protocadherin gamma-A10	-17.9
Cadherin	PCDHGB5	Protocadherin gamma-B5	-20.7
Cadherin	PCDHGB7	Protocadherin gamma-B7	-13.2
Cadherin	PCDHGC3	Protocadherin gamma-C3	-14.0
Cadherin	PCDH18	Isoform 2 of Protocadherin-18	-5.5
Cadherin	FAT1	Protocadherin Fat 1	-5.1
Cadherin	FAT4	Isoform 3 of Protocadherin Fat 4	-12.7
Cadherin	CDH1	Cadherin-1	61.9
Cadherin	CELSR2	Cadherin EGF LAG seven-pass G-type receptor 2	5.1
Cadherin	DSG2	Desmoglein-2	9.1
Collagen	COL1A1	Collagen alpha-1(I) chain	-6.0
Collagen	COL3A1	Collagen alpha-1(III) chain	-7.8
Collagen	COL4A2	Collagen alpha-2(IV) chain	4.8
C-type_lectin	CLEC1A	C-type lectin domain family 1 member A	-7.0
C-type_lectin	CD248	Endosialin	-8.9
C-type_lectin	LAYN	Isoform 2 of Layilin	-13.8
C-type_lectin	PLA2R1	Secretory phospholipase A2 receptor	-4.9
Immunoglobulin	ALCAM	Isoform 2 of CD166 antigen	-16.1
Immunoglobulin	AMIGO2	Amphoterin-induced protein 2	-4.4
Immunoglobulin	C10orf54	Platelet receptor Gi24	7.5

Figure 7 (Continued)

Domain	Gene name	Protein name	Maximum fold change
Immunoglobulin	CADM1	Cell adhesion molecule 1	23.0
Immunoglobulin	CADM4	Cell adhesion molecule 4	28.8
Immunoglobulin	CEACAM1	Carcinoembryonic antigen-related cell adhesion molecule 1	20.3
Immunoglobulin	CLMP	CXADR-like membrane protein	-13.1
Immunoglobulin	CNTFR	Ciliary neurotrophic factor receptor subunit alpha	32.0
Immunoglobulin	F11R	Junctional adhesion molecule A	33.7
Immunoglobulin	GPR124	G-protein coupled receptor 124	-4.6
Immunoglobulin	IGDCC4	Immunoglobulin superfamily DCC subclass member 4	-13.1
Immunoglobulin	IGFBP7	Insulin-like growth factor-binding protein 7	5.1
Immunoglobulin	IGSF3	Immunoglobulin superfamily member 3	4.8
Immunoglobulin	IGSF8	Isoform 3 of Immunoglobulin superfamily member 8	-6.3
Immunoglobulin	IL1R1	Interleukin-1 receptor type 1	-9.2
Immunoglobulin	KDELC2	KDEL motif-containing protein 2	5.4
Immunoglobulin	L1CAM	Isoform 2 of Neural cell adhesion molecule L1	10.5
Immunoglobulin	MXRA8	Matrix-remodeling-associated protein 8	-15.5
Immunoglobulin	NCAM1	Isoform 2 of Neural cell adhesion molecule 1	26.1
Immunoglobulin	NRCAM	Isoform 3 of Neuronal cell adhesion molecule	11.6
Immunoglobulin	PDCD1LG2	Programmed cell death 1 ligand 2	-26.5
Immunoglobulin	PDGFRA	Alpha-type platelet-derived growth factor receptor	-20.6
Immunoglobulin	PDGFRB	Beta-type platelet-derived growth factor receptor	-8.8
Immunoglobulin	PLXNA1	Plexin-A1	-6.3
Immunoglobulin	PLXNA3	Plexin-A3	-16.0
Immunoglobulin	PLXNB1	Isoform 2 of Plexin-B1	-9.4
Immunoglobulin	PLXNB2	Plexin-B2	-5.2
Immunoglobulin	PLXND1	Plexin-D1	-6.4
Immunoglobulin	PTK7	Inactive tyrosine-protein kinase 7	-10.1

Figure 7 (Continued)

Domain	Gene name	Protein name	Maximum fold change
Immunoglobulin	PTPRM	Receptor-type tyrosine-protein phosphatase mu	-5.6
Immunoglobulin	PVR	Isoform Beta of Poliovirus receptor	-9.3
Immunoglobulin	PVRL2	Isoform Alpha of Poliovirus receptor-related protein 2	-9.1
Immunoglobulin	PVRL2	Poliovirus receptor-related protein 2	-6.3
Immunoglobulin	ROBO2	Roundabout homolog 2	-4.5
Immunoglobulin	ROR1	Tyrosine-protein kinase transmembrane receptor ROR1	-7.4
Immunoglobulin	ROR2	Tyrosine-protein kinase transmembrane receptor ROR2	-4.0
Immunoglobulin	SEMA4C	Semaphorin-4C	-5.0
Immunoglobulin	SEMA4D	Semaphorin-4D	22.4
Immunoglobulin	TYRO3	Tyrosine-protein kinase receptor TYRO3	8.1
MHC	FCGRT	IgG receptor FcRn large subunit p51	-5.8
MHC	HFE	Isoform 5 of Hereditary hemochromatosis protein	-8.0
MHC	HLA-A	HLA class I histocompatibility antigen, A-24 alpha chain	-5.1
MHC	HLA-C	HLA class I histocompatibility antigen, Cw-2 alpha chain	-6.2
MHC	HLA-E	HLA class I histocompatibility antigen, alpha chain E	10.5
MHC	MICA	MHC class I polypeptide-related sequence A	-6.1
MHC	ULBP1	NKG2D ligand 1	-4.4
MHC	ULBP2	NKG2D ligand 2	-5.1
TNF	TNFRSF10B	Tumor necrosis factor receptor superfamily member 10B	-15.2
TNF	CD40	Tumor necrosis factor receptor superfamily member 5	4.1
TNF	NGFR	Tumor necrosis factor receptor superfamily member 16	23.1
TNF	TNFRSF10D	Tumor necrosis factor receptor superfamily member 10D	-5.6
TNF	TNFRSF1B	Tumor necrosis factor receptor superfamily member 1B	52.2

Figure 8

INTERPRO: Protocadherin gamma, 23.2 fold enrichment, p = 0.004		
Uniprot	**Gene Name**	**Protein Name**
Q9Y5H3	PCDHGA10	protocadherin gamma subfamily A, 10
Q9Y5G6	PCDHGA7	protocadherin gamma subfamily A, 7
Q9Y5G0	PCDHGB5	protocadherin gamma subfamily B, 5
Q9Y5F8	PCDHGB7	protocadherin gamma subfamily B, 7
Q9UN70	PCDHGC3	protocadherin gamma subfamily C, 3

INTERPRO: Immunoglobulin-like fold, 3.4 fold enrichment, p = 0.007		
Uniprot	**Gene Name**	**Protein Name**
Q13308	PTK7	PTK7 protein tyrosine kinase 7
Q9H6B4	CLMP	adipocyte-specific adhesion molecule
Q13740	ALCAM	Activated leukocyte cell adhesion molecule
Q8TDY8	IGDCC4	immunoglobulin superfamily, DCC subclass, member 4
O75144	ICOSLG	inducible T-cell co-stimulator ligand
P14778	IL1R1	interleukin 1 receptor, type I
P40189	IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)
Q9BTN0	LRFN3	leucine rich repeat and fibronectin type III domain containing 3
Q6PJG9	LRFN4	leucine rich repeat and fibronectin type III domain containing 4
Q9BRK3	MXRA8	matrix-remodeling associated 8
P16234	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
P09619	PDGFRB	platelet-derived growth factor receptor, beta polypeptide
P15151	PVR	poliovirus receptor
Q92692	PVRL2	poliovirus receptor-related 2 (herpes virus entry mediator B)
Q9BQ51	PDCD1LG2	programmed cell death 1 ligand 2

GO biological process: Regulation of leukocyte activation, 6.7 fold enrichment, p = 0.045		
Uniprot	**Gene Name**	**Protein Name**
P98172	EFNB1	ephrin-B1
O75144	ICOSLG	inducible T-cell co-stimulator ligand
P40189	IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)
Q92692	PVRL2	poliovirus receptor-related 2 (herpes virus entry mediator B)
Q9BQ51	PDCD1LG2	programmed cell death 1 ligand 2
P07996	THBS1	thrombospondin 1
P04626	ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)

Figure 8 (Continued)

GO biological process: Positive regulation of protein kinase activity, 5.0 fold enrichment, p = 0.044		
Uniprot	**Gene Name**	**Protein Name**
P78536	ADAM17	ADAM metallopeptidase domain 17
P30542	ADORA1	adenosine A1 receptor
O60266	ADCY3	adenylate cyclase 3
P09603	CSF1	colony stimulating factor 1 (macrophage)
P31431	SDC4	syndecan 4
P07996	THBS1	thrombospondin 1
P36897	TGFBR1	transforming growth factor, beta receptor 1
O14763	TNFRSF10B	tumor necrosis factor receptor superfamily, member 10b
P04626	ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)

GO biological process: Positive regulation of cell motion, 5.9 fold enrichment, p = 0.059		
Uniprot	**Gene Name**	**Protein Name**
P78536	ADAM17	ADAM metallopeptidase domain 17
P09603	CSF1	colony stimulating factor 1 (macrophage)
P40189	IL6ST	interleukin 6 signal transducer (gp130, oncostatin M receptor)
P16234	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
P09619	PDGFRB	platelet-derived growth factor receptor, beta polypeptide
P07996	THBS1	thrombospondin 1
P36897	TGFBR1	transforming growth factor, beta receptor 1

INTERPRO: GPCR, rhodopsin-like superfamily, 6.7 fold enrichment, p = 0.048		
Uniprot	**Gene Name**	**Protein Name**
Q14439	GPR176	G protein-coupled receptor 176
Q15743	GPR68	G protein-coupled receptor 68
P30542	ADORA1	adenosine A1 receptor
P08172	CHRM2	cholinergic receptor, muscarinic 2
P30559	OXTR	oxytocin receptor
P43116	PTGER2	prostaglandin E receptor 2 (subtype EP2), 53kDa

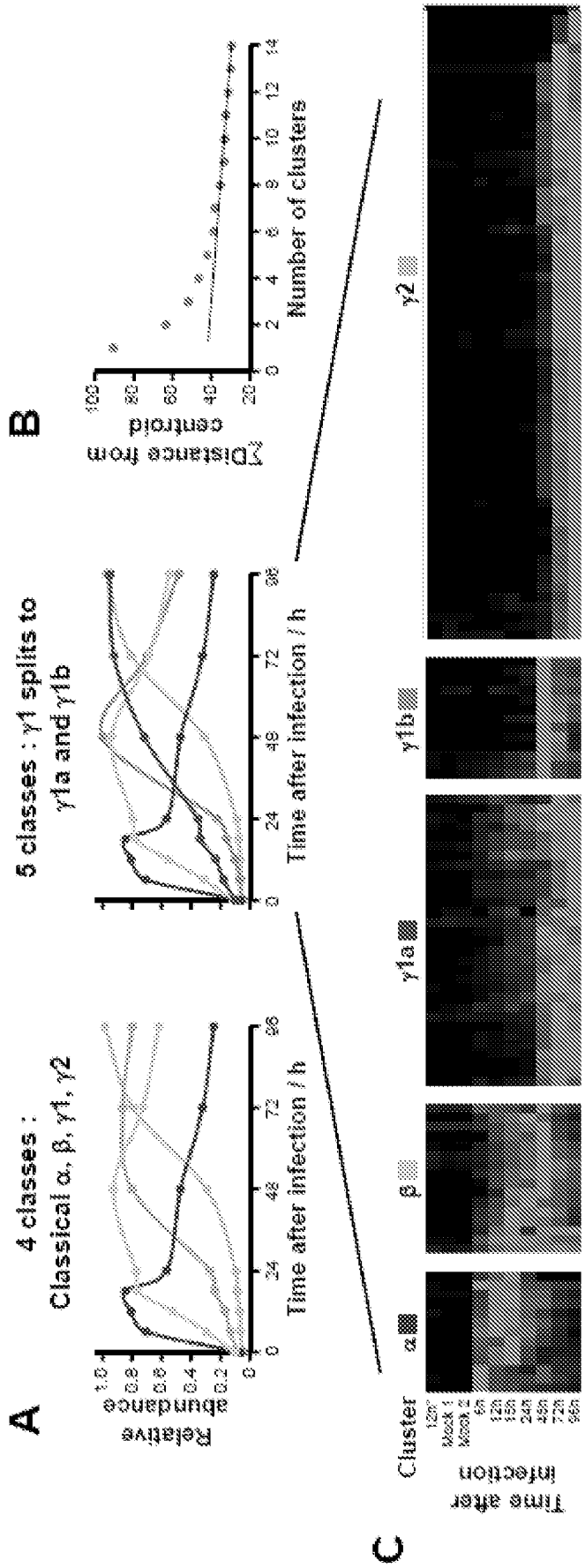

A
4 classes :
Classical α, β, γ1, γ2
Relative abundance
Time after infection / h
5 classes : γ1 splits to γ1a and γ1b
B
Distance from centroid
Number of clusters
C
Cluster
α
β
γ1a
γ1b
γ2
Time after infection

Figure 9

Figure 9 (Continued)

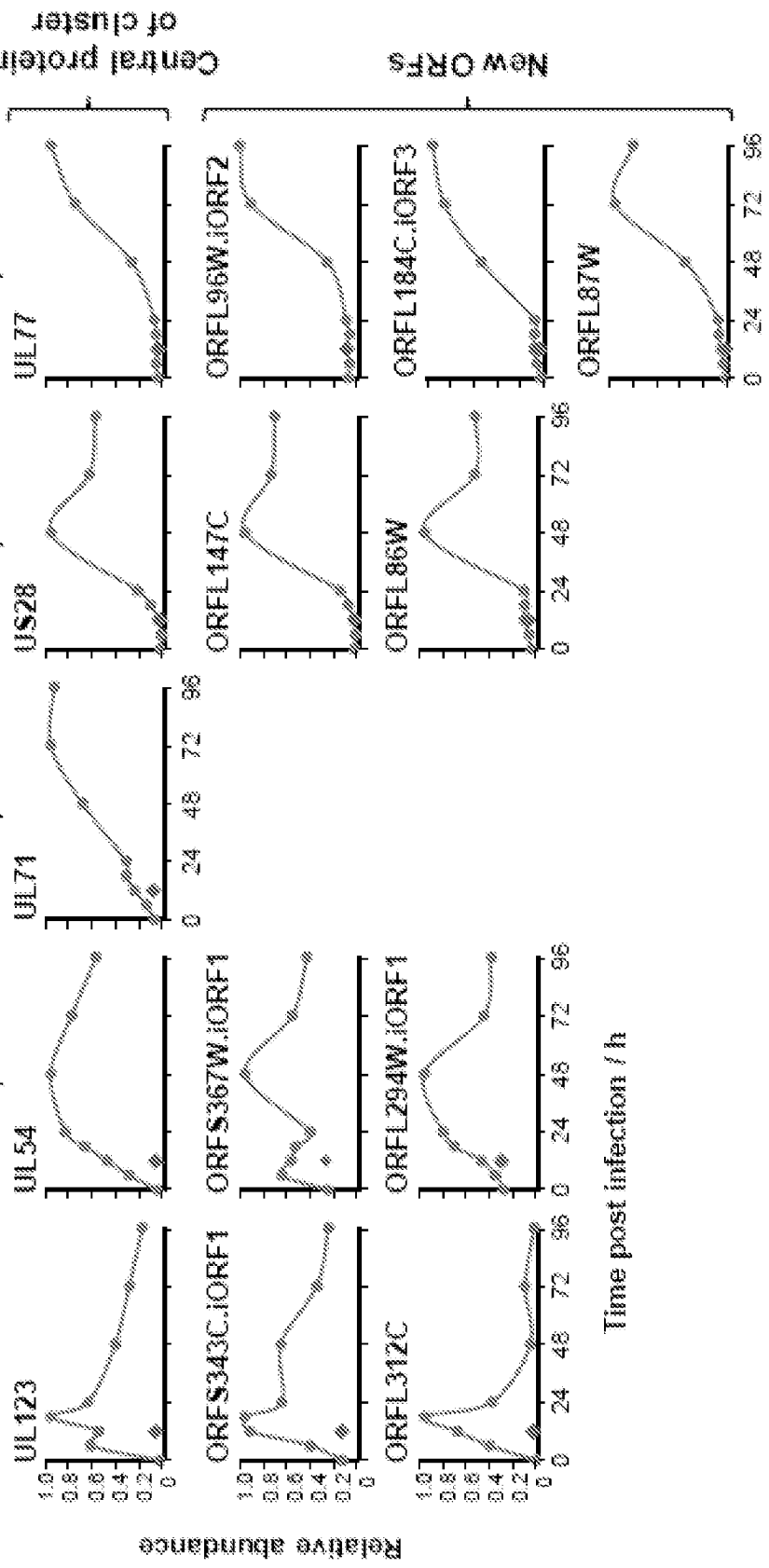


Figure 10

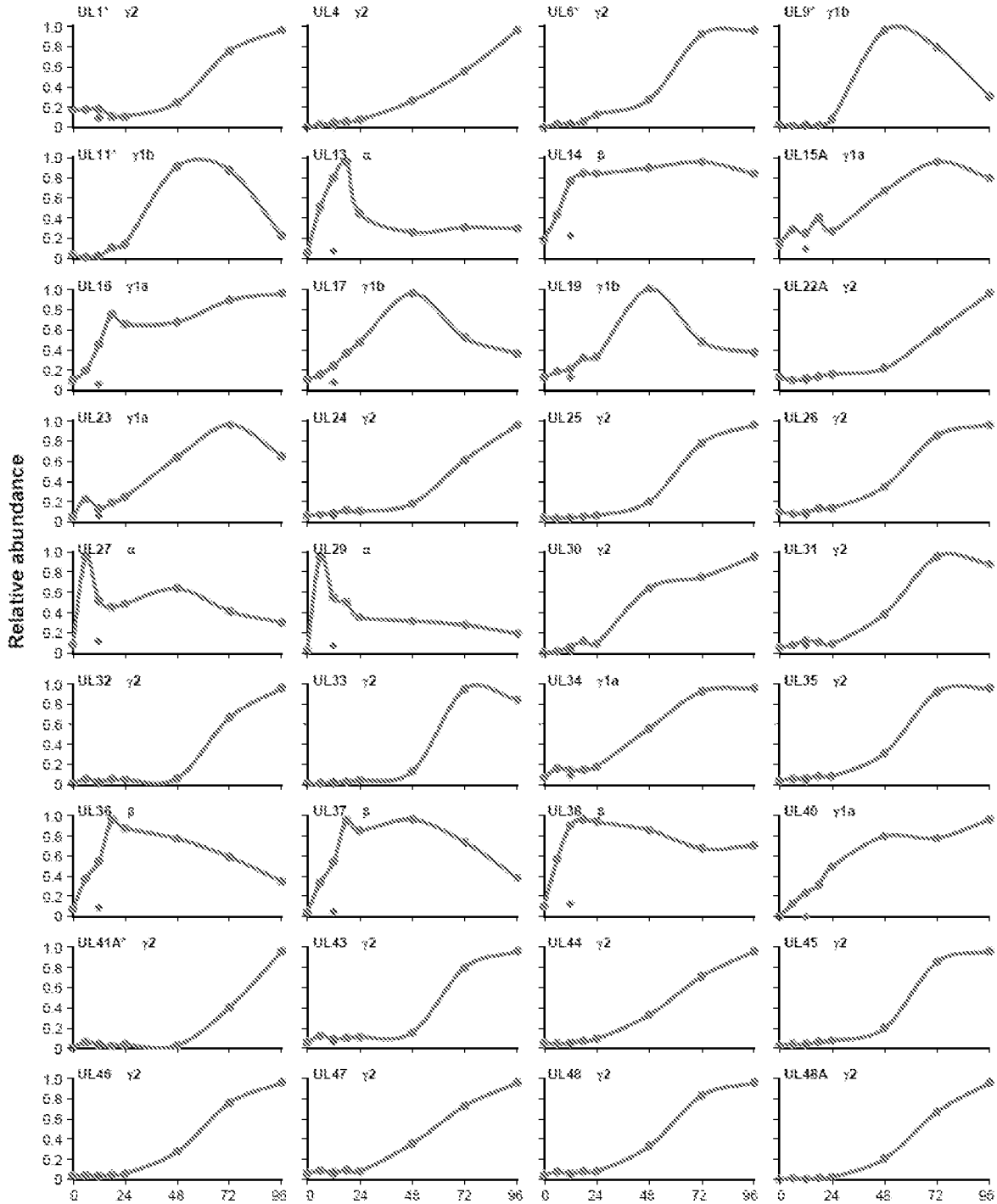

Relative abundance
UL1* γ2
UL4 γ2
UL6* γ2
UL9* γ1b
UL11* γ1b
UL13 α
UL14 β
UL15A γ1a
UL16 γ1a
UL17 γ1b
UL19 γ1b
UL22A γ2
UL23 γ1a
UL24 γ2
UL25 γ2
UL26 γ2
UL27 α
UL29 α
UL30 γ2
UL31 γ2
UL32 γ2
UL33 γ2
UL34 γ1a
UL35 γ2
UL36 β
UL37 β
UL38 β
UL40 γ1a
UL41A* γ2
UL43 γ2
UL44 γ2
UL45 γ2
UL46 γ2
UL47 γ2
UL48 γ2
UL48A γ2
0
0.2
0.4
0.6
0.8
1.0
0
24
48
72
96

Figure 10 (Continued)

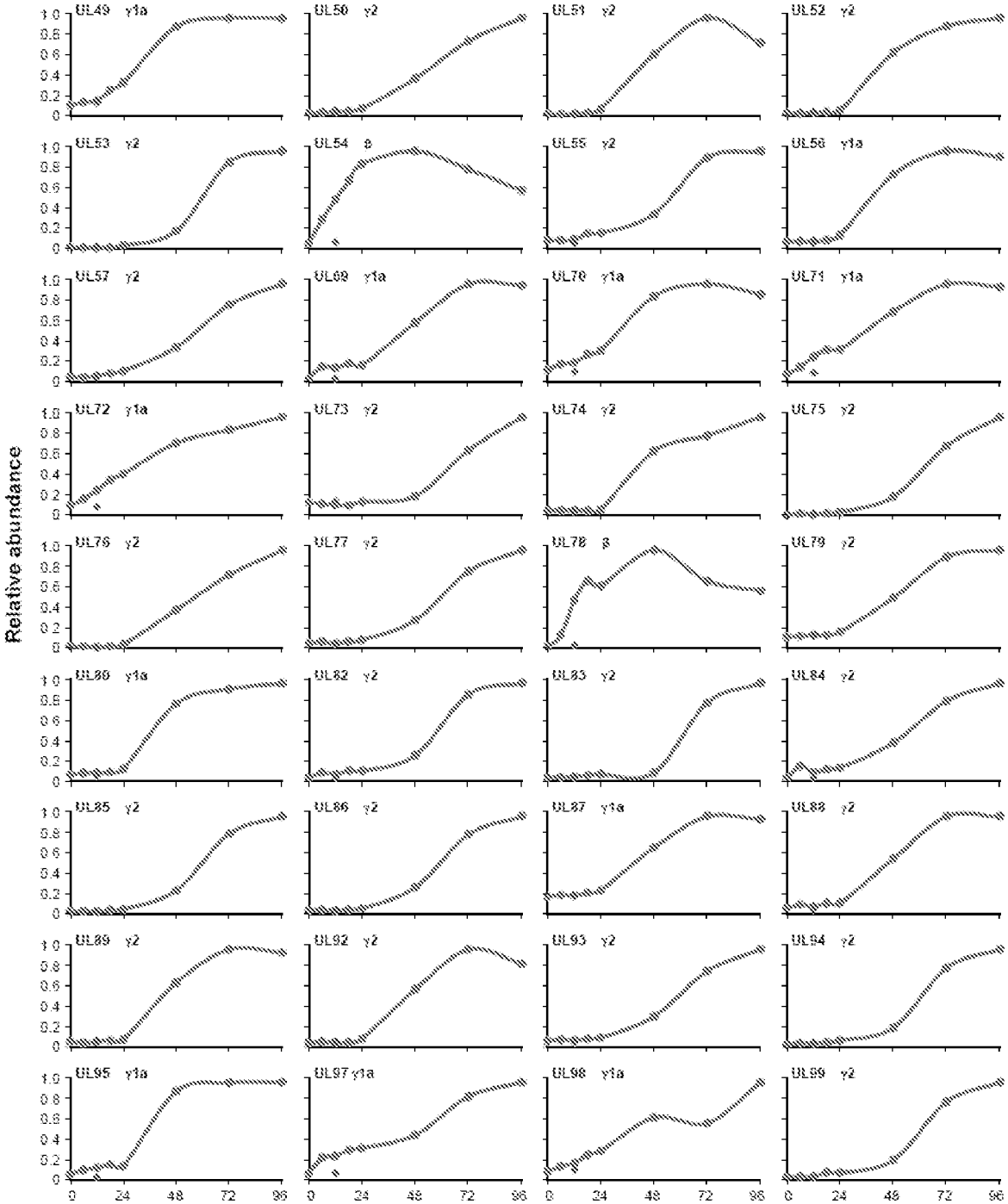


Figure 10 (Continued)

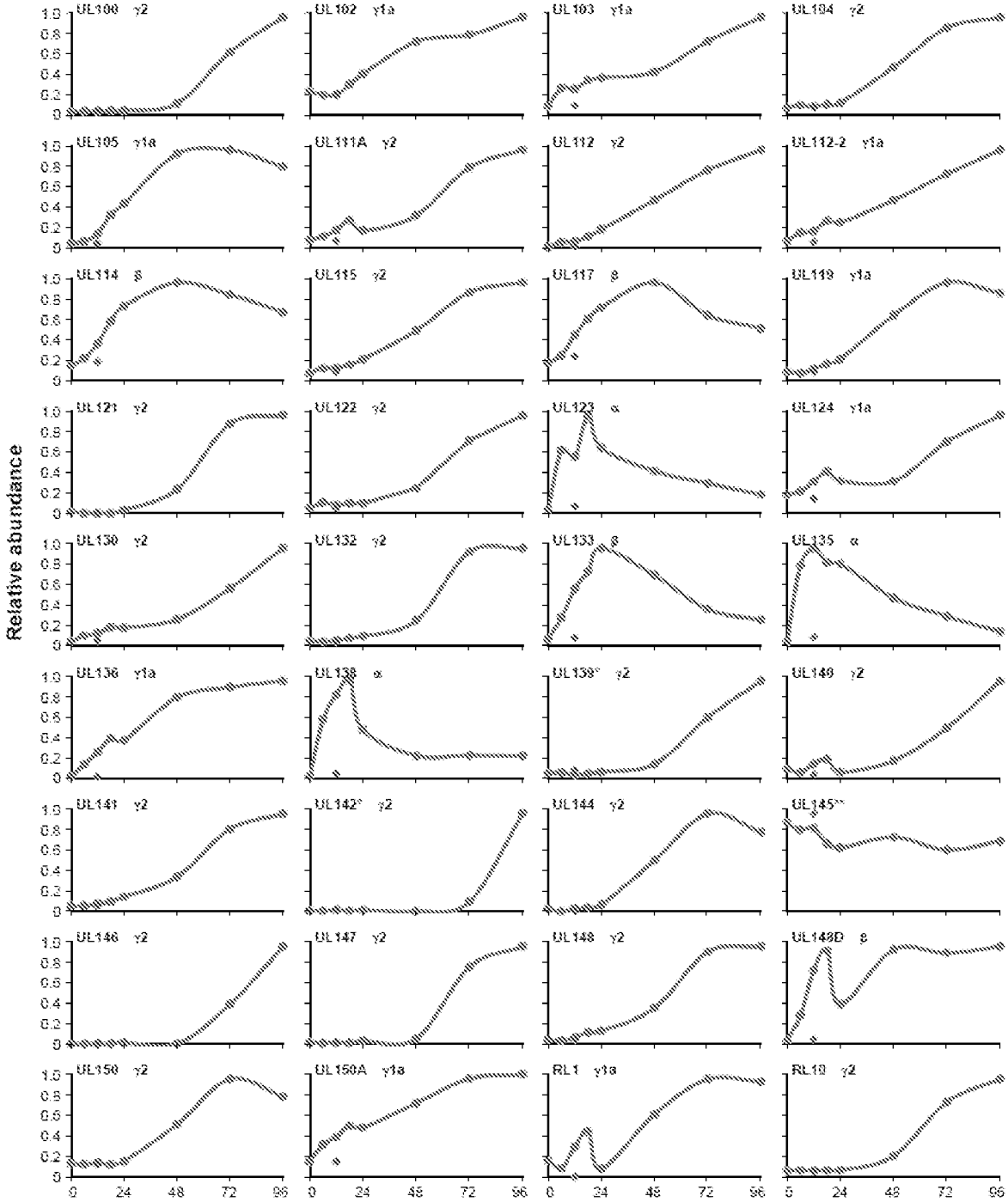


Figure 10 (Continued)

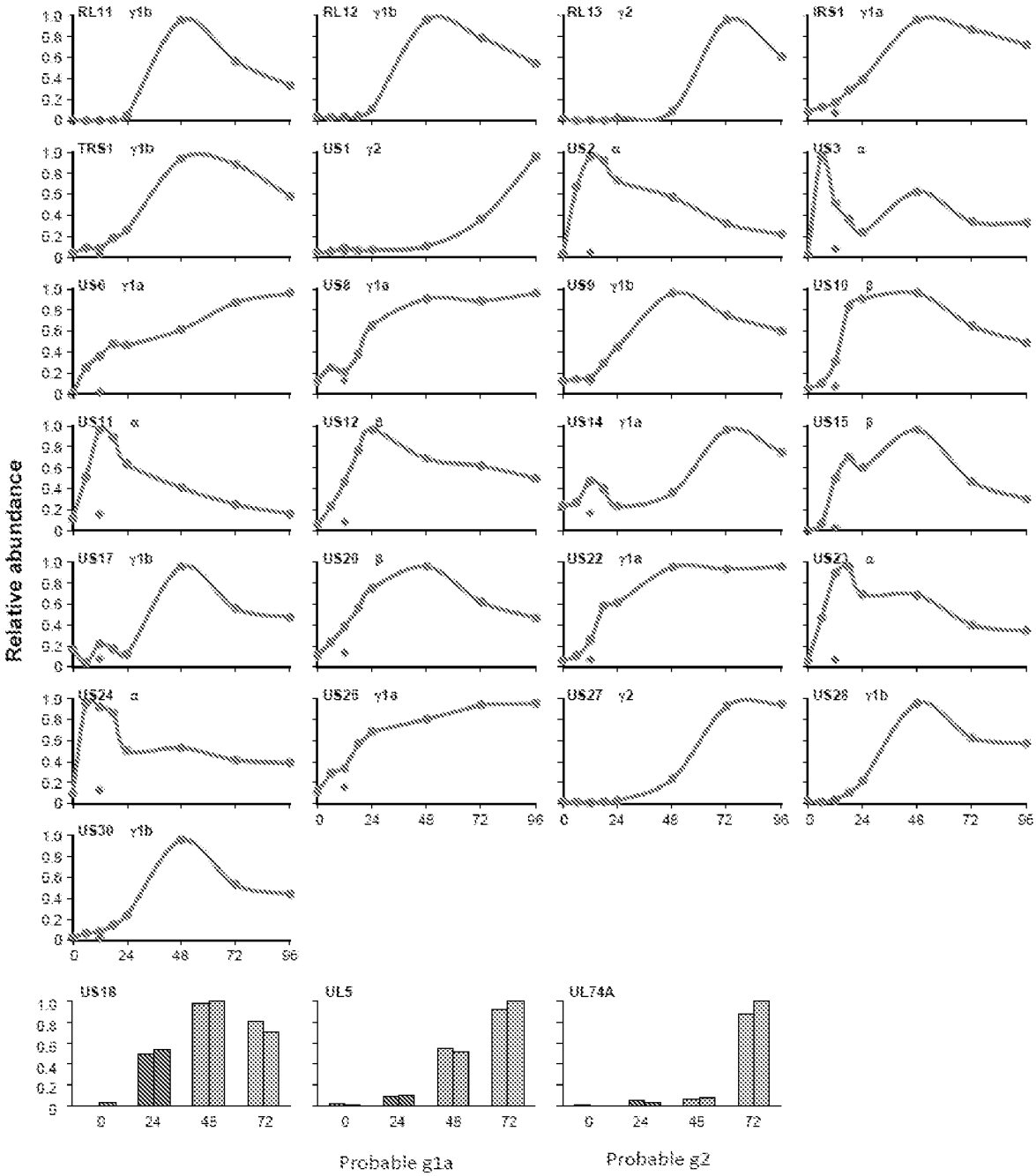
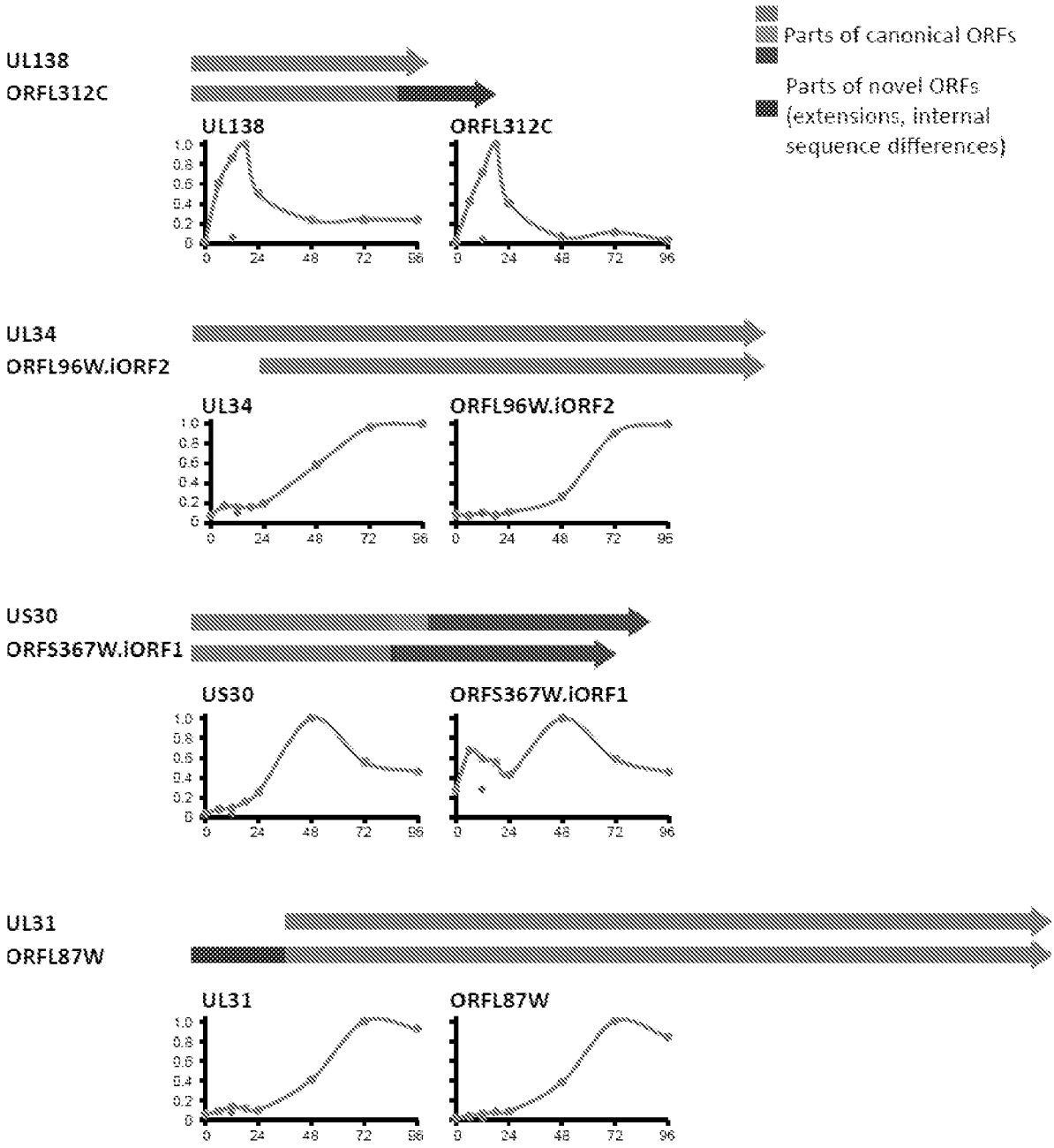


Figure 11

Strand	Gene Name	Genetic region	Family	Start	Stop
+	RL11	10-25	RL11	9142	9846
+	RL12	10-25	RL11	9850	11094
+	UL9	10-25	RL11	16947	17648
+	UL11	10-25	RL11	18642	19460
+	UL17	10-25	Other	23554	23868
+	UL19	10-25	Other	25080	25376
+	ORFL86W	38-39	New ORF	38059	38538
-	ORFL147C	85-87	New ORF	87362	85932
-	US9	205-235	US6	204910	204167
-	US17	205-235	US12	212321	211440
+	US28	205-235	GPCR	225435	226499
+	US30	205-235	Other	227854	228903
-	TRS1	205-235	US22	234759	232393

Figure 12



C: Relationship between four novel ORFs and their canonical HCMV counterparts, with temporal profiles.

Figure 13

Strand	Description	Gene name	Start (1st exon)	Stop (1st exon)	Start (2nd exon)	Stop (2nd exon)	Relates to canonical gene	Peptide redundancy
-	Non-canonical	ORFL147C	87362	85932			UL56	Unique
-	Non-canonical	ORFL184C.iORF3	111379	111134			UL75	Redundant to ORFL185C
+	Non-canonical	ORFL294W.iORF1	193172	193441			UL150	Redundant to ORFL294W
+	Non-canonical	ORFL86W	38059	38538			UL30A, UL31	Unique
-	Non-canonical	ORFS343C.iORF1	211213	210869			US16	Unique
-	Relates to canonical	ORFL312C	187950	187468	187368	187174	UL138	Unique
+	Relates to canonical	ORFL96W.iORF2_(UL34)	45204	46364			UL34	Unique
+	Relates to canonical	ORFS367W.iORF1_(US30)	228420	228903			US30	Unique
+	Relates to canonical	ORFL87W_(UL31)	38099	40114			UL31	Unique

Figure 14

Gene	Uniprot	GI Number	Description	Sum PM1 + PM2 peptides	Sum WCL1 + WCL2 peptides	Peptide ratio (PM1 + PM2) : (WCL1 + WCL2)	Viral protein class	Early Expression
UL11	Q6SWB9	82013976	Protein UL11	7	0	PM only	γ1b	Yes
UL142	D2K3T4	395455117	Membrane glycoprotein UL142	7	0	PM only	γ2	No
UL9	F5H9T4	384952364	Membrane glycoprotein UL9	4	0	PM only	γ1b	Yes
UL1	Q6SWC8	82013985	Glycoprotein UL1	4	0	PM only	γ2	No
UL5	F5HHY9	82013982	Protein UL5	2	0	PM only	γ1a	Yes
UL41A	F5HFG3	395455127	Protein UL41A	12	2	6.00	γ2	No
RL12	Q6SWD0	82013987	Uncharacterized protein RL12	32	6	5.33	γ1b	Yes
UL33	Q6SW98	82055331	G-protein coupled receptor homolog UL33	14	3	4.67	γ2	No
UL119	F5HC14	391359343	Viral Fc-gamma receptor-like protein UL119	26	7	3.71	γ1a	Yes
UL16	F5HG68	395455121	Protein UL16	7	4	3.50	γ1a	Yes
RL10	F5HI32	395406822	Protein IRL10	14	2	3.50	γ2	No
UL100	Q6SW43	82013927	Envelope glycoprotein M	27	8	3.38	γ2	No
UL40	Q6SW92	82013961	Protein UL40	3	1	3.00	γ1a	Yes
US6	Q6SW00	82013896	Unique short US6 glycoprotein	3	1	3.00	γ1a	Yes
UL144	F5HAM0	363805602	Membrane glycoprotein UL144	3	1	3.00	γ2	No

Figure 14 (Continued)

Gene	Uniprot	GI Number	Description	Sum PM1 + PM2 peptides	Sum WCL1 + WCL2 peptides	Peptide ratio (PM1 + PM2) : (WCL1 + WCL2)	Viral protein class	Early Expression
US28	Q80KM9	82058001	Envelope protein US28	14	5	2.80	γ1b	Yes
US27	F5HDK1	380875404	Envelope glycoprotein US27	24	9	2.67	γ2	No
RL11	Q6SWD1	82013988	Membrane glycoprotein RL11	18	7	2.57	γ1b	Yes
UL75	Q6SW67	82013944	Envelope glycoprotein H	32	13	2.46	γ2	No
US9	F5HC33	384951451	Membrane glycoprotein US9	15	7	2.14	γ1b	Yes
UL148D	D2K3U5	77543601	Protein UL148D	2	1	2.00	β	Yes
US20	F5HGH8	395455141	Membrane protein US20	4	2	2.00	β	Yes
UL78	B8YEA3	395455130	Protein UL78	7	4	1.75	β	Yes
UL55	F5HB53	380876915	Envelope glycoprotein B	71	45	1.58	γ2	No
UL136	F5HF35	391359344	Protein UL136	3	2	1.50	γ1a	Yes
US14	F5HD92	384951455	Membrane protein US14	3	2	1.50	γ1a	Yes
UL73	F5HHQ0	380876918	Envelope glycoprotein N	3	2	1.50	γ2	No
UL132	D2K3S7	395455115	Envelope glycoprotein UL132	31	21	1.48	γ2	No
UL141	Q6RJQ3	82013863	Protein UL141	30	21	1.43	γ2	No
UL14	Q6SWB7	82013974	Uncharacterized protein UL14	4	3	1.33	β	Yes
UL22A	F5HF90	384952467	Glycoprotein UL22A	5	4	1.25	γ2	No

Figure 14 (Continued)

Gene	Uniprot	GI Number	Description	Sum PM1 + PM2 peptides	Sum WCL1 + WCL2 peptides	Peptide ratio (PM1 + PM2) : (WCL1 + WCL2)	Viral protein class	Early Expression
UL37	Q6SW94	82013963	UL37 immediate early glycoprotein	10	9	1.11	β	Yes
US12	F5HE44	395455137	Uncharacterized protein US12	4	4	1.00	β	Yes
UL103	F5HA10	395455111	Tegument protein UL103	5	5	1.00	γ1a	Yes
UL74	F5HGP1	395406816	Envelope glycoprotein O	9	10	0.90	γ2	No
UL71	C8BLE7	391359355	Tegument protein UL71	12	14	0.86	γ1a	Yes
UL34	C8CPD5	384952480	Transcriptional regulator UL34	22	28	0.79	γ1a	Yes
UL133	Q6SW10	82013903	Protein UL133	2	3	0.67	β	Yes
US8	F5HB52	384951444	Membrane glycoprotein US8	5	27	0.56	γ1a	Yes
UL50	Q6SW81	82013953	Nuclear egress membrane protein	15	9	0.56	γ2	No
UL52	Q6SW79	82013952	DNA packaging protein UL32	15	28	0.54	γ2	No
UL17	F5HHT4	391359348	Protein UL17	3	6	0.50	γ1b	Yes
UL115	F5HCH8	380876917	Envelope glycoprotein L	3	6	0.50	γ2	No
UL94	F5HAC7	391359347	Capsid-binding protein UL94	11	25	0.44	γ2	No
UL13	F5HGX4	82013975	Protein UL13	3	8	0.38	α	Yes
UL148	F5H8Q3	395455119	Membrane protein UL148	6	16	0.38	γ2	No
UL99	F5HI87	395455101	Tegument protein UL99	3	8	0.38	γ2	No

Figure 14 (Continued)

Gene	Uniprot	GI Number	Description	Sum PM1 + PM2 peptides	Sum WCL1 + WCL2 peptides	Peptide ratio (PM1 + PM2) : (WCL1 + WCL2)	Viral protein class	Early Expression
UL56	F5HC79	395455102	Tripartite terminase subunit UL28 homolog	10	28	0.36	γ1a	Yes
UL123	F5HCM1	380875407	55 kDa immediate-early protein 1	27	81	0.33	α	Yes
UL122	Q6SW29	82013917	Viral transcription factor IE2	10	30	0.33	γ2	No
UL135	F5HAQ7	384952459	Protein UL135	10	32	0.31	α	Yes
UL98	F5HF49	391738012	Alkaline nuclease	7	27	0.26	γ1a	Yes
UL146	F5HBX1	395406771	Chemokine vCXCL1	4	17	0.24	γ2	No
UL89	Q6RXE9	82013867	Tripartite terminase subunit UL15 homolog	6	27	0.22	γ2	No
IRS1	Q6SW04	82013899	Protein IRS1	12	70	0.17	γ1a	Yes
UL57	F5HDQ6	380876875	Major DNA-binding protein	14	105	0.13	γ2	No
UL112-2	Q6SW37	82013923	Early phosphoprotein p84	9	68	0.13	γ2	No
US22	F5HDC7	395455143	Tegument protein US22	4	36	0.11	γ1a	Yes
UL48	Q6SW84	82013956	Deneddylase UL48	5	58	0.09	γ2	No
UL44	A9YU18	270355806	DNA polymerase processivity factor	18	216	0.08	γ2	No
UL45	Q6SW87	82013958	Ribonucleoside-diphosphate reductase UL45	3	41	0.07	γ2	No
UL86	F5HGT1	395406774	Major capsid protein	9	149	0.06	γ2	No
UL32	Q6SW99	82013966	Tegument protein pp150	4	74	0.05	γ2	No

Figure 14 (Continued)

Gene	Uniprot	GI Number	Description	Sum PM1 + PM2 peptides	Sum WCL1 + WCL2 peptides	Peptide ratio (PM1 + PM2) : (WCL1 + WCL2)	Viral protein class	Early Expression
UL80	Q6SW62	82013940	Protease precursor	2	40	0.05	γ1a	Yes
UL83	Q6SW59	82013937	65 kDa phosphoprotein	13	378	0.03	γ2	No
UL36	C8CPD7	270355799	Tegument protein vICA	2	60	0.03	β	Yes
UL25	F5HGJ4	395406800	Phosphoprotein 85	2	76	0.03	γ2	No

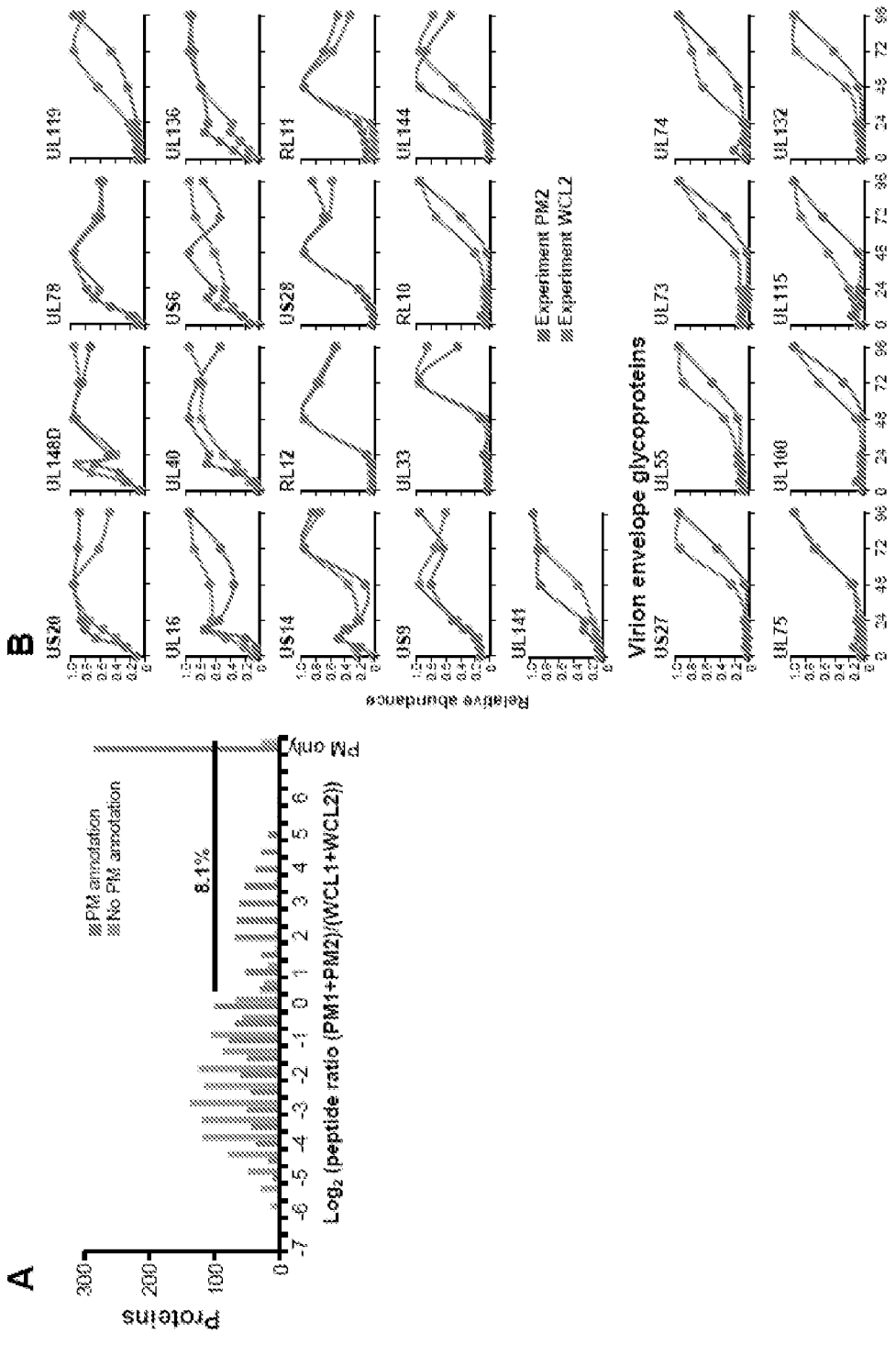

A
Proteins
PM annotation
No PM annotation
8.1%
PM only
Log2 (peptide ratio (PM1+PM2)/(WCL1+WCL2))
B
Relative abundance
Experiment PM2
Experiment WCL2
Virion envelope glycoproteins
Time post infection / h

Figure 15

Figure 16

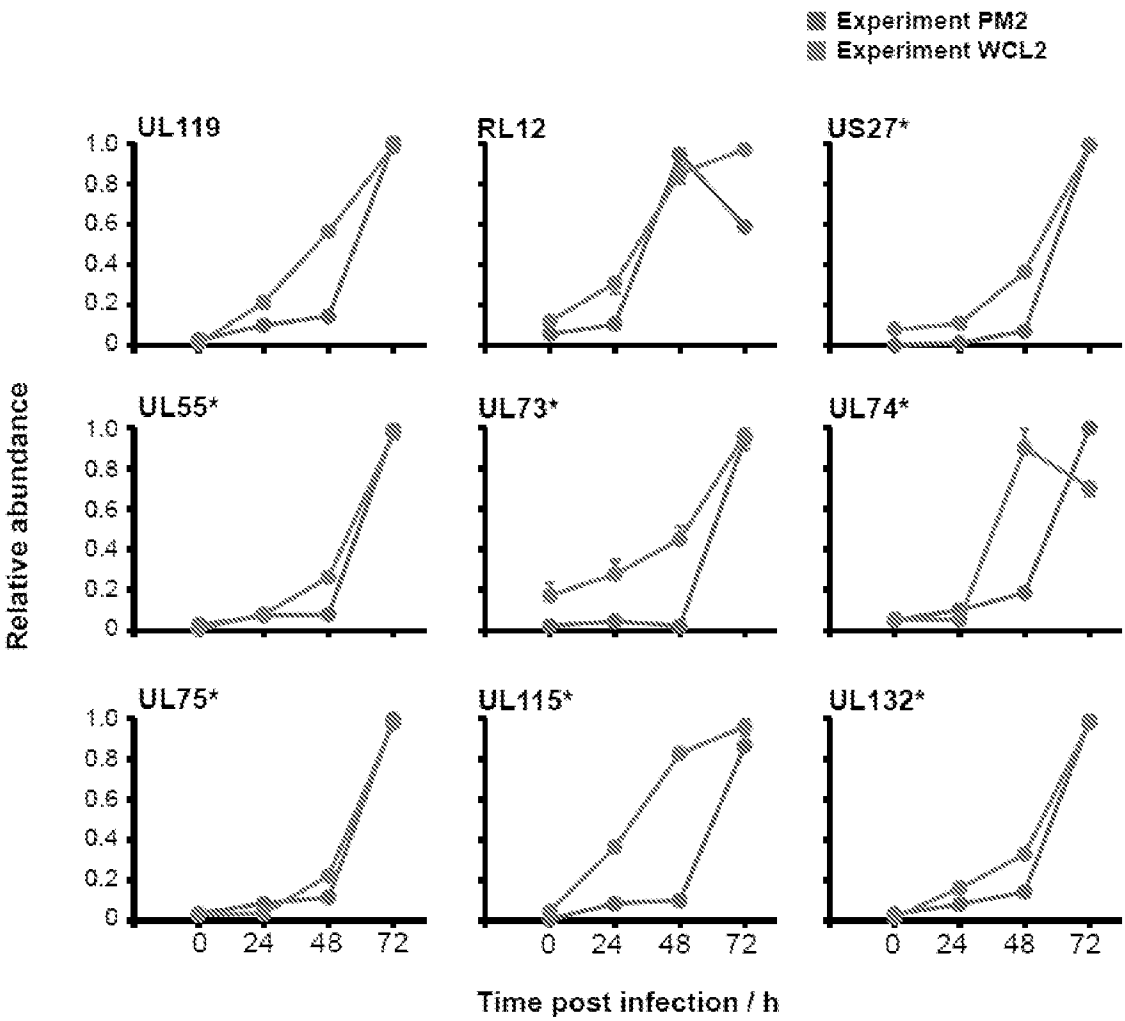
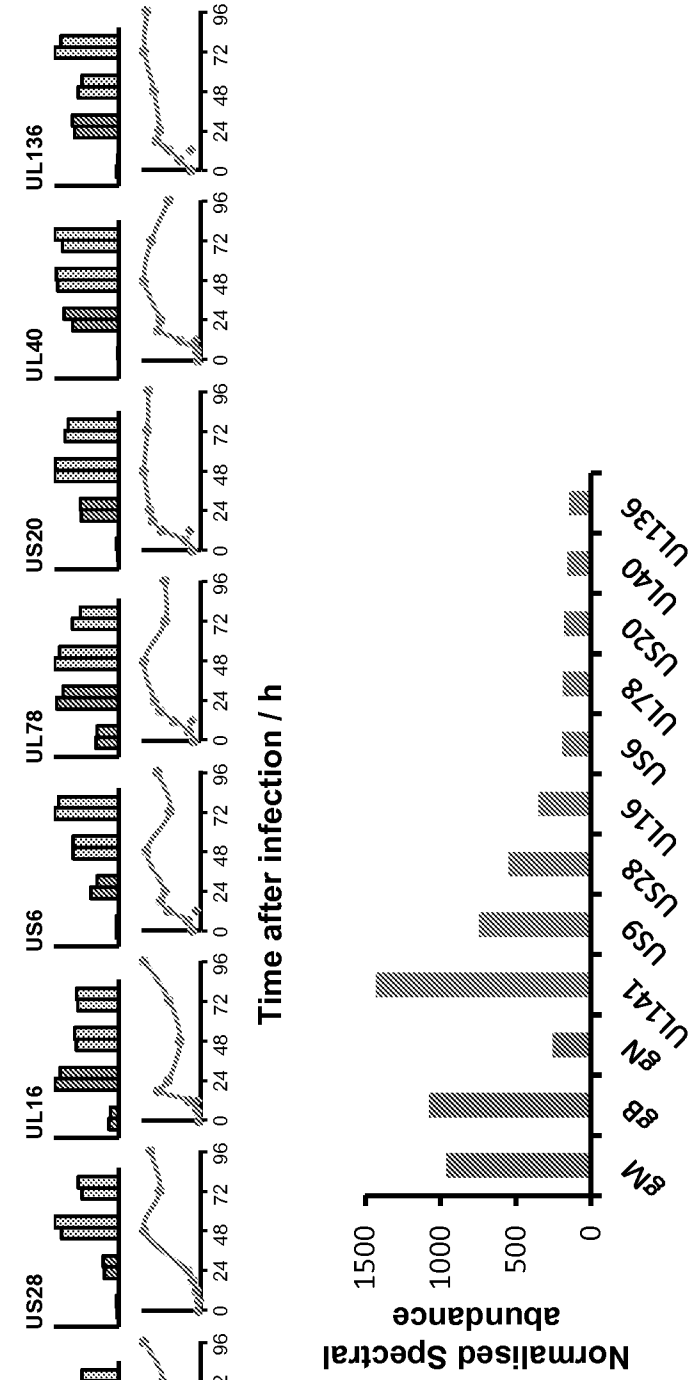

Experiment PM2
Experiment WCL2
UL119
RL12
US27*
UL55*
UL73*
UL74*
UL75*
UL115*
UL132*
Relative abundance
1.0
0.8
0.6
0.4
0.2
0
0 24 48 72
Time post infection / h

Figure 17


Relative Abundance
UL141
US9
US28
UL16
US6
UL78
US20
UL40
UL136
0 24 48 72 96
Time after infection / h
Normalised Spectral abundance
1500
1000
500
0
gM
gB
gN
UL141
US9
US28
UL16
US6
UL78
US20
UL40
UL136

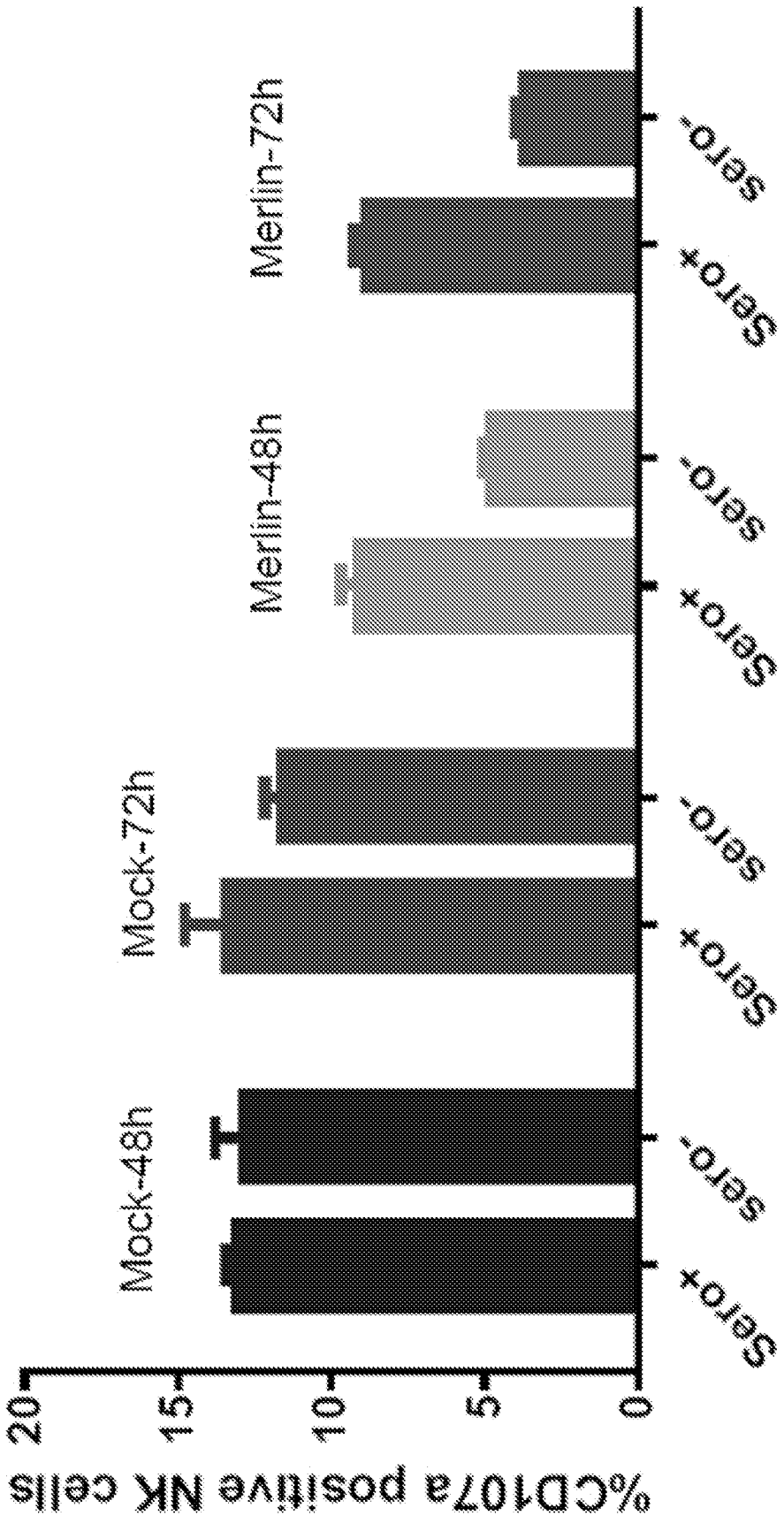

%CD107a positive NK cells
0
5
10
15
20
Mock-48h
Mock-72h
Merlin-48h
Merlin-72h
Sero+
Sero-
Sero+
Sero-
Sero+
Sero-
Sero+
Sero-

Figure 18