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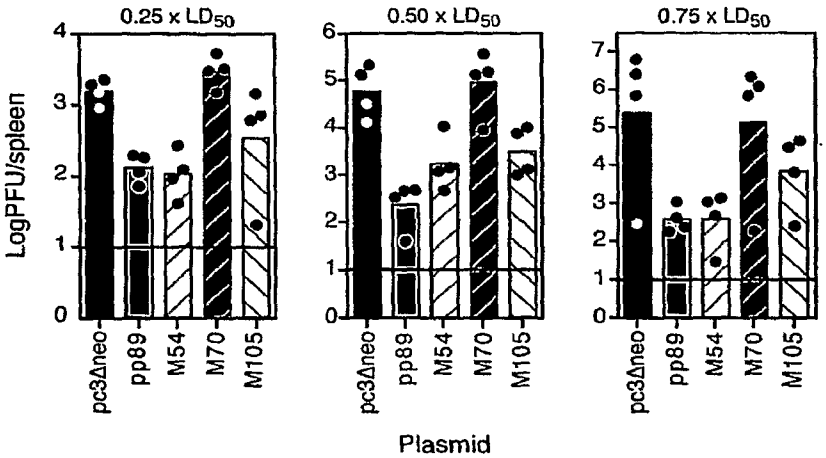
(54) Title: VACCINE FOR VIRUSES THAT CAUSE PERSISTENT OR LATENT INFECTIONS



(57) Abstract: The invention is in general directed to methods and compositions for preventing or treating infections by viruses involved in persistent and/or latent infections. The methods and compositions are directed toward the prevention and treatment of infections caused by viruses such as, for example, herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses, including, for example, cytomegalovirus.

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Vaccine for Viruses that Cause Persistent or Latent Infections

Statement of Federally Sponsored Research

This invention was made with Government support under Grant Number R01A1051557 by the National Institute of Health. The Government may have certain rights in this invention.

Field of the Invention

The invention is in general directed to methods and compositions for preventing or treating infections by viruses involved in persistent and/or latent infections.

Priority

Priority is claimed to U.S. Provisional Application serial number US 60/781,123, filed March 10, 2006, and entitled Vaccine for Human Cytomegalovirus, which is referred to and incorporated herein by reference in its entirety.

Background

Most current vaccines target diseases that cause acute infections and are then cleared by the immune system. In vaccine development, a significant inclusion criterion has been the extent to which a given immunogen is able to generate a strong T-cell response. However, this strategy has not been optimal for persistent, or latent infections, such as those caused by human cytomegalovirus (HCMV). In fact, some immunogens generate very strong T-cell responses, but are ineffective as vaccines against viruses that cause persistent or latent infections.

Vaccines are often targeted against immunodominant proteins of the virus. That is, vaccines often use the same antigens that are recognized and targeted by the immune system of a healthy host. HCMV candidate vaccines in preclinical and clinical testing are focused on eliciting CD8+ T cell or neutralizing antibody responses toward HCMV proteins that are known to be targeted during HCMV infection of the immunocompetent, healthy host. The HCMV targets for CD8+ T cell-mediated immunity being tested are most commonly the immunodominant UL83-pp65 and IE1-pp72 proteins. While CD8+ T cells specific for these viral proteins are believed to be protective, recent results in an animal model suggest that CD8+ T cells against immunodominant CMV antigens may not provide any protection despite their high numbers in the infected host.

In the United States, approximately 40,000 newborns are congenitally infected with human cytomegalovirus (HCMV) annually. For many years, it has been recognized that human cytomegalovirus (HCMV) is efficiently transmitted to the fetus during pregnancy, with 0.5 to 2.5% of all newborns showing evidence of congenital infection. Unfortunately, the in utero infection is not benign, and 5 to 10% of the congenitally infected infants will be symptomatic at birth, with serious neurological defects. (for review, see (67)). Of the 5% to 10% that are symptomatic at birth, most

develop sequelae such as microcephaly, sensorineural hearing loss, optic atrophy and chorioretinitis, and motor disabilities. Even the infected children who appear asymptomatic at birth are at high risk, as 10 to 15% of these children will show varying degrees of neurological damage later in life. The problem is intensified by the large increase in the number of young children in day care centers as the transmission rate of HCMV among children in these centers is high, and these children will frequently transmit the virus to their seronegative mothers or day care providers. The annual seroconversion rate for women with infected children is 30% as compared to a 3% rate for women with uninfected children. Moreover, immunization with the Towne strain of HCMV, which has been tested as a potential vaccine, did not significantly decrease the transmission rate. Since it is this group of women who most commonly will be pregnant, the risk to the newborn is significant. While the serological status of the mother positively correlates with protection of the newborn from disease, recent evidence strongly suggests that prior maternal immunity is not completely protective against neonatal disease from recurrent infection or infection with a different HCMV strain (4, 21). The devastating consequences of in utero infection make it imperative to develop an effective and safe vaccine that will prevent both acute infection and the establishment of latency. In addition to the effect in newborns, HCMV disease in other populations, such as, for example, transplant recipients, including both solid tissue and bone marrow transplants, can be quite severe, and has gained greater attention as the number of transplants has significantly increased.

Recovery from HCMV disease correlates with a cellular immune response rather than the presence of CMV-neutralizing antibodies (59, 70). Initially, it appeared that most of the HCMV-specific CTLs were directed against the HCMV UL83 (pp65) matrix phosphoprotein with relatively low levels of CTLs specific for the HCMV IE1 72-kDa protein (a functional homolog of the MCMV gB) and the structural glycoprotein B (1, 5, 23, 28, 55, 78). Subsequently, it was found that the frequency of CD8+ CTLs directed against IE1 is similar to that against pp65 (30, 43), and that multiple HCMV proteins are potential targets for CD8 T cells (14, 50).

An effective vaccine against HCMV disease has been an elusive goal for many years, even though many of the antigenic targets of the neutralizing antibody and CD8+ T cell responses have been identified (for reviews, see (26, 67)). Clinical trials using the tissue culture-passaged Towne strain was found to induce both neutralizing antibodies and CTLs and provided limited protection against severe disease in transplant recipients and in volunteers given a low dose HCMV challenge, but failed to prevent infection in women exposed to young children shedding HCMV. The envelope glycoprotein B (gB) has been the basis for virus neutralizing antibody inducing vaccines, both as a subunit vaccine (adjuvanted with MF59) as well as a recombinant replication deficient canarypox vector ALVAC-CMV(gB). Both vaccines were found in clinical trials to be well tolerated, and although the subunit gB vaccine was found to elicit high levels of HCMV neutralizing antibodies in seronegative volunteers, ALVAC-CMV(gB) was only able to elicit neutralizing antibodies after subsequent boosting with Towne. Preliminary results have been obtained following vaccination of

seronegative subjects with the pp65 expressing ALVAC-CMV(pp65) vector, as strong pp65-specific CTL levels were elicited as well as CTL precursor frequencies similar to those found in HCMV seropositive subjects. Other vaccination approaches that have undergone preclinical testing in mice include plasmid DNA (pDNA) encoding gB or pp65, a peptide of the conserved CD8+ T cell epitope of pp65, dense bodies, and more recently a recombinant vaccinia virus Ankara that expresses gB (2, 16, 17, 46, 69, 91). The key question, however, is whether they will protect against infection in seronegative individuals.

There is a need for an HCMV vaccine that can prevent HCMV infection, and that could limit HCMV replication, and possibly vertical transmission from mother to fetus or viral dissemination and disease in the transplant recipient.

Herpes simplex virus type 2 (HSV-2) is a medically important pathogen worldwide, with a seroprevalence rate that has been increasing in the US over the last two decades. HSV-2 infects between 10 and 50% of the population worldwide, and in the US, it is estimated that 20% of the population is infected (for review, see (92)). A unique property of the herpesviruses is that they can enter latency, a state characterized by the absence of infectious virus and limited viral gene expression. In response to various stimuli, the virus reactivates, replicates, and produces infectious virions. HSV-2 infection is usually initiated following sexual contact of a seronegative individual with someone who is shedding infectious virus. The primary infection of genital, perigenital, or anal mucosal skin sites is followed by transmission most commonly to the sacral ganglia where the virus establishes latency. Reactivation from the ganglia then leads to infection and viral shedding in the vagina or skin of the penis. The frequent reactivation of genital herpes not only is a source of physical discomfort and psychological stress, but also can cause serious disease in the newborn, which often leads to death. A major problem in controlling sexual transmission is that shedding of virus may be asymptomatic, and the incidence of HSV-2 infections continues to increase. Although antivirals are available, the lifelong persistence of this virus provides a strong impetus for the development of a vaccine that will prevent infection and the establishment of latency.

There is a need for the development of an effective vaccine that prevents infection and the establishment of latency, thus eliminating the possibility of recurrence. While most vaccine strategies to date have failed in human clinical trials, the immunological data gained over the years have shown that HSV-2 infection is controlled by both innate and adaptive immune responses, with CD8 and CD4 T cells playing a major role in viral clearance from the lesion. To provide the basis for a protective T cell based vaccine, recent work has identified many of the HSV-2 proteins that are primed by infection. However, the cellular and antibody responses to HSV-2 infection are not sufficient to provide sterilizing immunity and protection against recurrent infection and viral shedding. Thus, immune responses generated by a successful vaccine must be more effective than natural immunity.

Summary

The invention is in general directed to methods and compositions for preventing or treating infections by viruses involved in persistent and/or latent infections. The methods and compositions are directed toward the prevention and treatment of infections caused by viruses such as, for example, herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses, including, for example, cytomegalovirus.

Brief Description of the Drawings

Figure 1 is a graphical depiction of the results of DNA immunization of mice with M54 (DNA polymerase) or M105 (helicase) showing consistent protection against challenge virus replication in the spleen. Four BALB/c mice per group were i.d. immunized 3 times in 2 weeks with either empty vector DNA (pc3Δneo) or DNAs encoding IE1, M54, M70, or M105. Two weeks after the last immunization, mice were i.p. challenged with 1 of the 3 LD_{50} doses of SG-MCMV shown. On day 6 postchallenge, spleens were removed and homogenized for MCMV titer determination. Bars and circles represent the group means and individual Log_{10} of the virus titers for each of the spleens, respectively. The horizontal lines indicate the limits of detection for the highly sensitive plaque assay.

Figure 2 is an example of a timeline of immunization and challenge infection.

Figure 3 In vitro and in vivo expression of the MCMV homologs of HCMV DNA polymerase (M54), primase (M70), and helicase (M105). A) The MCMV ORFs, cloned into pcDNA3.1/V5-His-TOPO, were expressed using the T7 promoter by coupled in vitro transcription/translation reactions (i.e. TNT T7 Quick) with [^{35}S]methionine. A portion of each reaction was subjected to reducing SDS-PAGE on a 7% polyacrylamide gel and the labeled proteins were detected by autoradiography. Numbers and lines on the left indicate the positions and relative molecular weights (in kDa) of the proteins in the marker. Vect indicates the TNT reaction performed with the DNA vector alone. Predicted molecular masses for the encoded proteins are: M54, 128.8 kDa; M70 (untagged), 109.6 kDa; and M105, 111.4 kDa. B) After mutating the M70 clone to yield the V5- and 6xHis-tagged M70*, plasmids were transiently transfected into COS-7 cells and whole cells were lysed and solubilized in reducing SDS-PAGE sample buffer 48 h posttransfection. Lysate proteins were resolved by SDS-PAGE as above and electroblotted to a nitrocellulose membrane that was subsequently probed with a mouse-anti-V5 monoclonal antibody. Numbers at left are as in (A), and Vect indicates the lysate from cells transfected with empty plasmid vector. The predicted molecular mass for the M70* protein is 114.7 kDa.

Figure 4 Protection against virus replication in the spleen elicited by M54 and M105 in an independent experiment. Six BALB/c group were either left untreated (Naïve) or immunized as in FIG. 2. Three weeks after the last immunization, mice were i.p. challenged with 0.5 x LD_{50} of SG-MCMV, and on day 6 postchallenge, spleens were harvested and titered as in FIG. 2. Bars, circles, and the horizontal line are described in FIG. 2.

Figure 5 Flow cytometric analyses of the CD8 T cell responses in BALB/c mice immunized with DNAs expressing IE1, M54, or M105 using transiently transfected stimulator cells. Mice were i.d. immunized 4 times with either empty plasmid vector (Vect DNA) or plasmid DNA expressing IE1, M54, or M105. To measure CD8 T responses elicited by MCMV infection, another group of mice was i.p. infected with 1.2 □ 10^5 PFU of TC-MCMV. Two weeks after the last DNA immunization or MCMV infection, mice were sacrificed for ICS assay. As described in the Examples, splenocytes were prepared, counted, and incubated in the presence of brefeldin A with BALB SV40 (H-2^d) stimulator cells that were transfected 48 h earlier with plasmid DNA expressing either IE1, M54, or M105 as shown (Stimulation). After stimulation, splenocytes were surface stained with a PE-Cy5-anti-mouse-CD8a, fixed, stained intracellularly with FITC-anti-mouse-IFNγ antibodies, and analyzed by flow cytometry. The scatter plot for 1 mouse per immunization/infection and stimulation group is shown, arbitrarily chosen as Mouse #2. Percentages shown are the percentage of CD8+ T cells that were IFN-γ+ after stimulation, with the cell number for CD8 and IFN- γ double positive cells calculated as the cell number in quadrant Q2 minus the background staining in gate P4.

Figure 6 CD8 T cell responses in BALB/c mice immunized with DNAs expressing IE1, M54, or M105. Groups of mice were DNA immunized or MCMV infected as in FIG. 4. A) Two weeks after the last DNA immunization or MCMV infection, 3 mice per group were sacrificed for ICS assay. The complete data for the experiment in FIG. 4 is shown, with bars representing the group mean percentages of CD8+ T cells that were IFN-γ+ for each vaccine group and symbols representing the individual values for each mouse in the group. Note that splenocytes from the same 3 TC-MCMV infected mice were tested with each of the 3 stimulator groups. B) Same as in (A) except that the ICS assay was performed on mice 3 weeks after the last DNA immunization or 4 weeks postinfection with TC-MCMV.

Figure 7 CD8 T responses in DNA immunized or TC-MCMV infected mice on d 5 postchallenge with SG-MCMV. Three BALB/c mice were immunized 3 times in 2 weeks with either empty vector or plasmid DNA expressing either IE1, M54, or M105. Another group of mice was i.p. infected with TC-MCMV as in FIG. 4. Seven weeks after the last DNA immunization or 6 weeks after MCMV infection, mice were i.p. challenged with 1.2 x 10^5 PFU of SG-MCMV, and the ICS assay was performed on the splenocytes of these mice on day 5 postchallenge as above. Bars and symbols are as in FIG. 5.

Figure 8 Amino Acid and Nucleotide Sequences of 23 Conserved, Essential Genes of HCMV (Strain AD169) and Amino Acid Sequences of Their MCMV (Strain Smith) Homologs.

Figure 9 Amino Acid Sequences of 12 Essential Genes of Herpes Simplex Virus Type 2 (Strain HG52) That Are Highly Conserved with HCMV (Strain AD169), and corresponding nucleotide sequences.

Detailed Description

It has been found, surprisingly, that a strong immune response against a virus that causes persistent or latent infections may be achieved by immunizing with DNA derived from a highly conserved gene, or encoding a highly conserved gene product. In contrast to traditional vaccines, which usually target proteins that are immunodominant, an effective response against a persistent or latent infection may be achieved by vaccines that target proteins that are otherwise not targeted by a natural immune response. The present invention also provides a new method for inducing an effective immune response against a virus that causes persistent or latent infections by, for example administering a DNA vaccine encoding essential viral genes in a priming step, and a killed virus or attenuated live virus in a boosting step. The present invention may be used to generate effective immunity against persistent or latent infection-associated viruses including, for example, herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses, including, for example, cytomegalovirus.

One benefit of using highly conserved viral proteins as vaccine targets is that the virus must express the targeted gene products in order to replicate and thus cannot escape immune detection by abrogating their expression. Another is that viral mutants that could otherwise escape CD8+ T cells specific for these genes would be less likely to arise due to the necessity for conservation in these genes to maintain the enzymatic activities of their encoded proteins.

In one embodiment of the invention, the vaccine consists of delivery of the plasmid DNA encoding essential, conserved viral genes and the killed virus or attenuated live virus preparation in priming and boosting steps. Those of ordinary skill in the art may determine the order and method of delivery. For example, the plasmid DNA is delivered to elicit specific CD8+ T cell responses against the conserved, essential proteins of the virus. Upon subsequent infection with HCMV, these CD8+ T cells can recognize and destroy virally infected cells within the host to limit the replication of the virus in target organs and prevent disease.

The priming arm of the immunization procedure consists of delivering purified plasmid DNA that expresses viral gene targets that elicit protective CD8+ T lymphocyte responses, while the boosting arm of the vaccine consists of delivering chemically killed or attenuated live HCMV to elicit virus neutralizing antibodies that help limit the dissemination of virus. Targeting antiviral CD8+ T cell immunity against the highly conserved, essential genes of HCMV is of particular importance because 1) the virus must express the targeted gene products in order to replicate and thus cannot escape immune detection by abrogating their expression, 2) viral mutants that could otherwise escape CD8+ T cells specific for these genes would be less likely to arise due to the necessity for conservation in these genes to maintain the enzymatic activities of their encoded proteins, 3) the CD8+ T responses to these gene products during HCMV infection have been found to be low overall, and thus plasmid DNA primed CD8+ T cells to these gene products could provide qualitatively better protection than the ultimately incomplete protection elicited by viral infection, and 4) the high level of

conservation between HCMV and the CMVs that infect model animals provides for efficacy data in the animal models to Phase I clinical testing in human subjects.

The vaccine may be used to immunize any individual. By "individual" is meant any animal, for example, a mammal, or, for example, a human, including, for example, patients in need of treatment. An FDA-approved, commercially licensed HCMV vaccine could, depending on its protective ability, be sold and administered by physicians or clinics to either specific at risk populations or possibly to all children as part of childhood immunization. By "at risk" population is meant any individual at risk for diseases caused by HCMV, or that may carry HCMV infection to others including, for example, women before their child-bearing years, children, children under age one, day care providers, and transplant recipients or transplant donors. By treating transplant donors, for example, before the transplant is donated, infection of the recipient may be avoided. Transplants may include, for example, hematopoietic stem cell and solid organ transplants.

Diseases

Diseases or conditions that may be treated, prevented, or exhibit an alleviation of symptoms according to the present invention include any disease or condition that involves the acute or latent infection by viruses that causes persistent or latent infections. These include, for example, diseases involving infection by herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses, including, for example, cytomegalovirus. It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

DNA Vaccination

The direct inoculation of pDNA ("Naked DNA" or "DNA Immunization") into animal tissues has become a widely used approach to vaccination as it overcomes many of the dangers and limitations associated with traditional immunization methods (for review, see (29)). DNA immunization has been shown to generate protective humoral and cell-mediated responses in a variety of infectious disease models, but its ability to present antigen-derived peptides on MHC class I complexes and generate anti-viral CD8+ T lymphocytes is the key correlate for protection against CMV disease (see above). This is in contrast to older protein-based immunization methods that induce primarily MHC class II-mediated responses and themselves are poor stimulators of CD8+ T lymphocyte responses. In addition, several methods for delivering pDNA have been developed to effectively generate immune responses, including biolistic (gene gun) delivery using microprojectiles, intramuscular (i.m.) and intradermal (i.d.) injections (administered by needle or Bioject needleless jet injection), and mucosal delivery (22, 72, 80, 84). Although i.d. DNA injections provide protection against systemic MCMV challenge (27, 62, 64), other approaches may be necessary for CMV immunization to achieve mucosal immunity. An additional approach, heterologous prime-boost using DNA as the priming step, is emerging as an effective means for vaccination against such pathogens as

HIV, herpes simplex virus, hepatitis viruses B and C, Mycobacterium tuberculosis, and the malaria causing Plasmodium parasites, with clinical trials already underway in some cases (for review, see (87)). Heterologous DNA prime-boost been shown to elicit synergistic levels of T cell and antibody immunity that are not observed with repeated boosts with the same antigen delivery system, and the mechanisms underlying this synergism are beginning to be defined (20, 54). Coupled with their ability to generate high levels of protective antibodies, heterologous prime-boost vaccination may provide the long awaited tool for vaccination against pathogens recalcitrant to control using the traditional vaccination strategies.

The DNA vaccine may be administered using any appropriate method, including, for example using a replicating or a non-replicating viral vector, such as, for example, an adenovirus or vaccinia virus vector, a purified plasmid vector, or other form of DNA vaccine known to those of ordinary skill in the art.

By "derived from a highly conserved gene" is meant that the DNA encodes either part or all of a protein that is highly conserved, or the DNA sequence is the same as either part, or all of a highly conserved gene." By "part" is meant at least 20, 30, 40, 50, 60, 70, 80, or 90% of a protein or gene sequence. One method to determine whether a gene is highly conserved is to determine its % FastA aa identity, guidance for this determination may be found, for example, in the present application, including, for example, in Table 1.

Although many examples of the present application discuss the use of mouse CMV, it is understood by those of ordinary skill in the art that the present methods may comprise the use of human CMV, and human CMV genes and proteins. For example, DNA encoding for highly conserved proteins may comprise protein-coding segments from HCMV, such as HCMV having the DNA sequence provided in GenBank accession number GI|28373214 (NC001347).

Murine Model of HCMV infection

The serious problems associated with HCMV infection have made it imperative to understand the pathogenesis and immunology of this virus in order to develop strategies for its prevention and treatment. However, progress with the human virus has been slow primarily because the strict species-specificity of the virus has precluded studies in animal models. As an alternative, many in vivo studies have utilized as a model murine CMV (MCMV) infection of mice, which greatly resembles its human counterpart with respect to acute infection, viral gene expression, establishment of latency, host immune response to the viral gene products, and reactivation after immunosuppression. These similarities coupled with the ease of performing experiments with large numbers of mice, the availability of many genetically-defined inbred strains, and the vast body of knowledge on murine immunobiology has made this model system extremely attractive. One of the greatest values of this model is that a large amount of information can be obtained at a relatively low cost and in a

reasonable period of time. This knowledge can then be used to efficiently design and prioritize the far more complicated and expensive studies for the development and testing of a human vaccine.

The molecular organization of the CMV genome, the transcriptional patterns during the permissive infection, the mechanisms involved in viral DNA replication, and the in vivo pathogenesis of the virus during acute and latent infection has been defined (51-53, 56, 57). MCMV homologues of HCMV DNA polymerase, glycoprotein B, and matrix proteins have been identified (10, 11, 15). Efforts have been made to develop a vaccine using this mouse model. ((27, 61, 62, 64, 88, 89, 93).

The MCMV genome is ~230 kbp in length and encodes at least 170 open reading frames (13, 56, 71). During the permissive infection, there are at least 3 distinguishable phases of gene expression (for review, see (60)). The IE gene products are those synthesized immediately upon infection and rely primarily on host factors for their expression. Early RNA and protein synthesis precedes viral DNA replication and is dependent on the prior expression of one or more IE genes. Finally the late genes are transcribed after the initiation of viral DNA synthesis.

MCMV infection is controlled by both innate and adaptive immune responses. The innate response, consisting of NK cells, macrophages, and the cytokines IFN-gamma, TNF-alpha, IL-12 and IFN alpha/beta, plays a central role in the initial resistance to infection (8, 31, 49, 65, 66, 68, 81). In addition, a cellular gene designated cmv1 controls the early splenic replication of MCMV and confers NK-cell mediated resistance (79). This gene has been identified as the killer cell receptor Ly49h, which activates NK cells against virally infected targets (7, 47).

Studies of HCMV immunity and disease in transplant recipients have shown the importance of cell-mediated immunity in protecting against HCMV disease (3, 77), and work in animal models, such as the MCMV model, has allowed for elucidating the protective roles of specific leukocyte subsets (74). The necessity of the adaptive component of cell-mediated immunity, the CD8+ and CD4+ T lymphocytes, to limit the acute, persistent, latent, and reactivating infections has been documented through depletion and adoptive transfer studies (reviewed in (73)). Immune reconstitution of immunoablated mice with MCMV-specific CD8+ T lymphocytes has been shown to reduce the viral load in the spleen, lungs, liver, and adrenals, while long-term depletion of CD4+ T lymphocytes in infected mice results in persistent infection in the salivary glands (41). The identity of the specificities of the antiviral CD8+ T cells has long been a subject of interest as the findings have strong implications for choosing viral antigens to use in antiviral cytoimmunotherapies and vaccines. While the identity of the immunodominant peptide of the immediate early 1 (IE1) gene product and the protective ability of IE1-specific CD8+ T cells in BALB/c mice have long been known (74), there had also been strong evidence pointing to the existence of CD8+ T cells that were generated against unidentified viral early (E) and late (L) gene products (75). With the advent of more reliable methods for the detection and quantification of specific CD8+ T cells, the identities of additional CD8+ T cells specificities have been revealed. These include the HCMV UL83-pp65 homologs M83-pp105 and M84-p65, the antiapoptotic gene product M45, the MCMV immunoevasin gene product m04 (gp34),

and two additional genes unique to MCMV, m164 and m18 (24, 34-40). One common feature of these MCMV genes is their expression at either E or E/L times of infection.

The identification of these E and E/L gene products as CD8+ T cell targets was initially paradoxical due to the known expression of immunoevasin E genes that encode glycoproteins that block cell surface presentation or recognition of virus derived antigenic peptides on MHC Class I complexes (73). The MCMV m152 gene product gp37/40 retains peptide loaded Class I complexes in the ER-cis-Golgi intermediate compartment, and the m06-gp48 reroutes these complexes to the lysosome for degradation (24, 45, 48, 76, 92). The m04 gene product gp34 binds to MHC Class I complexes without hindering their transport to the cell surface, but appears to prevent recognition of the complex by CD8+ T cells (44). Mutational analysis of MCMV has demonstrated the relative roles of the known immunoevasins in MHC Class I downregulation as well as some of the cooperative and competitive interactions among the immunoevasins (42, 85). In addition, the m152 deletion mutant was demonstrated to be attenuated in T cell competent mice (45), and cells infected with wild type, but not m152 deleted, MCMV are not recognized by M45-specific CD8+ T lymphocytes (24, 37). This is a significant result, as M45 has been shown to be a dominant antigen during the acute and memory response in C57BL/6 mice. It also has important ramifications for vaccine design, as cytoimmunotherapy with a specific CTL line for this dominant antigen was not effective in limiting viral replication (37).

The murine model has been used to test a prime-boost approach consisting of intradermal (i.d.) DNA immunization with a pool of 13 plasmids expressing MCMV proteins followed by intraperitoneal (i.p.) vaccination with formalin-inactivated MCMV (FI-MCMV) generated strong neutralizing Ab as well as antigen-specific CD8 T cells and confers complete short-term protection against infection in BALB/c mice following systemic challenge with highly virulent virus (64, 89). Sterilizing immunity had been achieved, as there was no detectable virus in either the spleen or salivary glands. Neither intradermal DNA immunization nor vaccination with formalin-inactivated MCMV alone provided complete protection. Further research investigated protection against an intranasal (i.n.) mucosal challenge and whether the protection was long-term. It was found that the viral titers in the spleens and lungs and in the majority of the salivary glands were below the limits of detection at all time points following systemic challenge. Following mucosal challenge, although complete sterilizing immunity was not achieved, viral titers in the lungs and spleen were reduced 1,000 to 10,000 fold, and titers in the salivary glands were reduced 10,000 fold at times corresponding to the peak of replication in the unimmunized controls.

Using the mouse CMV (MCMV) model of infection, immunization of mice with plasmid DNAs encoding conserved, essential genes of MCMV is able to provide protective immunity against subsequent MCMV replication in the spleen of the vaccinated mice. Delivery of the whole, killed MCMV virus or attenuated live virus particles elicits antibody responses against the glycoproteins in

the viral envelope that can neutralize the virus and help to limit the spread of the virus from organ to organ.

A prime-boost approach consisting of DNA immunization with a pool of 13 plasmids expressing murine cytomegalovirus (MCMV) proteins followed by vaccination with formalin-inactivated MCMV (FI-MCMV) generates strong neutralizing Ab as well as antigen-specific CD8 T cells and confers complete short-term protection against infection in BALB/c mice following systemic challenge with highly virulent virus. As detailed in the examples, a smaller pool of plasmids may be used to generate an immune response. A smaller pool may include DNA plasmids expressing at least two, at least three, at least four, at least five, or at least six MCMV proteins. As shown in the examples, this pool may include, for example, DNA that encodes all or part of gB, M54, and M105. Each DNA sequence may be included on a separate plasmid, or one plasmid may include more than one DNA sequence. In other protocols, the three MCMV DNA plasmids (one of which was not in the original 13) were injected followed by immunization with formalin-inactivated MCMV. The most important finding was that this dual immunization protocol generated long-term sterilizing immunity in the lungs, spleen, and salivary glands of all BALB/c mice challenged systemically.

Boosting Vaccines

Either inactivated or attenuated live virus may be used in the boosting step of the present invention. Virus may be inactivated by, for example, chemical means known to those of ordinary skill in the art, including, for example, chemical treatment, or treatment with extreme temperatures, such as heat. Formalin treatment, for example, is one method of inactivating live virus. In other embodiments, attenuated live virus is used in the boosting step. The attenuated live virus may, for example, be the Towne strain of HCMV. In exemplary embodiments, for treatment of humans, the Towne strain of HCMV is used in the boosting step.

Herpes simplex Virus 2 Infection

A. HSV-2 Genome Organization and Growth Cycle

The HSV-2 genome is ~ 154 kbp in length and encodes at least 84 open reading frames (ORFs). During the permissive infection, there are at least 3 phases of gene expression, immediate early (IE), (E), and late (L) (70, as referenced in Example 16). The IE gene products are synthesized immediately upon infection and rely primarily on host factors and at least one input virion protein (VP16) for expression. Early RNA and protein synthesis precedes viral DNA replication and is dependent on the prior expression of one or more IE genes. Finally the late genes are transcribed after the initiation of viral DNA synthesis.

B. Immune Responses to HSV-2 Infections

HSV-2 infection is controlled by both innate and adaptive immune responses (41, 67 as referenced in Example 16). The adaptive immunity involves neutralizing and non-neutralizing antibodies and specific cell-mediated immune responses, with both CD8 and CD4 T cells having a major role. These immune responses modulate the infection, but do not prevent recurrent infection or

infection with another HSV-2 isolate. Their importance, however, is highlighted by the more frequent recurrences and increased disease severity seen in immunocompromised individuals. Analysis of recurrent HSV-2 genital lesions has also shown that infiltration of cytotoxic T lymphocytes (CTLs: CD4+ and CD8+) correlates with the clearance of virus from the lesion (44 as referenced in Example 16).

Neutralizing antibodies in HSV-2 infected individuals are primarily directed against gB and gD. Early work indicated that in humans, the CD8 T cell responses to HSV-2 proteins were relatively narrow, with the following ORFs detected: gB2, gD2, gE2, UL46, UL47, UL49, ICP0, ICP4, ICP22, ICP27, UL7, and UL25 (40, 42, 43, 58, 86, 87 as referenced in Example 16). Recently, an extensive analysis with peptides representing 48 HSV-2 ORFs, showed that the CD8 T cell responses were broader (35 as referenced in Example 16). All 48 ORFs were detected, and there was significant diversity in the pattern of responses between different individuals. The greatest frequency of responses were specific for ORFs UL39, UL25, UL27, ICP0, UL46, and UL47. It should be noted, however, the ORFs analyzed were primarily IE and viral structural proteins.

The herpesviruses are proficient at immune evasion, and HSV-2 is no exception. HSV-1 and HSV-2 down-regulate MHC class I presentation of viral antigen by a mechanism that involves interaction of the viral protein ICP47 with the transporter protein associated with antigen presentation (TAP) (24, 32, 88 as referenced in Example 16). This interaction prevents TAP from transporting viral peptides into the lumen of the endoplasmic reticulum, where they would form a complex with MHC class I molecules and be transported to the surface of the cell for recognition by CD8+ CTLs. Another mechanism of immune evasion involves viral effects on dendritic cells, the professional antigen presenting cells (APCs). HSV-2 impairs the function of murine dendritic cells and can induce cell death (37 as referenced in Example 16). In particular, HSV-2 infection of bone marrow-derived dendritic cells impairs their allostimulatory ability and production of IL-12, and hence may inhibit the priming of naïve T cells against HSV-2 infection. A study of the mechanisms governing the initiation of protective Th1-directed T cell immunity following intravaginal inoculation of HSV-2 in mice indicated that there was a rapid recruitment of submucosal dendritic cells to the infected epithelium (96 as referenced in Example 16). These cells remained uninfected but did acquire viral antigen and presumably traveled to the lymph nodes where they presented the viral antigen in the context of MHC class II molecules to CD4+ T cells. Recently, it has been found that HSV-2 infection of human monocyte-derived dendritic cells also results in apoptosis, but uninfected dendritic cells can phagocytose cell fragments from the dying cells and cross-present the antigens (8 as referenced in Example 16). Thus, the host may counter the viral effects on dendritic cells by priming T cells in the lymph nodes via cross-presentation of viral antigens by uninfected dendritic cells.

C. HSV-2 Vaccine Trials

Many approaches have been taken to develop a vaccine against HSV-1 or HSV-2 (for review, see (36, 41, 78 as referenced in Example 16)). Almost all have shown some level of protective

efficacy in animal models, but have failed in human clinical trials, despite their ability to elicit strong neutralizing antibody responses. An approach used in the 1980s was to develop vaccines that consisted of inactivated HSV viral preparations. One included formalin inactivated fractions of HSV-1 proteins from infected cells, and this was tested in HSV discordant couples to prevent genital disease (74-76 as referenced in Example 16). Heat inactivated HSV-2 and HSV-1 virion preparations were also tested in Italy (49 as referenced in Example 16). Unfortunately, the studies were not performed in double blind, randomized, clinical trials, making interpretation of the results difficult. Another vaccine utilized preparations of detergent-dissociated viral glycoproteins. Although this vaccine protected against acute infection and central nervous system disease in animal models, and elicited an immune response in humans, it showed no protection in clinical trials (2, 15, 54, 79 as referenced in Example 16).

Various live-attenuated HSV vaccines have been tested, as it was believed that they would generate a much broader immune response. These vaccines have been produced either by multiple passages of the virus in tissue culture or by mutation of specific viral genes. A problem with these vaccines is that a balance of high immunogenicity and reduced virulence must be achieved. One live-attenuated vaccine against HSV-2 currently being developed consists of HSV-2 with a deletion of the protein kinase domain of the large subunit of ribonucleotide reductase ICP10 (4 as referenced in Example 16 as referenced in Example 16). This domain has polarizing Th2 activity and is required for efficient viral replication and latency reactivation. The vaccine (ICP10DPK) generates protection in animal models, and results of the initial trials indicate that this vaccine has some therapeutic efficacy (3, 16 as referenced in Example 16). Another live attenuated HSV-2 vaccine was derived by deleting both copies of the $\gamma_1$34.5 gene, UL55-56, UL43.5 and the US10-12 (69 as referenced in Example 16). Although this vaccine was immunogenic and could protect guinea pigs from disease, it did not protect against infection.

An alternative to a live-attenuated HSV vaccine is one that contains replication-impaired HSV. One approach consisted of either HSV-1 or HSV-2 that had a deletion of gH, and hence the virus could only undergo one round of replication (13, 22 as referenced in Example 16). These vaccines were protective in animal models, but the gH negative HSV-2 viral vaccine showed no protection against recurrence when tested for therapeutic efficacy in humans (14 as referenced in Example 16). A second approach has been to derive replication defective HSV-1 and HSV-2 viruses that do not express ICP8 (UL29) and one of the proteins (UL5) of the helicase-primase complex (for review, see (19 as referenced in Example 16). The *dl*5-29 HSV-2 vaccine was protective against lethal viral infection in mice, and showed protective efficacy when used as a prophylactic or therapeutic vaccine in guinea pigs. A major advantage of this vaccine is that it does not establish latency. Clinical trials with this vaccine are planned.

As another approach, vaccines with recombinant HSV glycoproteins, primarily gB and gD, were developed. A vaccine developed by Chiron, consisted of gD and gB from HSV-2 with the adjuvant MF59 (17 as referenced in Example 16). Another vaccine, developed by GlaxoSmithKline, contained HSV-2 gD along with the adjuvant alum and deacylated monophosphoryl lipid A (82 as referenced in Example 16). Both vaccines were tested in HSV-2 serodiscordant couples. Although the Chiron vaccine did not yield statistically significant protection against HSV-2 infection, the GlaxoSmithKline vaccine showed a significant protective effect against disease specifically in women (but not in men) who were seronegative for both HSV-1 and HSV-2. Interestingly, in this latter study, it appeared that prior infection with HSV-1 also conferred some protection against HSV-2 disease, although the vaccine did not augment the level of protection. Peptide vaccines have also been considered as an alternative approach, but the difficulty is finding the right combination of immunogenic peptides that will be protective in individuals with different HLA genes (7, 26 as referenced in Example 16).

Several viral vectors that can express HSV antigens, usually gD, have also been tested: vaccinia virus, adenovirus, Oka varicella zoster virus, and vesicular stomatitis virus (VSV) (1, 5, 6, 23, 25, 53, 64 as referenced in Example 16). Although these vaccines showed protection in animal models, they have not yet been transferred to human clinical trials. These vaccines, with the exception of VSV, have the disadvantage of potentially reduced efficacy in individuals with prior immunity to the vectors.

Formulation

While the compositions and methods of the present invention will typically be used in therapy for human patients, they may also be used in veterinary medicine to treat similar or identical diseases. The compositions may, for example, be used to treat mammals, including, but not limited to, primates and domesticated mammals. The compositions may, for example be used to treat herbivores. The compositions of the present invention include geometric and optical isomers.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

The exact dosage will depend upon the route of administration, the form in which the composition is administered, the subject to be treated, the age, body weight /height of the subject to be treated, and the preference and experience of the attending physician. .

The compositions of the present invention may include pharmaceutically acceptable salts. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate,

estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20.sup.th ed.) Lippincott, Williams & Wilkins (2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

Administration of pharmaceutically acceptable salts of the DNA molecules described herein is included within the scope of the invention. For example, pharmaceutically acceptable salts may be prepared from non-toxic bases including organic bases and inorganic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, and the like. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, basic amino acids, and the like. Pharmaceutically acceptable salts may be found in, for example, S. M. Berge et al., Journal of Pharmaceutical Sciences 66:1-19 (1977).

Methods of delivering DNA vaccines, as well as formulations and methods of administration may be found in, for example, U.S. patent numbers 6,806,084 and 5,580,859. The DNA vaccine may, for example, be formulated to include transfection-facilitating proteins, viral particles, gold particles, liposomal formulations, charged lipids and calcium phosphate precipitating agents, or it may not include these components. Those of ordinary skill in the art may determine the appropriate formulation, considering factors such as the route of administration, for example, intradermal, intramuscular, or intranasal. Methods of administration may comprise the use of replicating or non-replicating vector.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries.

Kits

The present invention further provides kits comprising vaccine compositions or components that may be used to prepare vaccine compositions. For example, such kits may comprise DNA molecules of the present invention, such DNA molecules may be, for example, formulated for vaccine delivery. Such kits may further comprise a second vaccine composition, comprising, for example, an attenuated live or an inactivated virus. Or, for example, such kits may provide chemicals that may be used to inactivate viruses, such as, for example formalin; such kits may further comprise virus that has not yet been chemically inactivated.

Kits may also include instructions, and other components needed for immunization, such as, for example, nasal, muscular, or dermal delivery systems, such as, for example, needles, syringes, and inhalation or misting devices.

Examples

While the examples presented below discuss studies in MCMV, these examples are illustrative of methods that may be used with other persistent or latent viruses. Thus, examples that, for example, present methods of determining appropriate DNA sequence, or delivery method to use in the immunization protocol, are illustrative of methods that may be used in other viruses to determine the appropriate DNA sequence or delivery method. Amino acid sequences of exemplary HCMV conserved genes are presented in Figure 8, along with corresponding nucleotide sequences. In some instances, the nucleotide sequence presented encodes a longer protein than the amino acid sequence in the Figure; those of ordinary skill in the art may determine whether the full length, or a truncated version of the nucleotide sequence is appropriate. Those of ordinary skill in the art would also recognize where the nucleotide sequence may vary from the nucleotide sequence encoding the corresponding protein, for example, where the nucleotide sequence is the complement of the coding sequence. In addition, although a particular strain of HCMV, AD169, is used in Figure 8, those of ordinary skill in the art recognize that other strains, and related viruses, may also be used.

Example 1: Long-Term Protection (31 weeks) Against Systemic and Mucosal Challenge Following Dual Vaccination of Mice with Three MCMV Plasmids (encoding IE1, M84, and gB) and Formalin-Inactivated Virus

Three MCMV plasmids were given i.d. followed by injection of FI-MCMV. The choice of plasmids was based on previous results that showed that the plasmids expressing IE1 and M84 were highly protective but together they did not generate sterilizing immunity even when the DNA immunization was followed by injection of FI-MCMV. Therefore a plasmid that expressed glycoprotein B, which is the major target of neutralizing antibody during the natural infection, was added. At week 30, one group of mice was challenged mucosally with tissue culture derived virus and at week 31, a second group was challenged systemically with salivary gland derived virus. Organs (spleen, liver, lungs, and salivary glands) were harvested at days 6, 10, 14, 18, 24 and 32 postchallenge to determine viral titers. In the lungs of mice challenged mucosally, the viral titers were somewhat reduced in the mice that had received the MCMV plasmids alone and markedly reduced in the mice that had received the MCMV plasmids and FI-MCMV; by day 32 postchallenge, no virus could be detected in the lungs of the dually immunized mice. In the salivary glands of mice challenged mucosally, the reduction in titer in the dually immunized mice was even more striking, and for most mice, the titer was below the limits of detection. The most important finding was that this

dual immunization protocol generated long-term sterilizing immunity in the lungs, spleen, and salivary glands of mice challenged systemically. (93)

Example 2: Multiple Epitopes in the MCMV Early Gene Product M84 Are Efficiently Presented In Infected Primary Macrophages and Contribute to Strong CD8+ T-Lymphocyte Responses and Protection Following DNA Immunization.

Following DNA vaccination of BALB/c mice with MCMV IE1 or M84, a similar level of protection against MCMV infection was achieved (89). However, the percentage of antigen specific CD8+ T cells elicited by IE1 was higher than that by M84 as measured by intracellular cytokine staining (ICCS) when splenocytes were stimulated with an epitope peptide. These results raised the question of why there were major differences in the CTL responses between the two vaccines while both displayed similar protective effects against a MCMV challenge. To further investigate the M84 specific CTL response following i.d. DNA immunization, a modified ICCS assay was developed in which antigen-presenting cells (APCs) expressing full-length M84 were used as a stimulator. Using this modified ICCS assay, a much higher percentage of M84 specific CD8+ T cells were detected when compared to the response to the single defined epitope. By immunizing mice with plasmids expressing subfragments of the M84 gene, at least two additional CD8+ T cell epitopes were demonstrated in M84. These results provide an explanation for the correlation between the strength of immune responses and the viral protection following DNA based vaccine immunization. The IE1 and M84 specific CD8+ T cell responses following MCMV infection of BALB/c mice with the modified ICCS assay was also further investigated. Only a modest increase in the percentage of M84 specific CD8+ T cells was detected when the additional epitopes were used in the assay. These results highlight the importance of keeping in mind that antigens that do not elicit a protective response during the infection may be highly protective when administered by DNA vaccine. (88).

Example 3: CD8 T Responses to IE1, M84, and gB in BALB/c Mice Immunized with the 3 MCMV Plasmids Encoding IE1, M84, and gB or gB pDNA Alone

Groups of BALB/c mice were i.d. immunized with either 1) pc3Δneo vector alone, 2) gB pDNA alone, or 3) a pool of IE1, gB, and M84. Another group of mice was i.p. infected with TC-MCMV. Nine days after the last pDNA immunization or MCMV infection, splenocytes were harvested for CD8 T cell quantification by ICS assay. Splenocytes were stimulated in vitro with either the dominant IE1 nonapeptide or with J774 (H-2d) macrophages infected with recombinant vaccinia viruses expressing either gB or M84.

Stimulation of the splenocytes from the vector alone-immunized mice using the gB-expressing J774 cells resulted in a low background staining level of 0.08%. In contrast, mice i.d. immunized with the gB pDNA alone had a mean of 1.84% of gB-specific CD8 T cells, and mice immunized with the IE1, gB, and M84 pDNA pool had a mean of 0.32%. Infection with MCMV

elicited gB-specific CD8+ T cells to a mean level of 0.66%. Splenocytes were also stimulated with J774 cells expressing M84 as well as the IE1 peptide to document that CD8 T responses were generated against these antigens in the IE1, gB, and M84 group. Taken together, these results demonstrate that MCMV gB contains H-2d restricted MHC Class I epitopes and that both pDNA immunization and MCMV infection prime gB-specific CD8+ T cells in BALB/c mice. It is suspected that the CD8+ T cells themselves do not confer significant protection as several experiments have indicated that there is no significant decrease in MCMV titers in the spleens of gB pDNA immunized mice following short-term intraperitoneal (i.p.) challenge.

Example 4: Identification of ORFs that Augment the Protection Against Mucosal Challenge in BALB/c Mice – Protection Against Short-term and Long-Term Systemic or Mucosal Challenge Following Immunization with gB and/or gH/gL plasmids and FI-MCMV

One approach to improve protection against mucosal challenge is to include a vector encoding the virus neutralizing antibody target glycoprotein H (gH). Previous studies have shown that MCMV gH is able to elicit complement independent virus neutralizing antibodies in mice following immunization with soluble gH protein. In HCMV infected cells, trafficking of gH to the cell surface requires the formation of a gH/gL/gO complex by disulfide linkage of gH to gL followed by interaction with gO. Because the proper trafficking and glycosylation pattern, and possibly native immunogenicity, of gH may require the coexpression of the accessory glycoproteins, a vector was constructed that coexpresses MCMV gH and gL (MCMV lacks an obvious gO homolog) to use in the DNA pool to increase the levels or longevity of viral neutralizing antibody responses. A plasmid was also constructed that expresses a truncated version of gB, which will be secreted and thus may prime for a higher level of neutralizing antibody.

Groups of mice were immunized with: 1) DNA vector plus PBS in alum; 2) DNA vector plus FI-MCMV in alum; 3) gB plasmid plus PBS in alum; 4) gB plasmid plus FI-MCMV in alum; 5) gB truncated plasmid plus PBS in alum; 6) gB truncated plasmid plus FI-MCMV in alum; 7) gB plus gH/gL plus PBS in alum; 8) gB truncated plasmid plus gH/gL plus PBS in alum; and 9) as a repeat of the above, gB plus IE1 plus M84 plus FI-MCMV in alum. DNA injections were i.d., while all injections of FI-MCMV or PBS in alum were i.p.. Blood samples were collected pre-challenge and tested for neutralization antibody. All mice that received the FI-MCMV acquired neutralizing antibody prior to mucosal or systemic challenge, and although preliminary, one interesting finding is that groups that received the truncated gB plasmid plus PBS in alum showed a rapid rise in neutralizing titer after both mucosal and systemic challenge while the groups that received gB plasmid plus PBS in alum only showed a rapid rise in neutralizing titer after systemic challenge.

As a complement to the above experiment, groups of mice were immunized by priming with combinations of the gB and gH/gL DNAs and subsequent boosting with FI-MCMV in order to carefully evaluate the antibody and protective responses primed by the viral glycoprotein DNAs and

to determine whether the priming provides additional protection from long-term mucosal or systemic challenge. In this experiment, the focus is on the immunization groups that receive FI-MCMV boosts so that the immunity and protection in the various DNA prime groups can be directly compared to the group that only received the FI-MCMV boosts. Groups of mice were immunized as above with the following: 1) vector DNA plus PBS/alum, 2) vector DNA, 3) gB DNA plus FI-MCMV/alum, 4) gH/gL DNA plus FI-MCMV/alum, 5) gB+gH/gL DNAs plus FI-MCMV/alum, or 6) gB+gH/gL+IE1+M84 DNAs plus FI-MCMV/alum. As a positive control for antibody responses, another group of mice was i.p. infected with live MCMV. Blood samples were collected prior to i.p. or i.n. challenge, and on day 14 postchallenge, target organs were harvested for MCMV titer determination. Additionally, half of the mice were left unchallenged for later determination of long-term protection levels.

Prechallenge virion-specific serum IgG was quantified by ELISA. Prior to the first FI-MCMV boost, priming with gB pDNA either alone or together with gH/gL or gH/gL+IE1+M84 resulted in low-level seroconversion in 2 of 4 mice per group, whereas none of the gH/gL alone primed mice had seroconverted. Three weeks after the first boost, all of the mice except for the PBS/alum boosted mice had seroconverted. Compared with the mean ELISA titer of the vector + FI-MCMV group, the other groups had slightly higher ELISA titers, suggesting that the pDNA priming with the gB or gH/gL pDNAs provided measurable B cell priming. Three weeks after the second FI-MCMV boost, the mice primed with gH/gL either alone or in combination with the other plasmids (gB or gB+IE1+M84) had ELISA titers approximately 2-fold higher than those in the mice primed with vector and boosted with FI-MCMV and similar to those in the mice infected with live SG-MCMV. The mice primed with gB alone and boosted with FI-MCMV had similar ELISA titers as those primed with vector alone and boosted with FI-MCMV. With the caution that there is variability inherent in the use of endpoint titers, these data suggest that at the time of challenge there was a trend towards higher ELISA titers in the three mouse groups primed with gH/gL compared with those primed with the vector or gB pDNA alone.

Example 5: Salivary IgA responses and protection in BALB/c mice mucosally (intranasally) immunized with FI-MCMV with or without mucosal adjuvants

As discussed above, i.d. pDNA priming followed by i.p. FI-MCMV boosting appears to confer complete protection against viral replication in the spleen, salivary glands, lungs, and liver following i.p. challenge. In addition, this parenteral prime/boost vaccine was able to provide complete protection of the spleen, salivary glands, and liver in the majority mice following i.n. challenge. However, in the lungs of the i.n. challenged mice, virus was detectable in the majority of the mice, though at reduced levels when compared to the vehicle only immunized controls. Therefore it was sought to determine whether i.n. delivery of the FI-MCMV could increase the mucosal protection against MCMV at the initial site of replication following i.n. challenge. Because mucosal responses

are generally poor to protein antigens following i.n. immunization, the ability of two commonly used experimental mucosal adjuvants, cholera toxin (CT) and immunostimulatory CpG DNA (CpG), to elicit enhanced levels of mucosal immunity and protection was also tested.

In the lungs following i.n. challenge, all of the mice immunized i.n. with either PBS or FI-MCMV together with CT, CpG, or both had MCMV titers similar to those in the control group that received PBS + alum i.p. In contrast, the mice that were i.n. immunized with FI-MCMV alone or were i.p. immunized with FI-MCMV alone had a mean titer in the lungs that was reduced 35-fold below controls. However, the protection provided by i.n. immunization with FI-MCMV alone was lower in the salivary glands, with a mean titer reduction of only 4-fold below controls. In contrast, i.p. immunization with FI-MCMV either alone or with alum provided mean titer reductions of approximately 40-fold. Finally, following i.p. challenge, i.n. immunization with FI-MCMV alone did not provide protection in the lungs, liver, or salivary glands when compared with controls. This was in sharp contrast to the high level of protection to i.p. challenge that was conferred by i.p. immunization.

Intranasal immunization with FI-MCMV together with CT or CT+CpG resulted in the deaths of some mice following i.p. or i.n. MCMV challenge. This did not occur in control mice that were i.n. immunized with the adjuvants alone, indicating that the deaths were not caused merely by CT toxicity. These results suggest that there may be a deleterious interaction between the antigen and adjuvants. The virus titers in the PBS + adjuvant controls were comparable to those in the control mice immunized i.p. with PBS + alum. However, following i.p. challenge, the mice that were i.n. immunized with FI-MCMV + CpG had virus titers in the liver and lungs that were 50 to 100-fold higher than controls.

This study may indicate that there may not be an advantage to i.n. immunization with FI-MCMV; and that it is difficult to extrapolate effects of adjuvants from experiments that use different antigens for immunization.

Example 6: Assay of Protection Provided by Dual Immunization in Other Strains of Mice

A pilot study was conducted to test the efficacy of the dual immunization protocol in a mouse strain other than the BALB/c. C57BL/6 (H-2b) mice were immunized with: 1) DNA vector alone; 2) DNA vector plus PBS in alum; 3) DNA vector plus FI-MCMV in alum; 4) 13 MCMV DNA plasmids alone; 5) 13 MCMV DNA plasmids plus PBS in alum; or 6) 13 MCMV DNA plasmids plus FI-MCMV in alum. All DNA injections were i.d., while all injections of FI-MCMV or PBS in alum were i.p. Blood samples were collected pre-challenge, all of the FI-MCMV immunized mice acquired neutralizing antibody. Twenty-six weeks after the last FI-MCMV boost, mice were i.p. challenged. Six and 10 days following challenge, spleens and salivary glands, respectively, were harvested for MCMV titer determination.

Mice immunized with the 13 MCMV DNA plasmids alone or with the 13 MCMV DNA plasmids plus PBS in alum did not show significant protection in any organ. Although this result was

expected for the salivary glands, the lack of protection in the spleen indicated that DNA immunization with these MCMV plasmids alone was not able to elicit protective CD8+ T cell responses. However, the titers in the spleens of the DNA vector plus FI-MCMV in alum immunized mice were 45-fold lower than those in the DNA vector alone immunized mice. Importantly, the viral titers in the spleens of mice immunized with the 13 MCMV DNAs plus FI-MCMV immunized mice were below the limit of detection for 3 of 4 mice tested. In addition, the salivary glands of 3 of 4 of the mice immunized with DNA vector plus FI-MCMV in alum had undetectable levels of MCMV. Most significantly, all 4 of the mice immunized with 13 MCMV DNA plasmids plus FI-MCMV had undetectable levels of MCMV in their salivary glands. Although the numbers were small, these results showed that the immunization of an H-2b mouse strain with FI-MCMV is effective in providing long-term protection against viral replication in both the spleen and salivary glands following systemic challenge. They also indicated that sequential immunization with the 13 MCMV DNA plasmids plus FI-MCMV provides additional protection.

Example 7: DNA immunization with the MCMV homologs of the highly conserved HCMV DNA polymerase (M54) or helicase (M105) genes elicits a protective response

MCMV (strain Smith) genes that are essential for viral DNA replication (71): M54 (DNA polymerase - 50% FastA identity over 415 amino acids to HCMV UL54); M105 (helicase – 43% FastA identity over 861 amino acids to HCMV UL105); and M70 (primase – 36% FastA identity over 982 amino acids to HCMV UL70) were tested for their ability to confer immunity.

Four BALB/c mice per group were intradermally immunized 3 times within 2 weeks with either the vector plasmid alone (pc3Δneo) or this plasmid expressing the MCMV IE1 gene or the conserved, essential genes M54, M70, or M105. Two weeks after the last immunization, mice were intraperitoneally challenged with virulent MCMV at one of three doses, 0.25 x, 0.50 x, or 0.75x the 50% lethal dose (LD_{50}), and 6 days following challenge, spleens were harvested and homogenized for measurement of the load of infectious challenge virus. Results in Figure 1 are shown as the log10 of plaque forming units (PFU) of virus per spleen, with bars representing group means and circles representing values from individual mice. In addition to the positive control IE1 pDNA, the pDNAs encoding M54, and M105 were protective against viral replication in the spleen following all of the i.p. challenge doses. (Figure 1) Following challenge with the low dose of MCMV, the reductions in titer provided by immunization with the M54 and M105 pDNAs were comparable to that in the IE1 group. While the virus titer reductions in the spleens of the M54 and M105 immunized mice were not as high as those in the IE1 immunized mice following the intermediate challenge dose, following the high challenge dose, both IE1 and M54 immunization resulted in greater than 600-fold reductions in viral titers, and M105 resulted in a 60-fold reduction. M70 pDNA, which interestingly has the lowest percent aa identity to its HCMV homolog, was not protective.

Example 8: Identification of MCMV ORFs that are protective across different mouse strains

Other combinations of genes that may generate a more vigorous protective mucosal response in BALB/c mice may be identified. The related homologous human CMV genes may then be useful for more protective mucosal responses in humans. There may also be a different subset of genes that are required for protection in animals with a different H-2 haplotype.

Immunity established following natural CMV infection may suppress dissemination of the virus and disease, but if the virus persists, latency is established, the virus can reactivate, and individuals can be reinfected with a different strain of CMV. Thus, immunization must be more effective than natural infection. The most visible populations of CD8 T cells (as well as CD4 T cells and antibodies) in seropositive individuals may be immunodominant, but not immunoprotective. Highly conserved, essential nonstructural proteins may be excellent targets in infected cells for "primed" CD8 T cells, but during the natural infection there are still to be discovered immunoevasive mechanisms that prevent naïve T cells from being primed against these antigens. However, delivery of these antigens by DNA immunization might elicit the protective response.

Recent work characterizing the CD8+ T cell responses to the CMVs strongly suggests that while the CD8+ T cell repertoire that is primed by infection is not significantly affected by the known viral immunoevasins (24, 25, 50), the immunoevasins can inhibit primed CD8+ T cells from reducing the level of viral replication. For example, it has been shown that MCMV infection of C57BL/6 mice primes high levels of M45-specific CD8+ T cells. However, following adoptive transfer of these cells into irradiated recipients, expression of immunoevasins in the tissues infected with wild-type, but not mutant, virus inhibits the presentation of viral peptides and prevents the M45-specific CD8+ T cells from controlling viral replication (37). These findings have at least two important implications for rational vaccine design. First, while immunological assays can characterize the CD8+ T cell repertoire elicited by CMV infection, the ability of each specific CD8+ T cell subset to provide control of viral replication must be directly assessed by a protection assay. Secondly, since previous infection with the CMVs does not provide complete protection against reinfection or reactivation and in utero transmission of virus, the CMV infection may skew the CD8+ T cell repertoire so that the virus can establish and maintain persistent and latent infection in the midst of high numbers of primed, but ineffective, CD8+ T cells. During the infection, it is possible that naïve CD8 T cells are not primed against conserved nonstructural essential proteins (see Table 1), as the virus cannot sustain mutations in these proteins to evade the immune responses. Therefore, in order for a CMV vaccine to provide sterilizing immunity, the vaccine induced CD8+ T cell responses may need to include specificities to essential viral proteins that do not prime the CD8 T cells in the context of the viral infection.

One approach to increase the breadth of the immune response generated by the DNA vectors already being used and to identify additional MCMV genes that elicit protection is to use a DNA expression library constructed from the known MCMV ORFs for DNA vaccination. To determine

additional MCMV ORFs that are protective in the 3 mouse haplotypes, MCMV genes that are highly conserved with their respective HCMV homologs (see table 1) are cloned and tested (71). Many of these are early genes that encode proteins that contribute to viral DNA synthesis and are conserved with other herpesviruses. In addition, with the exception of M114, all of the HCMV homologs have been shown to be essential for virus replication in primary fibroblasts (12, 90). As described above, M54 and M105 genes are protective in the spleens of BALB/c mice following i.p. challenge. Interestingly, the nonprotective M70 has the least amino acid identity to the HCMV UL70. The PCR products of these genes are ligated into an eukaryotic expression vector (i.e. pcDNA3) such that a carboxyterminal Flag tag is added to facilitate protein detection. Resultant transformants are be screened for the presence of insert in the correct orientation by restriction analysis, and the 5' and 3' ends of each ORF are sequenced. Expression of each protein is demonstrated in an in vitro transcription/translation reaction or in an in vivo transient expression assay. In the initial screening experiments, for example, 12 mice per group are i.d. immunized 3 times in 2 weeks with pools of 5 or 6 of the genes in the table that have not yet been tested in a particular mouse strain. As a negative control, a group of mice is immunized with the empty plasmid vector. Two weeks after the last injection, mice are i.p. challenged with 1 of 3 sublethal challenge doses of virulent SG-MCMV, to improve the interpretation of the data, multiple doses are given. Spleens are harvested on day 6 postchallenge for MCMV titer determination. In order for a DNA pool to be considered protective, there is a spleen titer reduction of at least 5-fold relative to the vector immunized group in at least two of the challenge groups. To test for the protective ability of the DNA pools in mice of differing MHC haplotypes, the pools are screened in the CMV sensitive BALB/c (H-2^d), CBA (H-2^k), and 129/J (H-2^b) strains. The goal is to construct a minimal DNA pool that contains the fewest number of the conserved essential MCMV genes needed to protect across all 3 mouse haplotypes.

Table 1: Highly Conserved Proteins of HCMV and MCMV

MCMV gene (HCMV functional homolog)	% FastA aa Identity with HCMV (aa Overlap length)	
M44 (DNA pol processivity subunit)	59 (351)	UL44
M50 (Egress)	46 (252)	UL50
M51 (DNA packaging/cleavage)	55 (78)	UL51
M52 (DNA packaging/cleavage)	44 (250)	UL52
M53 (Egress)	49 (280)	UL53
M54 (DNA polymerase)	50 (415)	UL54
M55 (Glycoprotein B) (gB)	44 (929)	UL55
M56 (DNA packaging/cleavage)	42 (696)	UL56
M57 (ss DNA binding protein)	51 (597)	UL57
M70 (DNA primase)	36 (982)	UL70
M71 (unknown)	41(201)	UL71
M77 (Pyruvoyl decarboxylase)	49 (478)	UL77
M79 (Unknown)	49 (246)	UL79
M87 (Unknown)	59 (408)	UL87
M89 Exon 2 (DNA cleavage protein)	65 (673)	UL89
M92 (Unknown)	50 (199)	UL92
M105 Helicase, helicase-primase subunit	43 (861)	UL105

Example 9: Confirming antigen-specific CD8+ T cell responses

Once the members of the minimal cross-strain-protective DNA pool have been identified by screening above, it is important to confirm that each of the DNAs generates a antigen-specific CD8+ T cell response. With the exception of M100 (gM), protection elicited by the conserved MCMV genes above would likely be mediated by CD8+ T cells as they likely encode nonstructural antigens. The levels of antigen-specific CD8+ T cells elicited by immunization with each of the protective DNAs comprising the minimal pool may be quantified. In addition, the levels of CD8+ T cells specific for these MCMV genes may be measured following MCMV infection in order to determine whether these antigens are part of the natural CD8+ T cell repertoire. It is quite possible that these conserved genes elicit CD8+ T responses after DNA immunization but not MCMV infection due to the virus misdirecting the response in order for it to persist and establish latency.

The CD8+ T cell responses may be quantified by a modified ICS assay that uses transfected cells as stimulators (94) For example, 4 mice per group are i.d. immunized with either empty DNA vector or each of the protective DNAs of the minimal pool. In addition, a group of mice is i.p. infected with TC-MCMV. Ten days after MCMV infection or the last DNA immunization, splenocytes are isolated and stimulated in culture with syngeneic, highly transfectable cell lines (e.g. K41 H-2^b, BALB SV40 H-2^d, etc.) that were transfected with either empty vector or the protective DNA. Following stimulation, splenocytes are stained with fluorescent CD8- and IFN-gamma-specific antibodies and enumerated by flow cytometry as above. Because the transfected cells express the full-

length ORF, all the possible epitopes that can be naturally generated in the proteasome and loaded onto MHC Class I complexes may be presented, eliminating the need to immediately define the minimal MHC Class I epitope of each antigen. Using this method the majority of the ORFs of MCMV strain Smith were screened for the generation of antigen-specific CD8+ T cells in C57BL/6 mice following MCMV infection (94). Taking the ICS assay data from the DNA immunized and MCMV infected mice together, one can quickly assess the immunological basis of the observed protection across the mouse haplotypes as well as address the question of whether infection with wild-type MCMV is able to suppress the priming of naïve CD8+ T cells that are specific for these otherwise protective antigens during infection. As described above, M84 is found to be the prototypical CD8+ T cell antigen of MCMV that is highly antigenic and protective following DNA immunization, but minimally antigenic during MCMV infection.

Example 10: Identifying nonstructural E genes that elicit a CD8+ T cell response

In this example, nonstructural early genes that elicit a CD8+ T cell response were identified, the present example also demonstrates that antigen-specific CD8+ T cell responses may be obtained using methods of the present invention.

Mice, cells, and viruses, and viral purification. Three- to 4-week old specific pathogen-free female BALB/c mice were purchased from Harlan Sprague Dawley, Inc. and housed in microisolator covered cages in the Pacific Hall vivarium, University of California, San Diego. Mice were allowed to acclimate at least one week prior to immunization or MCMV infection.

NIH 3T3 (ATCC CRL 1658), COS-7 (ATCC CRL 1651), and BALB/c mouse embryonic cells (MECs) were propagated as previously described (24). BALB SV40 cells, an SV40 transformed H-2^d cell line (95), were grown in COS-7 media.

Salivary gland-derived MCMV strain K181 (SG-MCMV) was propagated in BALB/c mice and tissue culture-derived MCMV strain K181 (TC-MCMV) was prepared in MECs as previously described (96, 15). The titers of these stocks were determined by plaque assay on NIH 3T3 cells (27). The LD_{50} of this SG-MCMV stock in BALB/c mice used in this study was 8×10^5 PFU (63).

Plasmid construction and expression. Construction of pc3Δneo-pp89, expressing the cDNA of IE1-pp89 was described previously (89). Cloning of the M54, M70, and M105 genes of MCMV MW97.01, a virus derived from a bacterial artificial chromosome of Smith strain MCMV, into pcDNA3.1/V5-His-TOPO (Invitrogen Life Technologies) has also been described (97). For the studies reported here, the complete sequences of the 3 cloned ORFs were determined (Eton Biosciences, Inc., San Diego, CA) and compared with the published sequence of MCMV Smith (71), GenBank accession number U68299 (GI|21716071; NC004065). The coding sequences of the M54 and M105 ORFs were identical to the published sequence. The sequence of the M70 ORF was identical to the Smith strain sequence except for a single T insertion between the 3' end of the

MCMV-encoded ORF and the vector-encoded epitope tag sequences: a mutation that resulted in an immediate termination codon. This mutation yielded a complete, wild-type, but untagged, coding sequence for the M70 protein. Confirmation of complete, continuous reading frames were provided by coupled in vitro transcription-translation (TNT T7 Quick Coupled Transcription/Translation System, Promega Corporation) using [^{35}S]methionine, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and autoradiography following manufacturer's recommendations. To facilitate subsequent Western blot analysis of expression in transiently transfected COS-7 cells, the extraneous T of the M70 clone was deleted by QuikChange site-directed mutagenesis (Stratagene, Inc.) following the manufacturer's recommendations, and the resulting clone was verified by DNA sequencing.

Protein expression was confirmed by transient transfection of COS-7 cells using Effectene (Qiagen) followed by Western blot analysis. At 48 h posttransfection, cell lysates were made in reducing SDS sample buffer, solubilized at 42° C, resolved by SDS-PAGE, and proteins were transferred to nitrocellulose membranes. Plasmid expressed MCMV proteins were detected with a mouse anti-V5 tag-specific monoclonal antibody (Invitrogen) and SuperSignal West Pico reagent (Pierce) according to manufacturers' recommendations.

For i.d. immunization, plasmids were purified using Qiagen Endo-Free Mega or Giga columns and resuspended to approximately 2 mg of DNA per ml of endotoxin-free 10 mM Tris-HCl (pH 8).

Immunization, virus challenge, and virus titration. Plasmids were diluted immediately before injection in endotoxin-free 10 mM Tris-HCl (pH 8) buffered saline. Mice were i.d. injected with 30 µl of diluted plasmid either into 3 sites (10 µl per site) in the shaved flank near the base of the tail or into one i.d. site in the tail approximately 1.5 to 2 cm from the base. Mice were injected 3 times within 2 weeks and challenged 2 or 3 weeks after the last injection by i.p. injection with 0.5 ml of Dulbecco's phosphate buffered saline (DPBS) containing various sublethal doses of SG-MCMV.

On day 6 post i.p. challenge, mice were sacrificed and the spleens were aseptically removed and washed with DPBS. Spleens were homogenized in Dulbecco's modified Eagle medium containing 10% heat inactivated-newborn calf serum (Invitrogen Life Technologies) and 10% DMSO using 7 ml Tenbröeck homogenizers and homogenates were aliquotted and stored at –80° C until titration. The titer of infectious MCMV was determined by plaque assay of clarified homogenates using NIH 3T3 cells in 24-well dishes as previously described (27). The limit of sensitivity for this initial assay was 100 PFU per spleen. If the viral titer of a spleen was less than or equal to 5 times the detection limit (≤500 PFU per spleen), 100 µl of clarified homogenate from another aliquot of homogenate was used in a more sensitive plaque assay on NIH 3T3 cells in 10 cm dishes as previously described (63, 64), except the concentration of heat-inactivated newborn calf serum in the media was increased to 10%. The limit of sensitivity of this assay was empirically confirmed to be 10

PFU per spleen. The Log_{10} was taken of the individual viral titers in each group and the mean of the Log_{10} values was calculated.

Intracellular cytokine staining (ICS) assay. Levels of specific CD8 T cells elicited by DNA immunization were measured by ICS assay using transfected stimulator cells as described previously (97). For comparative purposes, CD8 T cell levels resulting from MCMV infection were measured in 3 BALB/c mice per group that were i.p. infected with 1.2×10^5 PFU of TC-MCMV 2 or 4 weeks prior to assay. Two to 3 weeks after the last pDNA immunization, 3 mice from each immunization or infection group were sacrificed for ICS assay. Briefly, BALB SV40 ($H\text{-}2^d$) cells were seeded into 96-well tissue culture plates and one day later, cells (ca. 60-75% confluent) were transfected with 0.5 μg of plasmid DNA and 1.25 μl of FuGene 6 (Roche) per well. Two days posttransfection, splenocytes were harvested, the erythrocytes were lysed (BD Pharm Lyse, BD Biosciences), and 8×10^5 splenocytes from the immunized or infected mice were added to duplicate wells of transfected BALB SV40 cells in the presence of brefeldin A (GolgiPlug, BD Pharmingen). For peptide stimulation, duplicate wells containing 2×10^6 splenocytes each were stimulated with 1 μM of the L^d-restricted nonapeptide epitope of IE1 (^{168}YPHFMPTNL^{176}) in the presence of brefeldin A. Peptide stimulated splenocytes served as gating controls for CD8 and IFN-γ staining. After 8 h stimulation at 37° C and 7% CO_2, duplicate wells of splenocytes were combined into 1 well of a 96-well round-bottom plate for staining. Splenocytes were surface stained overnight with phycoerythrin-Cy5 (PE-Cy5) conjugated anti-mouse CD8a (Ly-2) antibody clone 53-6.7 (eBioscience) and, following fixation and permeabilization (BD Cytofix/Cytoperm, BD Biosciences), splenocytes were stained with a fluorescein isothiocyanate (FITC) conjugated anti mouse IFN-γ antibody clone XMG1.2 (eBioscience). The lymphocytes were gated and the dual stained splenocytes were enumerated on a BD FACSCanto flow cytometer (BD Biosciences) with BD FACSDiva software at the Research Flow Cytometry Core Facility, VA Medical Center, La Jolla, California.

For the measurement of secondary CD8 T responses, DNA immunized or TC-MCMV infected mice were i.p. infected with 1.2×10^5 PFU of SG-MCMV, and on day 5 postinfection, splenocytes were harvested and analyzed by ICS assay as above.

Statistical analysis. One-way analysis of variance (ANOVA) tests were used to compare MCMV titers or CD8 T cell levels, and Fisher's protected least significant difference test (PLSD) was used as the post-hoc test for pairwise comparisons. Analyses were performed using StatView 4.51 software for Macintosh (Abacus Concepts, Inc.) and statistical significance was achieved when $P < 0.05$.

Cloning, sequencing, and expression of MCMV DNA pol (M54), primase (M70), and helicase (M105). The M54, M70, and M105 genes were cloned from MCMV MW97.01, a Smith strain derived bacterial artificial chromosome, into pcDNA3.1/V5-His-TOPO—a vector that provides carboxyterminal V5 epitope and 6xHis tags (97). The complete sequences of the cloned M54 and

M105 ORFs were identical to the published sequence (71) of MCMV strain Smith. The sequence of the cloned M70 ORF was identical to MCMV Smith except for a single T insertion between the 3' end of the M70 ORF and the vector-encoded epitope tag sequences. This mutation resulted in an immediate termination codon and thus a complete, but untagged, coding sequence for the M70 protein. Confirmation of complete, continuous reading frames for M54, M70, and M105 was provided by coupled in vitro transcription-translation (TNT T7 Quick) reactions and [^{35}S]methionine labeling (Fig. 3A). By SDS-PAGE and autoradiography, each of the plasmids was found to express a single labeled polypeptide with the predicted relative molecular mass: 128.8 kDa for M54, 109.6 kDa for the untagged M70, and 111.4 kDa for M105. Large-scale, endotoxin-free preparations of these DNA clones were prepared for i.d. immunization of mice.

To facilitate subsequent Western blot analysis following in vivo expression, the extraneous T at the 3' end of the M70 ORF was deleted by site-directed mutagenesis. The DNA sequence of the resulting M70 clone (designated M70*) was found to be identical to the parent except for the T deletion (data not shown). The M54, M70*, and M105 plasmids were transiently transfected into COS-7 cells and whole cell lysates were prepared in reducing SDS-PAGE sample buffer at 48 h posttransfection for Western blot analysis using a V5 tag-specific monoclonal antibody. Expression of M70* in COS-7 cells yielded a band corresponding to the predicted 114.7 kDA as well as a faster migrating band of equal intensity that may represent a proteolytic degradation product (Fig. 3B). No anti-V5 reactive band was observed following Western blot analysis of COS-7 cells transfected with the original mutant M70 clone. In addition, the predominant bands seen in the M54 and M105 lanes were of the expected sizes observed following expression in vitro (Fig. 3B). Duplicate blots were probed with a mouse-anti-MCMV hyperimmune serum, but no seroreactive bands were detectable. Taken together, these results demonstrate that the plasmids express the full-length, tagged ORFs, but that the encoded MCMV antigens do not elicit detectable antibody responses following repeated infection of BALB/c mice.

DNA immunization with the M54 and M105, but not M70, genes elicits protective responses in BALB/c mice. The next inquiry was whether protective prophylactic responses could be generated using any of the three conserved, essential genes in BALB/c mice. Because the gene products of M54, M70, and M105 and their respective HCMV homologs are not likely to be part of the viral envelope, any protective responses elicited following DNA immunization using these genes would likely be from cell-mediated, not neutralizing antibody, responses. To test for the protective efficacies of these plasmid DNAs, 4 BALB/c female mice per group were i.d. immunized in the shaved flank with either 1) pc3Δneo vector alone (20 μg) or with 10 μg of pc3Δneo plus 10 μg of either 2) IE1 (pp89), 3) M54, 4) M70, or 5) M105. Two weeks after the last immunization, mice were i.p. challenged with 1 of 3 sublethal doses of SG-MCMV: 0.25 x LD_{50} (2 x 10^5 PFU), 0.50 x LD_{50} (4 x 10^5 PFU), or 0.75 x LD_{50} (6 x 10^5 PFU). The spleens were harvested on day 6 postchallenge for MCMV titer determination.

In addition to the positive control IE1 DNA, the DNAs encoding M54, and M105 were protective against viral replication in the spleen following all of the i.p. challenge doses (Fig. 1). Following challenge with the low dose of MCMV, the mean reductions in titer provided by immunization with the M54 and M105 DNAs were comparable to that in the IE1 group (12- to 15-fold relative to vector alone immunized mice.) While the virus titer reductions in the spleens of the M54 and M105 immunized mice were not as high as those in the IE1 immunized mice following the intermediate challenge dose, following the high challenge dose, both IE1 and M54 immunization resulted in greater than 600-fold reductions in viral titers, and M105 resulted in a 60-fold reduction. Compared with their respective vector DNA alone immunized controls, titer reductions in the spleens of the M54 or M105 DNA immunized mice were statistically significantly except for the M105 group after the high dose (0.75 x LD_{50}) challenge (P=0.13). Finally, the M70 DNA, which interestingly has the lowest percent amino acid identity to its HCMV homolog, was not protective at any challenge dose level. These results identify M54 and M105 as protective members of a new class of protective antigens: the highly conserved, essential genes.

An independent experiment was performed to confirm the protective efficacies of the M54 and M105 DNAs. Groups of BALB/c mice were either left untreated (Naïve) or i.d. immunized in the tail 3 times in 2 weeks with 50 μg of vector DNA (Vect), IE1, M54, or M105 DNA. Three weeks after the last immunization, mice were i.p. challenged with 0.50 x LD_{50} (4 x 10^5 PFU) of SG-MCMV and spleens were harvested on day 6 postchallenge for viral titer determination. As in Fig. 2, immunization with the IE1 or M54 DNAs resulted in mean viral titer reductions in the spleen of greater than 700- and 500-fold, respectively, relative to the vector DNA alone immunized controls, with more variability in the levels of protection in individual mice in this experiment (Fig. 4). The viral titer reductions elicited by either of these plasmids were statistically significant (P<0.002 compared with Vect). In this experiment, immunization with the M105 DNA resulted in a more modest reduction in viral titers, with a mean level approximately 40-fold lower than the Vect group (P=0.059). Taken together, immunization with the M54 DNA provided a high level of protection similar to that elicited by the immunodominant IE1 DNA, while immunization with the M105 DNA elicited more moderate virus titer reductions.

Immunization with M54 or M105 elicits specific CD8 T responses that rapidly increase following viral challenge. Protective responses elicited by DNA immunization with the conserved, essential genes encoding DNA modifying enzymes would likely be due to specific adaptive cell-mediated immune responses, i.e. CD8 or CD4 T lymphocyte responses. DNA immunization with IE1 or M84 expressing plasmids, injected either alone or in combination, elicit strong CD8 T cell responses and protection against viral replication in the spleen after sublethal i.p. challenge (62, 89). Enumeration of pM84-specific CD8 T cells in DNA immunized or MCMV infected mice by ICS assay resulted in consistently higher numbers of IFN-γ+ CD8+ T cells following stimulation of splenocytes with cells expressing full-length M84 protein compared with the epitope peptide defined

by Holtappels et al. (37, 88). These results led to the measurement of cell-mediated responses against the full-length protective M54 and M105 gene products rather than an attempt to map all of the H-2^d restricted epitopes of these gene products and possibly overlook some of the protective specificities. An ICS assay was used in which splenocyte stimulation was mediated by BALB SV40 cells, a highly transfectable SV40 transformed H-2^d cell line (95), that were previously transfected with DNAs expressing full-length MCMV ORFs. This technique was recently used to characterize the specificities of the CD8 T cell repertoire of MCMV infected C57BL/6 mice using plasmids encoding all 170 of the known MCMV ORFs (97).

For measurement of specific CD8 T responses in DNA immunized mice, 7 week old female BALB/c mice were i.d. immunized in the tail with 25 μg of either empty plasmid vector (Vect) or plasmid DNA expressing IE1, M54, or M105. Mice were immunized 3 times in 2 weeks, and an additional booster was given either 2 (Fig. 6A) or 3 weeks (Fig. 6B) prior to ICS assay. Additional groups of mice were i.p. infected with 1.2 x 10^5 PFU of TC-MCMV either 2 weeks (Fig. 5A) or 4 weeks (Fig. 5B) prior to ICS assay in order to compare the specific CD8 T cell levels of DNA immunized with MCMV infected mice. For the ICS assay, SV40 BALB stimulator cells in 96-well dishes were transfected with either IE1, M54, or M105 DNA 48 h prior to harvesting the splenocytes from DNA immunized or MCMV infected mice. To monitor transfection efficiency of the stimulator cells, additional wells were transfected with either IE1 DNA or a DNA expressing the enhanced green fluorescent protein (EGFP), pcDNA3-EGFP. Erythrocyte depleted splenocytes from 3 mice per group were incubated with stimulator cells in the presence of brefeldin A for 8 h prior to overnight surface staining with anti-CD8 antibody, intracellular staining with anti-IFN-γ antibody, and analysis by flow cytometry. Fig. 4 shows the flow cytometric results for one representative mouse (Mouse 2) per immunization of infection group. Background staining of splenocytes from the vector immunized mice was very low, between 0.01% to 0.02% of the CD8+ T cells stained IFN-γ positive regardless of the DNA used to transfect the stimulator cells.

Fig. 6A shows the resulting CD8 T cell levels in the mice at 2 weeks after the last DNA immunization or 2 weeks after MCMV infection. Levels of IE1-specific CD8 T cells in IE1 DNA immunized or MCMV infected mice were comparable, with mean levels of 0.38% and 0.32%, respectively. Overall, these levels are lower than those obtained when splenocytes are stimulated with the dominant IE1 epitope peptide, most likely resulting from the lower probability of a primed CD8 T cell coming into contact with a stimulator cell presenting the single IE1 epitope compared with splenocytes bathed in a large excess of only the stimulating peptide. At the time of stimulation, transfected stimulator cells were routinely 85-100% confluent and 60-70% of cells were transfected as measured either by direct fluorescence of EGFP transfected cells or by immunofluorescent staining of IE1 transfected cells (data not shown). Nevertheless, the levels of IE1-specific CD8 T cells in DNA immunized or MCMV infected mice were statistically significantly higher than vector immunized mice (P= 0.001 and 0.003, respectively). All mice immunized with M54 DNA or infected with

MCMV had M54-specific CD8 T cells detectable after stimulation with M54 transfected stimulator cells, with the DNA immunized mice having slightly higher, but more variable, levels (mean 0.39%, range 0.20% - 0.58%) relative to the MCMV infected mice (mean 0.18%, range 0.15 – 0.21%) (Fig. 6A). The responses in the M54 immunized mice were significantly higher than in vector immunized controls (P=0.006) but not the MCMV infected mice (P=0.06). The M54-specific responses in the MCMV infected mice also were not statistically higher than vector controls (P=0.12). Immunization with M105 DNA or MCMV infection elicited M105-specific CD8 T cells, with DNA immunization again eliciting high but variable levels (mean 0.74%, range 0.52 – 1.16%) compared with MCMV infection (mean 0.30%, range 0.20 – 0.35%). Similar to the M54 test groups above, the CD8 T cell responses in the M105 DNA immunized mice were significantly higher than vector immunized mice (P=0.006), while the responses in the MCMV infected mice were not statistically different than the controls (P=0.15). However, the M105-specific responses to DNA immunization and MCMV infection were significantly different in this group (P=0.045).

The CD8 T cell levels were subsequently tested in mice that were rested an additional week after the last DNA immunization (3 weeks total) or 2 weeks after MCMV infection (4 weeks total). Overall, these results (Fig. 6B) were very similar to those obtained above. The most notable exception is that the M54-specific CD8 T responses in the M54 DNA immunized mice were significantly increased relative to the MCMV infected mice (P<0.001). The mean M54-specific CD8 T responses in the MCMV infected mice were comparable between the 2 experiments (0.18% and 0.21%), suggesting that the increases observed in the M54 DNA immunized mice may have resulted from slower kinetics of the CD8 response to M54 DNA compared with the IE1 or M105 DNAs. In this experiment, the M105-specific CD8 T cell levels in the MCMV infected mice were significantly higher than vector immunized controls (P=0.03), but not statistically different than the M105 DNA immunized mice (P=0.11). Taken together, the results from these two experiments demonstrate that the M54 and M105 DNAs elicit antigen-specific CD8 T cell responses, with perhaps the response to the M54 DNA having slower kinetics. M54- and M105-specific CD8 T cell responses were also detectable following acute i.p. infection with MCMV, although only the responses to M105 at 4 weeks pi were statistically higher than vector controls. There was also a strong trend for the M54 and M105 DNAs to elicit higher levels of CD8 T cell levels than those resulting from MCMV infection, with MCMV infection eliciting statistically significant CD8 T cell levels against M54 or M105 in 1 of 2 experiments.

The secondary response to the M54 and M105 gene products was measured to determine how the CD8 T cells primed by DNA immunization responded to viral challenge. MCMV infection does not prime significant levels of IE1- or M84-specific CD8 T cells in vector alone immunized mice by 5 d postchallenge (89). In contrast, CD8 T cells in IE1 or M84 DNA immunized mice were able to respond vigorously by this early timepoint, indicating that a secondary response had occurred. Whether the low M54- or M105-specific CD8 T cell levels primed by MCMV infection would

increase following subsequent viral challenge or whether these antigens' subdominance during infection hinders expansion of the primed CD8 T cells was also a goal of this example. To this end, 3 DNA immunized mice per group were i.p. challenged with 1.2 x 10^5 PFU of SG-MCMV on week 7 after the last immunization, while 3 of the MCMV infected mice were similarly re-infected with SG-MCMV 6 w after primary MCMV infection. On d 5 postchallenge or reinfection, splenocytes were isolated and analyzed by ICS assay as above.

The mean levels of specific CD8 T cells in the vector alone immunized mice on d 5 postchallenge were 0.06%, 0.09%, and 0.10% when stimulated with cells expressing the IE1, M54, or M105 DNAs, respectively (Fig. 7). These results indicate that primary responses to these antigens were low overall at this time postinfection and show the magnitude of their possible contribution to the levels in the DNA immunized or MCMV infected mice. The mean percentage of IE1-specific CD8 T cells in the IE1 DNA immunized mice was 0.48% (Fig. 7). This value was slightly higher that the peak level observed prechallenge (0.38%, Fig. 6A). By comparison, the mean in the MCMV infected mice post-reinfection was 0.73%, which was at least 2-fold higher than the peak prechallenge level of 0.32% (Fig. 6A).

The CD8 T cell levels in the mice that were MCMV challenged on week 7 after the last immunization with M54 or M105 DNA were also 2- to 3-fold higher than their respective peak levels prechallenge. In contrast, in the mice previously infected with MCMV, the postchallenge levels of CD8 T cells specific for M54 and M105 were almost identical to their respective prechallenge levels. Although it is not known what the levels of specific CD8 T cells to M54 and M105 in this group of DNA immunized mice would have been without restimulation with challenge virus, IE1 or M84 DNA immunized mice had CD8 T cell levels that either decreased or stayed the same after 2 weeks post-last immunization (89). More specifically, the level of IE1 peptide-specific CD8 T cells was 5.2% at week 2 after the last immunization and then declined to 1.7% at week 4, while the level of M84 peptide-specific CD8 T cells was 1.1% at week 2 and 1.0% at week 4. Taken together, our data showed that the M54- and M105-specific CD8 T cells in the DNA immunized mice were able to rapidly respond to viral challenge with increasing levels of IFN-γ+ cells, while the IFN-γ secreting M54- and M105-specific cells in MCMV infected mice, unlike the IE1-specific CD8 T cells, were not stimulated by subsequent reinfection.

In this example, protective CD8 T cell targets of MCMV on the E genes were identified whose homologs in HCMV have been found to be essential for viral replication in cultured cells. HCMV UL54 and UL105 were demonstrated to be essential for oriLyt-dependent DNA replication in a transient transfection system (98), and their requirement for viral replication in vivo has been confirmed by the independent mutagenesis studies by Dunn et al. and Yu et al. (12, 90). UL54 encodes the DNA polymerase catalytic subunit, and based on aa homology with the HSV-1 helicase protein encoded by UL5, HCMV UL105 is believed to contain the helicase activity of the proposed helicase-primase complex (UL70-UL102-UL105). Thus, it is unlikely that MCMV would be able to

severely down regulate or abrogate expression of M54 and M105 in vivo in a productive infection in the face of cognate effector CD8 T cells. However, it remains a possibility that MCMV could down regulate the expression of M54 or M105 in infected tissues to a level that promotes a slower rate of replication and reduced pathogenicity but avoids the surface presentation of sufficient M54- or M105-derived peptides to be recognized by their cognate CD8 T cells. The similar protective abilities of the IE1 and M54 DNAs shown by our protection assay of acute-phase splenic viral replication following relatively high-dose systemic challenge with infectious virus does not illustrate a qualitative difference between the net protective abilities of IE1- and M54-specific CD8 T cells, but work is in progress to determine if there are any differential antiviral effects of these cells during chronic or latent infection.

DNA immunization with M54 or M105 consistently elicited CD8 T cell responses capable of IFN-γ secretion upon short-term incubation with transfected H-2^d stimulator cells. Thus, there exists at least one H-2^d-restricted antigenic peptide within each polypeptide sequences. It also appeared that the peak response to M54 may be delayed relative to M105. This is consistent with the previous finding that the kinetics of IE1- and M84-specific CD8 T cell responses also differed slightly (89).

When it was examined whether MCMV infection generated CD8 T cell responses to either M54 or M105, it was found that the acute infection also primed specific responses to these antigens, but the response to M105 reached statistical significance in only 1 of 2 experiments. M54-specific responses to acute MCMV infection in individual mice were between 9- to 39-fold over background levels in 2 experiments, while M105-specific responses in these experiments ranged between 20- and 49-fold over background. MCMV infection may therefore elicit specific CD8 T cell responses to antigenic peptide(s) of both M54 and M105, the variability in this response or in the assay used to detect these cells makes achieving statistical significance difficult with the group sizes, variability, and level of increases. Although the mean and individual CD8 T cell responses that were specific for M105 and IE1 were similar for the MCMV infected mice within each of the 2 experiments shown (Fig. 6A and 6B), the assay has not been rigorously optimized for each antigen. However, because the M54 and M105 DNAs were able to each elicit strong peak responses to their encoded antigens in each experiment relative to those elicited by MCMV infection (unlike the IE1 responses), further analyses would likely classify M54 and M105 among the subdominant antigens of MCMV in BALB/c mice. While acute MCMV infection may not prime high levels of specific CD8 T cells to M54 and M105, the efficacy of the CD8 T cells primed by DNA immunization demonstrates that M54- and M105-derived antigenic peptides are indeed presented by infected splenocytes in vivo.

Sylwester et al. and Munks et al. have comprehensively documented the repertoires of CD8 T cell immunity to HCMV and MCMV infection, respectively. In the case of HCMV, of the 33 seropositive subjects, only 3 (9%) had detectable UL54 peptide-specific CD8 T cell responses, and the levels were less than 1% (99), suggesting that UL54 encodes subdominant HLA-restricted antigenic peptides. UL105 was recognized by CD8 T cells in these subjects at a slightly higher

frequency, as 6 of 33 subjects (18%) had detectable UL105-specific CD8 T cell responses, but only 1 subject had a level of that was greater than 1%.

In a pool of 3 acutely infected C57BL/6 mice, the CD8 T cell repertoire included a low, but >5-fold above background, response to M54 (ca. 0.2% of CD8 T cells). However, there was no measurable response to M105 (97). In experiments with acutely infected BALB/c mice using the same methodology as used in the C57BL/6 study, similar mean responses were found to M54 of 0.2% of CD8 T cells, but higher levels of M105-specific CD8 T cells of 0.3-0.4%. While these responses primed to M54 and M105 during acute MCMV were low, it remained to be determined whether reinfection with MCMV would increase these CD8 T cell levels or whether the mechanism(s) that govern the apparent subdominance of these antigens during infection would prevent an increased secondary response. Upon reinfection of mice that the levels of M54- and M105-specific CD8 T cells (Fig. 7) were not appreciably higher than their respective levels in the acutely infected mice at 4 weeks postinfection (Fig. 6B). However, it is possible that there were further declines in CD8 T cell levels between week 4 (the last timepoint measured before reinfection) and week 6 (when mice were reinfected) post primary infection, and that subsequent reinfection resulted in increases of CD8 T cell responses back to their week 4 levels. In any event, the responses to M54 and M105 in the reinfected mice contrasted with the IE1-specific CD8 T cell levels that increased at least 2-fold upon reinfection with MCMV on the time points measured. Thus, if preexisting immunity to MCMV in the infected mice had prevented the subsequent infecting virus (or viral antigen) from entering the splenic compartment to restimulate secondary responses to M54 or M105, the secondary response to IE1 was not similarly abrogated. The generation of a secondary response to IE1 likely has a temporal advantage over the M54 and M105 E proteins, and thus increases in the IE1-specific CD8 T cells, which are highly protective, may have precluded sufficient E gene expression in infected splenocytes to restimulate the CD8 T cells primed against M54 and M105 epitopes. It is not known whether an increased dose of challenge virus would overcome the lack of secondary responses against M54 and M105, as secondary responses to these antigens in the DNA immunized mice were clearly observed. The secondary responses in the IE1 DNA immunized mice were not as high as those observed previously in ICS assays using the immunodominant IE1 L^d-restricted epitope peptide (24), possibly due to differences in the ICS assays used.

Having found that the responses to 2 of the 3 conserved, essential E genes of MCMV tested were protective against viral replication it remains to be found whether the CD8 T response to MCMV infection is purposely skewed by the virus to limit the responses to these antigens. The skewing in favor of an immunodominant, but ultimately ineffective, CD8 T response has been demonstrated with the lack of viral control in immunoablated C57BL/6 mice reconstituted with M45-specific CD8 T cells (7). It was shown that the D^b-restricted M45 peptide is very effective at priming a specific CD8 T cell response, presumably through cross presentation of M45 protein in uninfected dendritic cells, but that the MHC Class I presentation of this peptide in the infected tissues is

sufficiently blocked by the immunoevasin m152 to limit effector mechanisms of viral control. A mechanism by which negative skewing of the primary CD8 T response to viral antigens is not easily explained given the existing state of knowledge of T cell priming. However, the CMVs have successfully coevolved with and spread among their respective hosts over the last ~70 million years since the time of the mammalian radiation. Undoubtedly, the selective immune pressures of the host have helped to shape immunodominance hierarchy and the balance of the virus and host to establish a lifelong, persistent infection that is normally not pathogenic. A benefit of using DNA immunization to elicit virus specific CD8 T cells is that responses can be generated in the absence of the immunoevasins or antigenic competition between ≥170 viral proteins expressed during viral replication.

Example 11: Determining whether the minimal pool of combined DNAs together elicit CD8+ T cell responses that are at least as protective in all 3 mouse strains as are the individual DNAs

Experiments with DNA immunization against MCMV in BALB/c mice have shown that a combination of multiple plasmids that are each protective when used alone results in increased, and sometimes synergistic, protection levels (62-64, 89). However, before proceeding with the next experiments in which mice are primed with the minimal DNA pool, boosted with FI-MCMV, and challenged by mucosal and systemic routes, it may first be confirmed whether the DNAs in the pool negatively affect the protective responses. This possibility may conflict with results that indicate that individually protective pDNAs when mixed with other protective or nonprotective plasmids remain fully protective. Nevertheless, the duration of the experiments that employ boosting with FI-MCMV as well as the need for immunizing 3 mouse strains justify the need for performing an additional relatively short-term experiment. As an added measure, this experiment provides the best opportunity to characterize the combined immune responses by comparing the CD8+ T responses to each antigen in the minimal DNA pool when injected alone or as a pool. Notably, although coimmunization with the IE1 and M84 DNAs typically results in lower levels of IE1-specific CD8+ T cells and higher levels of M84-specific CD8+ T cells when compared with immunization with each of the pDNAs alone, coimmunization consistently provides a synergistic level of protection (89). Thus, when interpreting the CD8+ T cell data from the mice immunized with the minimal DNA pool, as long as protection is increased or maintained relative to single DNA immunization, decreases in individual CD8+ T cell levels will not constitute a suboptimal vaccine.

To measure the CD8+ T cell and protective responses of the minimal DNA pool, an experiment may be conducted in each of the 3 mouse strains above, with experiments staggered to reduce the daily workload. Sixteen mice per group will be i.d. immunized with the empty vector (pcDNA3) DNA, the minimal DNA pool, or each of the 2 or 3 individually protective DNAs that comprise the pool. Furthermore, if it is found that inclusion of the gB or gH/gL plasmid(s) augments

protection, the minimal DNA pool will also contain these plasmids. Seven to 10 days after the last immunization, 4 mice from each group will be sacrificed and splenocytes will be prepared for the ICS assay as above. Splenocytes will be stimulated with the appropriate syngeneic cell line transfected with either the empty pcDNA3 vector or one of the MCMV DNAs that was used for the injection. Splenocytes from the vector alone- and minimal DNA pool-immunized mice will both be stimulated with empty vector and each MCMV DNA expressing transfectant individually, while the splenocytes from the mice immunized with each individual component of the pool will be stimulated with cells transfected with either the empty vector or the DNA used for immunization.

Two weeks after the last immunization, mice will be i.p. challenged with a single dose of SG-MCMV shown in the screening experiments above to provide the optimal protection level for the DNAs in the minimal pool, and spleens will be harvested as above for MCMV titer determination. These results should quickly characterize the interaction the plasmids in the minimal DNA pool with regard to the resultant levels of CD8+ T cells and protection.

Example 12: Determining whether prime-boost vaccination with the minimal DNA pool and attenuated live or inactivated MCMV provide complete long-term protection in all 3 mouse strains against mucosal and systemic challenge:

The efficacy of the minimal DNA pool defined above when it is used as a priming step prior to boosting with attenuated live or inactivated MCMV may be evaluated. Because of the importance of the mucosal route for transmission of virus, the prime-boost vaccine's efficacy against i.n. challenge may be measured.

Experiments may be performed in each of the MCMV sensitive BALB/c (H-2^d), CBA (H-2^k), and 129/J (H-2^b) strains. Using the standard vaccination schedule (see Figure 2 for timeline), 52 mice per group will be immunized by either 1) i.d. priming with pcDNA3 vector and i.p. boosting with PBS + alum or 2) i.d. priming with the minimal DNA pool and i.p. boosting with attenuated live or inactivatedFI-MCMV. In the event that the experiment of Example 2 shows that immunization with the minimal DNA pool alone results in undetectable levels of virus in the spleens of all of the 3 strains of mice tested, a third immunization group that is primed with the minimal DNA pool and boosted with PBS+alum in order to further characterize the DNA-mediated protection may be included. Seven to 10 days after the last i.d. DNA immunization, an ICS assay will be performed on 4 mice from each immunization group in order to measure the levels of CD8+ T cells specific for each antigen in the DNA pool. Eleven to 12 weeks after the last i.p. boost, blood samples to be collected retro-orbitally for virion-specific IgG and virus neutralizing antibody quantification, and then 12 weeks after the last i.p. boost, mice will be challenged either i.n with TC-MCMV or i.p. with SG-MCMV. On days 3, 6, 10, 14, 21, and 32, 4 mice per immunization group will be sacrificed and the spleen, liver, lungs, and salivary glands will be removed for determining the viral load over the course of the acute infection.

Example 13: Determining whether the attenuated or inactivated virus, or challenge virus in the minimal DNA-primed/attenuated live or inactivated MCMV boosted mice establish latency

Reactivation of latent HCMV in immunosuppressed individuals such as solid organ or bone marrow transplant recipients, as well as in AIDS patients, is a serious problem and often leads to graft failure and severe CMV disease (67).

To examine the ability of the challenge virus to establish latency, as defined by the presence of viral DNA and reactivatable virus in the absence of infectious virus, 2 groups of 48 BALB/c female mice per group will receive either A) no vaccination or B) i.d. injection of vector DNA and i.p. injection of PBS/alum. Additionally, 1 group of 52 mice will be immunized with C) i.d. injection of the minimal DNA pool and i.p. injection of attenuated live or inactivated, such as FI-MCMV/alum (see table below for immunization groups). In this experiment, published methods (61) may be used to construct an MCMV with a loxP site in intron 3 of ie1 to use for formalin inactivation and immunization in order to distinguish its genome from that of the challenge virus. Tagging only the immunizing virus with a 35 bp loxP site in intron 3 of ie1 will allow the use of a highly-sensitive PCR protocol (61) for detecting and differentiating ie1 sequences derived from genomic DNA from wild-type K181 (challenge virus) and from inactivated vaccine MCMV, while maintaining the antigenicity and growth characteristics of the virus.

Eight weeks after the last immunization, 12 mice per group will be challenged either i.n. or i.p. with 1 of 2 sublethal doses of TC-MCMV or SG-MCMV, respectively (see table for routes and doses). These challenge conditions will allow for the determination of latency establishment following mucosal or parenteral challenge with a low dose or high dose of virus. In addition, 4 mice in the optimized pDNA pool/attenuated live or FI-MCMV/alum immunization group will be left unchallenged as a control for the PCR-based detection of genomic ie1 sequences from the FI-MCMV.

Table 2 Latency - Experimental Group Summary (number of mice)

Vaccination (# of mice)	Challenge route (#)	Challenge dose	Protection in lung/SG	Confirm latency	Co cultivation and PCR
None (48)	i.p. (12)	0.5 x LD_{50}	(4)	(2)	(6)
	i.p. (12)	0.05 x LD_{50}	(4)	(2)	(6)
	i.n. (12)	5 x 10^5 PFU	(4)	(2)	(6)
	i.n. (12)	5 x 10^4 PFU	(4)	(2)	(6)
Vector DNA +	i.p. (12)	0.5 x LD_{50}	(4)	(2)	(6)
PBS/alum (48)	i.p. (12)	0.05 x LD_{50}	(4)	(2)	(6)
	i.n. (12)	5 x 10^5 PFU	(4)	(2)	(6)
	i.n. (12)	5 x 10^4 PFU	(4)	(2)	(6)
Minimal DNA	i.p. (12)	0.5 x LD_{50}	(4)	(2)	(6)
pool +	i.p. (12)	0.05 x LD_{50}	(4)	(2)	(6)
FI-MCMV/ alum	i.n. (12)	5 x 10^5 PFU	(4)	(2)	(6)
(52)	i.n. (12)	5 x 10^4 PFU	(4)	(2)	(6)
	None (4)	None	(0)	(0)	(4)

Ten days postchallenge, 4 mice per each of the 4 combinations of i.p. or i.n. challenge route and low or high challenge dose will be sacrificed for MCMV titer determination in the lungs and salivary glands to confirm that complete protection was achieved. The remaining mice will be housed for at least 4 months to resolve the acute and persistent infection and allow the establishment of latency. Two mice per challenge route and challenge dose will be sacrificed to confirm the absence of infectious virus by titering homogenates of their salivary glands with a sensitive plaque assay. After confirmation of latency establishment, the remaining mice will be sacrificed for determination of: 1) the absence of infectious virus, 2) the relative level of latent viral DNA, and 3) the level of reactivatable latent virus. Briefly, spleens, salivary glands, liver, and lungs will be harvested and each divided into three fractions. One fraction will be Dounce homogenized for confirmation of the absence of infectious virus by plaque assay. Genomic DNA will be purified from the second tissue fraction and subjected to nested PCR for the amplification of the ie1 genomic region. This method reliably detects as little as a single copy of target DNA in a background of 1 μg tissue DNA and semi-quantitatively assesses the relative load of latent viral DNA (61). To confirm that the genomic DNAs are undegraded and free of PCR inhibitors, ß-actin sequences are amplified from the same DNA dilutions negative for MCMV DNA. In addition, tissues from the immunized but unchallenged mice will be processed in parallel to determine whether the viral DNA derived from the attenuated live or inactivated MCMV is still detectable. In any event, one can differentiate the ie1 sequences in FI-MCMV and live challenge viruses in 2 ways: 1) the PCR product from the nested reaction will be 310 bp in the challenge virus and ca. 350 bp in the attenuated live or inactivated MCMV, and 2) a labeled oligonucleotide probe specific for the loxP site in the attenuated live or inactivated MCMV will be able to detect by Southern blot any attenuated live or inactivated MCMV sequences contributing to the PCR product. Furthermore, the 188 bp PCR product that would result from amplification of IE1 cDNA is clearly distinguishable from genomic ie1 sequences in the inactivated or challenge virus. Finally, the remaining tissues harvested from the latent mice will be co cultivated on MECs to detect the presence of reactivatable virus (58). Thus, while the PCR will provide the most sensitive measure of the total load of latent viral DNA, the relative frequencies of MCMV reactivation by co cultivation will demonstrate the level of viral DNA that can potentially reactivate and cause recurrent disease or viral transmission.

Example 14: Determining whether prime-boost vaccination with the minimal DNA pool and attenuated live or inactivated MCMV provide complete protection against acute and latent MCMV infection in an outbred population

A vaccine's ability to provide sterilizing immunity against systemic and mucosal infection represents the gold standard for vaccination against CMV, as it guarantees that there is no persistent or reactivated virus that can be transmitted to the fetus in utero. To achieve this goal in humans, the

vaccine must be effective in the outbred population. In the experiments above, it may be demonstrated that priming of mice from each of the 3 mouse haplotypes—H-2^d, H-2^k, and H-2^b—with the minimal pool of conserved MCMV genes and boosting with FI-MCMV resulted in complete cross-strain protection. However, these experiments will have been conducted only in MCMV sensitive strains in order more unambiguously identify the protective conserved genes in the absence of strong, early NK responses. In addition, the MCMV sensitive strains provide the most stringent test of the ability of the DNA prime/FI-MCMV boost to provide sterilizing immunity, as any virus able to break through the vaccine-induced immunity is more efficiently replicated to detectable levels when compared to the innately resistant strains.

An immunization experiment in Swiss Webster outbred mice to determine whether the optimal prime-boost vaccine is completely protective against both acute and latent MCMV infection following systemic or mucosal challenge may be performed. To optimize the challenge conditions in this strain, Swiss Webster mice are immunized with either 1) vector DNA prime plus PBS/alum boost or 2) minimal DNA pool prime plus an attenuated live or inactivated virus, such as FI-MCMV/alum boost. Blood samples will be collected as above to determine the levels of virus-specific IgG and neutralizing antibody. Twelve weeks after the last boost, mice will be i.n. or i.p. challenged and target organs will be analyzed as to assess the level of protection following short-term challenge. The remainder of the challenged mice will then be housed and analyzed to confirm the establishment of viral latency and to quantify the levels of latent viral DNA load and reactivatable virus in the controls and the DNA primed/FI-MCMV boosted mice.

If one or more of the protective pools found in the initial screen of the conserved essential genes is not protective in all 3 mouse strains, a follow-up immunization experiment will be performed, with priority being given to the pools that protect 2 strains rather than only one. Therefore, a pool from the first screen that is protective in 2 strains will be subdivided to determine whether a single plasmid is responsible for the observed protection in the 2 strains. If a single plasmid is found to protect both mouse strains protected in the first screen, it will be added to the master pool. Once the master pool contains a minimum number of plasmids that cross-protect all 3 mouse strains, the immune responses and protection elicited by this pool will be evaluated in the numbered experiments above.

If the results from the second screen using individual plasmids show that the protection in the 2 strains was mediated by more than one plasmid, the protective plasmids will be ranked first by the number of strains they protect and then on the basis of the levels of protection they confer. Thus, the most complex master pool will consist of 3 of the conserved essential MCMV genes, each that protects only one H-2 haplotype, while the pool of intermediate complexity would contain 2 plasmids that together are capable of protecting all 3 strains (i.e. Plasmid 1—H-2^d and H-2^k strains and Plasmid 2—H-2^b and H-2^k strains).

If a master pool of the conserved essential genes above that cross-protects all 3 mouse strains cannot be constructed due to the lack of protection in one or more mouse strains, other MCMV ORFs may be systematically cloned and screened in pools of 15 different MCMV genes, with priority given to the most conserved genes and those in the IE, E, and E/L classes. Intradermal immunization with IE1 and M84 DNA vectors in a pool of 10 additional plasmids that are individually nonprotective is able to significantly reduce virus titers in the spleen following i.p. viral challenge. As little as one IE1 protective plasmid in a pool equivalent to 50 nonprotective plasmids provides full protection.

4 mice per group may be injected with each pool of 15 DNA vaccine candidates (2 μg of each plasmid), over a 14 to 20 day period. As a negative control one group will be injected with vector backbone alone. As in the screens above, boosts with formalin-inactivated virus will not be given so that one can more easily identify the protection provided by the DNA immunization. Two weeks post-vaccination, the mice will be challenged i.p. with 1 of 3 different sublethal doses of SG-MCMV. MCMV titers in the spleen will be determined, and if a pool of ORFs is found to be protective, then it will be subdivided into 3 pools of 5 ORFs, which will then be tested as above. If one of these subpools is protective, then each of the ORFs will be tested individually. Once the minimal pool of cross-strain protecting plasmids is defined, the numbered experiments above can be performed with this pool.

Example 15: Optimization of the route of DNA immunization for protective immunity against mucosal and systemic challenge.

Mucosal areas are important entry sites for the initial CMV infection. If priming with the protective DNAs and boosting with attenuated live or inactivated MCMV is not completely protective against mucosal challenge, methods may be determined for administering the protective DNAs that results in the optimal protection against mucosal infection. Parenteral administration of both the DNA (i.d.) and attenuated live or inactivated MCMV (i.p.), such as FI-MCMV, provides complete protection in the spleen, liver, and salivary glands of the majority of immunized mice following i.n. challenge (93). In addition, MCMV titers in the lungs of DNA primed/FI-MCMV boosted mice were reduced by greater than 3 Logs at peak times of replication when compared to controls. Thus, the dual parenteral immunization did allow for breakthrough of viral replication at the mucosal site of entry, but almost completely prevented viral dissemination to the other target organs. In addition, mice that were only primed with a trivalent DNA cocktail containing gB, gB, and M84 showed some protection in the lungs following i.p. challenge as well as a more rapid induction of virus-specific IgA in the lungs after i.n. challenge (93). These results suggest that the immunity provided by the DNAs and FI-MCMV is protective in the lungs, but that the choice of DNA-encoded antigens and their route of administration may be optimized to protect against mucosal infection.

Mice were i.n. immunized with FI-MCMV in order to augment the protection in the lungs following i.n. challenge. While i.n. immunization with FI-MCMV conferred protection in the lungs following i.n. challenge, the protection was identical to that following i.p. immunization with FI-MCMV and did not extend into other organs. Because mucosal responses are generally poor to protein antigens following i.n. immunization, groups of mice were i.n. immunized with FI-MCMV together with either one or both of two potent and commonly used mucosal adjuvants: cholera toxin (CT) and immunostimulatory CpG DNA (CpG) (33, 83). However, not only did neither or both adjuvants together with FI-MCMV augment virus-specific salivary IgA levels compared to FI-MCMV alone, the 'sublethally' i.p. and i.n. challenged mice that received these i.n. adjuvants with FI-MCMV had abnormally high viral titers in the liver, morbidity, and even mortality not observed in mice receiving the adjuvant(s) alone.

The efficacy of immunizing by i.n. or oral delivery of the DNA and by i.p. boosting with the attenuated live or inactivated virus, such as FI-MCMV, may be determined. The following methods of mucosal immunization may, for example, be used. The first method involves i.n. immunization with viral genes and plasmids encoding macrophage inflammatory protein 1 alpha and 2 (MIP-1 alpha and MIP-2) (19). It has been shown that this mode of immunization with a DNA plasmid encoding HSV glycoprotein gB gene enhanced mucosal and systemic Th-1 type immune responses and provided protection from HSV that was administered through the vagina. In these experiments, BALB/c mice are immunized 3 times at 5-day intervals with 100 μg of a plasmid pool encoding the protective DNA (together with gB and/or gH/gL if found to augment protection) along with 200 μg of plasmids encoding chemokines MIP-1 alpha and MIP-2. As controls, a group of mice will be immunized with the protective DNA (without chemokine DNAs) by i.d. route and another group will be i.n. immunized with empty DNA vector plus MIP-1 alpha and MIP-2 DNAs. The i.n. primed mice will be subsequently i.p. boosted with FI-MCMV + alum. Because the sequence of DNA priming and heterologous boost has been shown to affect the subsequent levels of mucosal and systemic immunity and protection (18), a fourth group of mice will be immunized first by i.p. injections of FI-MCMV + alum and then by i.n. administration of the MCMV ORF and MIP plasmids. Immunized mice will be i.n. or i.p. challenged with MCMV, and viral titers in the mucosal (lungs and salivary glands) and abdominal (spleen and liver) organs will be determined as above to assess the levels of mucosal and systemic protection, respectively.

Similar to coadministration with the MIP-1 alpha and MIP-2 chemokine plasmids, mucosal immunization with plasmids expressing the cytokines IL-2, IL-12, and IL-15 have been used to enhance Th1-mediated immunity and protection against mucosal viral challenge. While all three cytokines promote the development of CD8+T responses, IL-15 has been found to enhance the proliferation of memory CD8+ T cells, making the latter an attractive genetic adjuvant for long-term protection (83). Intradermal coadministration of an IL-2 plasmid with suboptimally protective MCMV genes was able to increase the level of protection against i.p. MCMV challenge, suggesting that this

approach may also be effective at enhancing plasmid-mediated mucosal protection. In experiments similar to those above, mice will be i.n. immunized with the protective DNA pool together with either IL-2, IL-12, or IL-15 DNAs prior to or subsequently after i.p. immunization with FI-MCMV. Protection against either i.n. or i.p. viral challenge will be measured as above.

The last method is based on a study showing that mucosal and systemic immune responses and protection against rotavirus infection was elicited following oral administration of plasmids encoding rotavirus genes in the form of encapsulated microparticles formed by poly (D,L-lactic-co-glycolic acid) (PLGA) (9, 32, 82). More recently, it has been demonstrated that oral administration of PLGA-encapsulated IL-2 DNA 2 days after an oral prime-boost vaccination with HIV env-gp160 DNA and recombinant vaccinia virus augmented gp160 specific serum antibodies, serum neutralizing antibodies, mucosal IgA, and systemic env-specific CTLs (86). Mice may be inoculated orally by gavage with 0.5 ml of the PLGA encapsulated plasmid DNA (100 μg/ml).

If the optimal DNA pool contains the gH and/or gH/gL plasmids, retro-orbital blood will be collected 4 weeks after the last oral immunization for examination of serum IgA, total IgG against gB and gH and virus structural proteins, and the IgG_{2a}/IgG_1 ratio. At the same time, vaginal IgA levels and complement-dependent neutralization titers will be determined. If the results are negative or borderline, the sera of the mice may be tested after an additional 2 weeks and then i.p. boost the mice with the attenuated live or inactivated MCMV. Four weeks later, the mice will be boosted i.p. with attenuated live or inactivated MCMV. Five weeks following the boost, retro-orbital blood will again be analyzed. The levels of vaginal, fecal, and nasal IgA will also be determined. The mice will be allowed to recover for 3 weeks, i.p. or i.n. challenged, and the MCMV titers in target organs will be determined.

Example 16: Eliciting a CD8+ T cell response against Herpes simplex virus 2

All references cited in this Example refer to reference numbers within this Example.

CD8 T cells specific for an immunodominant MCMV antigen are ineffective at limiting viral replication (33). Conversely, DNA immunization using a viral antigen that is scarcely immunogenic during infection elicits highly protective CD8 T cell responses (94, 95). Taken together, immunodominance during infection does not invariably correlate with protection, herpesviruses may skew the host T cell response to make dominant the specificities that favor viral persistence rather than clearance. The essential, nonstructural proteins that are highly conserved among the herpesviruses may represent a novel class of T cell targets. The rationale is that these genes must be expressed for viral replication, and the high amino acid conservation needed for maintaining protein activity limits immune escape by mutation. Of note, immunological studies of T cell specificities primed by infection with human CMV, MCMV, and HSV-2 have shown this class of targets to be largely subdominant (35, 42, 63, 84). This example provides three sets of assays to identify the conserved, essential HSV-2 genes that are protective using DNA vaccination, to determine the

appropriate combinations of those genes, and to determine an appropriate prime/boost protocol, as summarized in the following three Aims:

Aim A. Identification of the conserved, essential HSV-2 genes that are protective in mice by prophylactic DNA vaccination. Using the mouse lethal challenge model, DNA vaccines that express each of the HSV-2 conserved, essential genes will be tested. The genes will be tested both alone and in combination with DNA encoding secreted glycoprotein D2 (gD2), a major target of neutralizing antibodies. The protective genes will be then tested in combination with each other either in the presence or the absence of the gD2 DNA to identify the most protective DNA vaccine combination.

Aim B. Determination in the guinea pig model of the immunity and protection elicited by the optimal combination of conserved, essential HSV-2 genes. The combination will be tested by itself and in the presence of the gD2 plasmid DNA. The protective efficacy of the optimized pDNA vaccine both alone and in combination with DNA expressing gD2 will be evaluated in the more human relevant guinea pig model, and the protection will be compared to that generated by a subunit protein vaccine containing the gD2 protein in MPL/alum, which has been shown to be a partially, but significantly, protective vaccine in clinical testing.

Aim C. Determination of the immunity and protection in guinea pigs following prime-boost immunization with the optimized plasmid DNA vaccine and whole, killed HSV-2 plus MPL/alum. Whether the DNA mediated protection is augmented by boosting with a novel combination of whole, killed virus plus MPL/alum adjuvants that will likely elicit virus specific Th1 responses and neutralizing antibodies to gD2 as well as other viral envelope glycoproteins will be tested in a guinea pig model. Immune correlates of protection and the effect of the vaccine on latent viral DNA loads will be studied.

Aim A. Identification of the conserved, essential HSV-2 genes that are protective in mice by prophylactic DNA vaccination. The genes will be tested alone and in combination with DNA encoding secreted glycoprotein D2 (gD2). The protective conserved genes will then be tested in combination with each other in the presence and absence of gD2 DNA to identify the most protective DNA combination.

During infection, naïve CD8 T cells may not be primed against conserved, nonstructural essential proteins (see table below), as the virus cannot sustain mutations in these proteins to evade immune responses. Thus, to provide sterilizing immunity, the herpesvirus vaccine induced CD8+ T cell responses may need to include specificities to essential viral proteins that do not prime the CD8 T cells during the viral infection. Of note, immunological studies of T cell specificities primed by infection with human CMV, MCMV, and HSV-2 have shown this class of targets to be largely subdominant (35, 42, 63, 84). As described above, our preliminary results lend support to this hypothesis.

While clearance of HSV-2 lesions has been shown to correlate with CD8+ and CD4+ T cell immunity, prophylactic antibody responses to recombinant gD2 plus 3-d-monophosphoryl lipid A (3-d-MPL)/alum have been shown to provide significant protection in HSV-1 and -2 seronegative women (82). An optimal vaccine, therefore, should prime both protective cell mediated and humoral immunity. Plasmid DNA vaccines expressing various forms of gD2 (full-length, secreted, and intracellular) have been evaluated in the mouse and guinea pig models (83). Immunization of mice with DNA encoding either the full-length or secreted gD2 was protective against lethal intravaginal challenge, while immunization with a secreted gD2 pDNA (and to a lesser extent full-length gD2) was found in guinea pigs to significantly reduce acute phase lesion scores, but not viral shedding, after intravaginal challenge, and provided a modest, but statistically significant, reduction in recurrent lesions (83). In addition, several studies have shown that protection and/or immunity from gD2 or gB1 pDNA immunization can be augmented by boosting with attenuated vaccinia (20) or MVA (55) vectors or possibly with soluble gD2 protein. It is important to note that while the delivery of gD2 and/or gB2 soluble antigens or plasmids to mice and guinea pigs has shown statistically significant reductions in lethality, acute phase virus replication, and incidence and severity of acute phase lesions, the resultant responses still allow significant levels of acute phase viral replication, recurrent viral shedding, and latent viral genome load. Thus, even in these animal models of HSV-2 vaccine efficacy, there is a significant window for measuring increased protective responses that may be elicited by cell-mediated immunity to the conserved, essential HSV-2 genes. Moreover, inclusion of a secreted gD2 expression plasmid with conserved, essential HSV-2 genes may provide qualitatively enhanced protection, especially after subsequent boosting with a heterologous delivery method of gD2 and other virion structural proteins (see Aim C).

Choice of genes and construction of DNA expression vectors

To test whether our successful immunization strategy using the conserved, essential MCMV genes is also applicable to HSV-2, the HSV-2 genes that are essential and highly conserved with their respective HCMV homologs (see table) will be cloned and tested by DNA immunization. Many of these are early genes that encode proteins that contribute to viral DNA synthesis and are conserved with other herpesviruses. Because the PCR-based methods for cloning herpesvirus genes have previously been optimized and streamlined in the laboratory, the cloning of the HSV-2 ORFs should be straightforward. The PCR product will be ligated into an eukaryotic expression vector (pcDNA3) such that a carboxy terminal Flag tag is added to facilitate protein detection. Resultant transformants will be screened for the presence of insert in the correct orientation by restriction analysis, and the 5' and 3' ends of each ORF will be sequenced. Expression of each protein will be demonstrated in an in vivo transient expression assay or in an in vitro transcription/translation reaction. The HSV-2 ORFs (see table) to clone and test in vivo will be prioritized based on 1) their amino acid conservation with the CMVs and other herpesviruses and 2) their amino acid conservation with HSV-1. A plasmid

expressing a secreted form of gD2 will be similarly constructed except that an untagged gD2 lacking the transmembrane and intracellular domains will be amplified (31).

Table 3: Conserved, Essential Genes of HSV-2 Strain HG52 and Their HCMV AD169 Homologs

HSV-2 ORF	Protein	HCMV ORF	% Identity (aa overlap length)	FastA Scores* of HCMV ORF vs. EBV/VZV/HSV-1
UL5	HP complex protein	UL105	39% (753)	704/642/598
UL6	DNA cleavage-packaging	UL104	30% (521)	357/375/309
UL8	HP complex protein	UL102	35% (40)	Pos†/Pos/Pos
UL15	Terminase, DNA packaging	UL89	41% (674)	1181/1104/1206
UL17	DNA packaging	UL93	14% (433)	Pos/Pos/Pos
UL29	ICP8, ssDNA binding protein	UL57	25% (503)	352/220/298
UL30	DNA polymerase	UL54	38% (955)	343/326/423
UL32	DNA packaging	UL52	20% (397)	138/179/207
UL33	DNA packaging	UL51	22% (126)	Pos/97/106
UL34	Egress	UL50	24% (230)	Pos/Pos/Pos
UL42	DNA pol processivity	UL44	15% (53)	ND
UL52	HP complex protein	UL70	29% (771)	293/302/305

*FastA Scores >100 considered significant

†Pos, positionally conserved only; HP, helicase-primase; ND, not determined

Initial screening of DNA vectors

The initial screening experiments will be performed in the mouse model of lethal intravaginal infection for the most rapid evaluation of our novel approach. Due to the number of conserved, essential genes to test, two screening experiments will be conducted. Eight 6- to 8-week old BALB/c female mice per group will be i.d. immunized 3 times in 2 weeks with 50 μg of pDNA in the tail near the base. There will be two groups for each conserved gene. To test the protective efficacy of the conserved gene alone, one group will receive 25 μg of a conserved, essential gene pDNA plus 25 μg of empty vector. To determine if the conserved gene can enhance gD2 pDNA-mediated protection, the second group will receive 25 μg of a conserved, essential gene pDNA plus 25 μg of secreted gD2 pDNA. There will be two control groups. One control group will receive secreted gD2 pDNA plus empty vector as a control for gD2 pDNA-mediated protection alone. As a negative control, the second group will be immunized with only empty plasmid vector.

On days 14 and 20 after the last immunization, mice will be injected subcutaneously with 3 mg of medroxyprogesterone acetate (Depo-Provera) to synchronize the estrus cycle and to increase susceptibility to vaginal HSV infection, and on day 21, mice will be intravaginally challenged with 5

x 10^5 PFU of HSV-2 strain 333 as described elsewhere (83). Mice will be scored daily for 21 days for the severity of vaginal inflammation from 0 (no vaginitis), 1 (mild swelling or redness only), 2 (moderate swelling or erosions), 3 (severe genital maceration), or 4 (central nervous system involvement or death). To confirm vaginal viral replication and measure shedding, vaginal swab samples will be collected on days 1, 3, and 5 postchallenge and stored at –80° C in Vero cell medium containing antibiotics until titration by plaque assay on Vero cell monolayers. To measure the efficacies of the pDNA immunizations with conserved, essential genes with or without gD2 pDNA, statistical analyses (2-tailed) will be performed on 1) infection and mortality rates (Fisher's exact test), 2) daily lesion scores (Kruskal Wallis nonparametric analysis of variance plus pairwise comparison tests), and 3) levels of vaginal viral shedding (1-way analysis of variance plus pairwise Fisher's Least Significant Difference tests). Together, these analyses should identify any protective responses elicited by each of the conserved, essential HSV-2 genes. By using a combination of parameters to assess protection, differences in protection can be discerned and antigens that contribute weakly can be identified. Additionally, even if these protection levels are low when compared with the gD2 alone control, any responses to the conserved, essential genes that augment the gD2 pDNA-mediated protection may be identified.

RESULT 1 – One or more of the conserved, essential genes provides prophylactic protection against primary vaginal HSV-2 infection and/or disease.

Based on the results above, the plasmids of the HSV-2 conserved, essential genes will be ranked first according to their levels of protective efficacy alone and subsequently according to their levels of augmentation of gD2 pDNA-mediated protection. This ranking will be used to prioritize the subsequent experiment to determine the minimal combination of pDNAs that provides the highest level of protection. If only one conserved, essential gene of HSV-2 has a protective effect (either alone or by augmenting gD2 pDNA), this plasmid will be tested in the guinea pig model Aim B.

RESULT 2 – None of the conserved, essential genes provides significant protection following plasmid DNA immunization by itself or augments gD2 pDNA protection.

Because the selection of this novel group of antigens is based upon their potential to generate protective cell-mediated (CD4+ or CD8+ T) responses, it is important to consider that the antigens' putative MHC Class I epitopes may be restricted to Class I alleles not present in the BALB/c ($H\text{-}2^d$) model. Rather than repeat the immunization experiments in another mouse strain, which may have a different MHC restriction, the pDNAs would be tested, as in Aim B, directly in the guinea pig model of infection and disease. Results from this model would be more highly relevant to human infection, but because of the associated increase in cost and labor, the guinea pigs would be immunized with one of four pools of 3 conserved, essential gene pDNAs plus or minus gD2 pDNA in order to first demonstrate proof-of-concept before identifying which gene or genes is protective. As in the mouse experiments above, each pool of conserved, essential gene pDNAs will be tested in two groups. One

group will receive the pool of conserved essential gene pDNAs alone. The second group will receive the pool of conserved essential gene pDNAs in combination with gD2 pDNA so that augmentation of gD2 pDNA-mediated protection can be measured. Having identified one or more protective HSV-2 genes, the remaining time and funds on the grant would be spent on identifying the minimal pDNA combination that provides optimal protection in the guinea pig by immunizing groups with one or more of the protective pDNAs. If only one conserved, essential gene is found to be protective and if there is sufficient time remaining, it will be tested together with gD2 plasmid in Aim C to determine whether this resulting immunity and protection can be augmented by heterologous boosting of pDNA primed guinea pigs with whole, killed HSV-2 and MPL/alum.

Determination of minimal number of protective conserved, essential gene pDNAs that provides the optimal level of protection in mice against intravaginal HSV-2 challenge

Using the mouse model of MCMV immunity, immunization with two individually protective pDNAs can elicit CD8+ T cells specific for both antigens and provide a synergistic level of protection as measured by the reduction of challenge virus replication in the spleen (60). In addition, immunization of mice with a combined pool of 13 pDNAs expressing both individually protective and nonprotective plasmids resulted in the highest level of protection: a 10,000-fold reduction of challenge virus titers in the spleen compared with vector alone immunized controls (62). These results illustrate in a herpesvirus protection model that synergistic levels of pDNA-induced cell-mediated immunity and protection can be achieved by an optimized combination of plasmids. Additionally, it may be that an HSV-2 vaccine that is broadly protective across an outbred population would need to prime CD4+ and/or CD8+ T cells to more than one HSV antigen as the protective epitopes of each antigen may only associate with one or few HLA types. By the same reasoning, protective plasmids may express antigens that each contains epitopes that are presented in the same HLA context. In this case, immunization with a combined plasmid pool may result in a competition for the restricting HLA molecule and the resulting protective efficacy may not be increased, and characterization of an unnecessarily complex vaccine would be more laborious. Finally, it is possible that the cell-mediated immunity to a conserved, essential gene may provide protection against primary, but not recurrent, disease. Thus, it may be necessary to combine protective plasmids to achieve optimal protection against all phases of infection.

In this experiment, groups of eight BALB/c mice will be i.d. immunized as above with either 1) empty vector alone or 2) secreted gD2 pDNA + empty vector. Results from the above experiment should show whether coimmunization with gD2 pDNA affects the protection elicited by the conserved, essential gene pDNAs and also the relative levels of protection elicited by the conserved gene pDNAs and gD2 pDNA. The remaining mouse groups will be i.d. immunized with one or more protective conserved, essential gene pDNAs such that each pDNA will be retested alone or tested in combination with each of the other protective pDNAs. In addition, these combinations will be tested together with gD2 pDNA in order to measure the ability of each conserved gene pDNA combination

to augment gD2 pDNA-mediated protection. If more than 3 pDNAs are protective, the ranking of their individual protective efficacies will be used to prioritize their testing in all possible combinations in order to maintain the groups at a manageable number. Immunized mice will be intravaginally challenged as above and infection and mortality rates, daily lesion scores, and levels of vaginal viral shedding will be determined and analyzed as in the experiment above. These data will be used to quickly identify the simplest pDNA vaccine combination that provides the highest level of protection against intravaginal HSV-2 challenge such that it can be further evaluated in the guinea pig model.

Aim B – Determination in the guinea pig model of prophylaxis of the immunity and protection elicited by the optimal combination of conserved, essential HSV-2 genes.

Results from Aim A will have rapidly identified the best vaccine candidates and demonstrated proof-of-concept of using the conserved, essential genes of HSV-2 as novel targets for T cell immunity. In order to more rigorously test its protective potential, the optimized pDNA combination will be further evaluated in the guinea pig model of genital HSV-2 infection. The guinea pig model more closely mimics human disease, allowing for the testing of the vaccine for its efficacy in protecting against both primary and recurrent infection and disease (80, 81). In addition, the immunity and protection of the optimized pDNA vaccine will be compared with the most successful vaccination strategy in clinical trials to date, subunit vaccination with gD2 protein/MPL/alum. While gD2 protein/MPL/alum has shown significant protection against primary infection and disease, this vaccine appears to be ultimately limited in its ability to be protective in men or in HSV seropositive individuals, and it does not protect against infection (82). In Aim B, guinea pigs will be immunized with the optimized combination of HSV-2 conserved, essential genes (both in the presence and absence of secreted gD2 pDNA) and the resultant levels of immunity and protection with those elicited by subunit vaccination with gD2 protein with MPL/alum will be compared.

Experimental Design

Female Hartley guinea pigs will be purchased from Charles River and immunized at 4- to 6-weeks of age (300 – 400 g). Ten guinea pigs per group will be immunized 3 times in 6 weeks with 50 μg of pDNA i.d. in each flank (100 μg total). A negative control group will receive empty vector. One test group will receive the optimized combination of the protective conserved, essential genes alone, and the second test group will receive the optimized combination of the protective conserved, essential genes together with gD2 pDNA. An additional group will receive gD2 pDNA (plus empty vector) alone to serve as a control for any augmentation of the gD2 pDNA-mediated responses by the conserved, essential genes. As a positive control for protection and reference for immune response levels, a group will be immunized on days 0 and 32 by bilateral injection in the quadriceps with a total of 125 μl containing 5 μg of truncated, secreted gD2 protein plus 12.5 μg of MPL (Sigma) and 125 μg of alum (Pierce), as this has been shown to provide significant protection against both primary and

recurrent disease in guinea pigs (11). Secreted gD2 protein will be purified from the conditioned media of stably transfected CHO cells by lentil lectin and immunoaffinity chromatography as previously described (66). Finally, a mock subunit control group will be immunized with MPL and alum adjuvants only.

To measure antibody levels in immunized animals, blood will be obtained by toenail clip one day prior to challenge (week 9) and sera stored at –20°C. Sera will be tested for 1) gD2-specific IgG by ELISA using the purified gD2 protein above and 2) complement-independent virus neutralizing antibody by plaque reduction assay on Vero cells using 50-100 PFU of HSV-2 as described previously (34).

Three weeks after the last pDNA immunization and 5 weeks after the second subunit immunization, anesthetized guinea pigs will be intravaginally challenged as previously described (9). Briefly, the guinea pigs will be inoculated with virus by rupture of the vaginal closure membrane with a moistened calcium alginate tipped swab and by instillation of 0.1 ml of virus suspension containing 5.7 log10 PFU of HSV-2 strain 333 into the vaginal vault by means of a plastic catheter. Animals will be scored daily for lesion development based on a severity scale of 0 (no lesions), 1 (erythema only), 2 (single or few vesicles), 3 (large or fused vesicles), or 4 (ulcerated lesions). Lesions will be scored for up to 60 days by researchers blinded to the identity of the vaccine group in order to assess both acute phase and recurrent lesions. In addition, viral shedding in the vagina will be measured on days 2, 5, 7, and 10 postchallenge. Vaginal swabs will be placed into 1 ml of Vero cell medium containing antibiotics and stored at –80° C until titration by plaque assay on Vero cell monolayers. At the conclusion of the experiment, lumbrosacral ganglia from each guinea pig (6 to 8 per animal) will be dissected, pooled, rinsed with PBS and stored at –20 °C for the future extraction of DNA and real-time PCR quantification of latent HSV-2 DNA. In order to quantify the loads of latent HSV-2 DNA, cellular and viral DNA will be extracted using the DNeasy Tissue Kit (Qiagen) and subjected to real-time quantitative PCR using the ABI Prism 7000 detection system (Applied Biosystems). The HSV-2 primers and probe will be designed against a viral gene that is not present in the pDNA vaccine, and input DNA will be normalized using primers and a probe specific for the guinea pig lactalbumin gene (64).

Protection in the DNA immunized guinea pigs will be assessed by statistical analyses (as in Aim A) of 1) infection rates, 2) lesion scores through day 14 postchallenge (primary infection), 3) levels of vaginal virus through day 10 postchallenge (primary infection), 4) cumulative lesion scores through day 60 postchallenge (recurrent infection), and 5) quantity of latent HSV-2 DNA in the ganglia. The data from the conserved, essential pDNA combinations used either alone or plus gD2 pDNA will be compared with the gD2/MPL/alum subunit group to determine the protection elicited by the optimal pDNA combination relative to the current subunit strategy.

RESULT 1 – The pDNA vaccine that was optimized in the mouse experiments also significantly protects guinea pigs against intravaginal HSV-2 challenge.

In this case, in Aim C, whether the protection elicited by the optimized pDNA can be augmented by subsequent boosting with a novel combination of whole, killed HSV-2 together with MPL and alum adjuvants will be examined.

RESULT 2 – The pDNA vaccine that proved optimal in the mouse experiments does not significantly protect guinea pigs.

In this case, there will already be evidence in mice that the antigens are capable of priming CD8 T cells that can recognize loaded MHC complexes in infected tissues. One potential problem might be that the DNA vaccine-mediated priming of CD8 T cells may be suboptimal in the larger rodent. The next step would be to optimize the DNA delivery by immunizing guinea pigs with each pDNA pool adsorbed to poly-lactic coglycolide (PLG) microparticles. This delivery method has been shown in a variety of animal models, including guinea pigs and non-human primates, to enhance antibody or cellular responses to DNA vaccines by targeting the DNA to dendritic cells (for review, see (65). In addition, the same PLG formulation can simultaneously deliver several plasmids.

RESULT 3 – DNA immunization of guinea pigs with the pools of conserved, essential genes shows no protective effect alone and does not augment gD2 pDNA protection.

In this case, the priority would be to proceed to Aim C and test whether the protection elicited by the gD2 pDNA could be enhanced by subsequent boosting of guinea pigs with whole, killed HSV-2 together with the Th1 promoting adjuvant MPL and alum. In addition, guinea pigs may be are immunized with the pools of conserved, essential gene pDNAs adsorbed to PLG particles as above in Result 2.

Aim C – Determination of the immunity and protection in guinea pigs following prime-boost immunization with the optimized plasmid DNA vaccine and whole, killed HSV-2 plus MPL/alum

While the priming of mice with an MCMV gB pDNA before boosting with formalin-killed MCMV results in greater protection when compared with that from killed virion alone (61), prime-boost augmentation of protection using the conserved, essential genes of HSV-2 and gD2 pDNA may need to be tested specifically in the guinea pig model of HSV-2 disease. Whole, formalin killed virus preparations have been previously evaluated in clinical trials for prophylaxis or treatment of recurrent HSV infection, but these early studies suffered from methodological deficiencies, including the lack of objective measures of protection and the absence of a placebo groups in many cases (for review, see (41). In addition, trials using either whole, killed virus or detergent extracted glycoproteins did not utilize the highly immunogenic adjuvants that are available today, so it is not surprising that low or inconsistent antibody responses (and likely no cell mediated responses) were generated and that protection was not significant. More recently, the lipopolysaccaride derivative MPL has been shown to be a powerful adjuvant for Th1 type responses, and together with alum, a gD2 subunit vaccine has been shown to provide protection against symptomatic genital disease in HSV seronegative women (82). By itself, however, this subunit vaccine was able to provide only limited protection (46% and

39%) against HSV-2 infection in two phase 3 trials. Additional antibody specificities to other HSV-2 envelope glycoproteins (present in the virion particles) may be needed for optimal virus neutralization and protection. For example, immunization of guinea pigs with the defective HSV-2 mutant *dl5-29* elicited significantly higher levels of neutralizing antibodies compared with soluble gD2 protein, despite *dl5-29* immunization eliciting significantly lower levels of gD2-specific IgG (34). In addition to containing more neutralizing antibody targets, presentation of the HSV-2 glycoproteins in the context of the viral envelope may also elicit protective antibody responses to nonlinear epitopes that may not be present in soluble, subunit vaccines. Taken together, optimal protection against genital infection and disease may depend on the presence of both cell mediated and antibody responses. To this end, the combined efficacy of priming with the optimized combination of protective conserved, essential genes and gD2 pDNA followed by boosting with whole, killed HSV-2 plus MPL/alum will be tested.

Experimental Design

HSV-2 is propagated in Vero or BHK cells, and after CPE reaches 100%, extracellular virus will be purified from clarified supernatant by sucrose gradient ultracentrifugation using standard methods as described (68). In order to control for the unlikely possibility that DNA from the killed HSV-2 vaccine could be detectable by subsequent PCR of vaginal swabs or lumbrosacral ganglia, the virus used for the vaccine will be a lacZ-tagged HSV-2 Strain 333 (77) so that lacZ-specific primers and probe can be used to differentiate between the vaccine and challenge viruses. Briefly, the infectious virus bands will be diluted in buffer, pelleted, and resuspended in order to measure infectivity and protein content. The preparation is expected to have a purity of ~10^9 PFU per 5 μg of protein. This preparation will be inactivated by formalin and confirmed to be inactive by infectivity assay as described previously (62).

Fourteen female Hartley guinea pigs per group will be pDNA primed as in Aim B (3 i.d. injections in 6 weeks) and on weeks 9 and 13, mock i.m. boosted or i.m. boosted with whole, formalin killed HSV-2 plus MPL/alum. Specifically, groups will receive the following prime-boost combinations: 1) prime with empty vector pDNA and boost with MPL/alum (vehicle control); 2) prime with empty vector pDNA and boost with 5 μg of killed HSV-2 plus 12.5 μg of MPL (Sigma) and 125 μg of alum (Pierce); 3) prime with the optimized conserved, essential pDNA combination plus gD2 pDNA and boost with MPL/alum; 4) prime with the optimized conserved, essential pDNA combination and boost with killed HSV-2 as in group 2; 5) prime with gD2 pDNA and boost with killed HSV-2; and 6) prime with the optimized conserved, essential pDNA combination plus gD2 pDNA and boost with killed HSV-2. As a positive control and reference for both protection and immunity, group 7 will be primed and boosted as in Aim B with the gD2/MPL/alum protein subunit vaccine.

Blood samples will be collected one day prior to each of the two boosts as well as one day prior to challenge and sera stored for quantification of HSV-2 specific IgG and virus neutralizing

antibodies as in Aim B. To demonstrate antigen-specific T cell mediated (CD4+ T) immunity generated by the pDNA prime and protein boost, delayed-type hypersensitivity (DTH) responses will be measured in guinea pigs three days prior to the first killed HSV-2 boost (in guinea pigs set aside for DTH measurement) and three days prior to challenge (in animals to be challenged). Four guinea pigs per group will be i.d. injected in each ear with 10 μg of clarified, UV-inactivated Vero cell lysate from either uninfected or HSV-2 infected cells, and 24, 48, and 72 h later, the diameter of the induration will be measured by microcaliper to quantify the level of cellular infiltrate (38, 90). The responses to total HSV-2 cellular antigen will be calculated as the diameter differences between the indurations in the HSV-2 and negative control ears (background). Alternatively, to measure T cell responses to individual HSV-2 antigens, ears will be i.d. injected with lysates from 293T cells 48 h posttransfection with either empty vector (background control) or one of the conserved, essential gene pDNAs that comprises the pDNA priming combination (39). The magnitude of the inflammation will be measured and calculated as above. If the background from the untransfected cell lysate is too high, the conserved, essential gene product will be enriched by an anti-FLAG single-step immunoaffinity purification from larger scale transfections.

Four weeks after the last killed HSV-2 boost, the remaining guinea pigs will be intravaginally challenged and infection and disease will be measured as in Aim B. Because of the importance of a vaccine candidate in reducing viral reactivation and shedding in order to limit viral transmission, both lesion scores and viral shedding into the genital tract will be assessed in the guinea pigs through day 90 postchallenge. Vaginal swabs collected from the guinea pigs will be stored at –80 °C until DNAs are extracted and analyzed by real-time quantitative PCR. The HSV-2 primers and probe will be designed against a viral gene that is not present in the pDNA prime. As described above, lacZ-specific primers and probe will also be used in the PCR analyses to confirm that the viral DNA detected in the vaginal swabs is from challenge virus and not from the killed virus vaccine. Reactivating virus shedding in the control and vaccine groups will be compared with respect to incidence, frequency (mean number of days that viral DNA was isolated), and magnitude (number of viral genome equivalents) as previously described (11). At the conclusion of the experiment, lumbrosacral ganglia from each guinea pig (6 to 8 per animal) will be dissected, pooled, rinsed with PBS and stored at –20 °C. In order to quantify the loads of latent HSV-2 DNA, cellular and viral DNA will be extracted and subjected to real-time quantitative PCR as above. Input DNA will be normalized using primers and a probe specific for the guinea pig lactalbumin gene (64).

Although formalin killed MCMV may be used as a boost following pDNA immunization for the complete protection of mice against viral replication following systemic challenge (61, 62), it is possible that the same success may not be achieved using killed HSV-2 whole virion. It is possible that the concentrations of gD2 and gB2 protein in the envelope, the major targets of neutralizing antibodies, are not sufficient to elicit an optimal protective antibody response, and that only a minor contribution to protection is provided by other envelope glycoproteins. Thus, in a boosting strategy

may be employed that is more focused on the gD2 and gB2 proteins. A potential strategy would be to deliver these antigens by modified vaccinia virus Ankara (MVA) in a repeat experiment designed as outlined above. MVA is a highly attenuated vaccinia virus that has been safely used as a vaccine against smallpox and more recently as a vaccine vector. MVA can deliver one or more foreign genes into most human and mammalian cells and induce both humoral and cell mediated responses, even in a host with preexisting poxvirus immunity (91). As described above, heterologous prime-boost methods continue to show great promise in providing enhanced immunity compared to repeated boosts with the same antigen delivery method, and MVA vector-based experimental vaccines (used alone or in combination with DNA vaccines) against HIV and malaria are currently in phase I clinical trials.

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The entirety of each patent, patent application, publication and document referenced herein hereby is incorporated by reference. Citation of the above patents, patent applications, publications and documents is not an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

Singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a subset" includes a plurality of such subsets, reference to "a nucleic acid" includes one or more nucleic acids and equivalents thereof known to those skilled in the art, and so forth. The term "or" is not meant to be exclusive to one or the terms it designates. For example, as it is used in a phrase of the structure "A or B" may denote A alone, B alone, or both A and B.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and systems similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the processes, systems, and methodologies that are reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of ordinary skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, and yet these modifications and improvements are within the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. Thus, the terms and expressions which have been employed are used as terms of description and not of limitation,

equivalents of the features shown and described, or portions thereof, are not excluded, and it is recognized that various modifications are possible within the scope of the invention. Embodiments of the invention are set forth in the following claims.

5

What is claimed is:

1. A method of preventing or treating a viral infection, comprising administering to an individual a DNA molecule comprising at least one DNA sequence derived from a highly conserved viral gene.
2. The method of claim 1, wherein said virus causes a persistent or a latent infection.
3. The method of claim 1 or 2, wherein said virus is selected from the group consisting of herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses.
4. The method of claim 1 or 2, wherein said virus is a cytomegalovirus.
5. The method of claim 1 or 2, wherein said virus is human cytomegalovirus.
6. The method of any of claims 1-5, wherein said DNA molecule is purified plasmid DNA.
7. The method of any of claims 1-6, further comprising administering a boosting vaccine comprising an attenuated live or an inactivated virus.
8. The method of claim 7, wherein said virus is chemically inactivated.
9. The method of claim 8, wherein said chemical inactivation is formalin inactivation.
10. The method of claim 7, wherein said virus is attenuated.
11. The method of claim 10, wherein said virus is HCMV and said attenuated virus is the Towne strain of HCMV.
12. The method of claims 1-11, wherein said DNA molecule comprises at least two DNA sequences derived from at least two highly conserved viral genes.
13. The method of claims 1-11, wherein said DNA molecule comprises at least three DNA sequences derived from at least three highly conserved viral genes.
14. The method of claims 1-11, wherein said DNA molecule comprises at least four DNA sequences derived from at least two highly conserved viral genes.
15. The method of claims 1-11, wherein said DNA molecule comprises 5 to 10 DNA sequences derived from 5 to 10 highly conserved viral genes.
16. The method of claims 1-15, wherein said highly conserved viral genes are selected from the group consisting of CMV genes mouse gB, M54, M105, human gB, UL54, and UL105.
17. A method of preventing or treating HCMV infection in an individual comprising administering a DNA molecule comprising at least one DNA sequence derived from a highly conserved, essential HCMV gene.
18. The method of claim 16, wherein said individual is pregnant.
19. The method of claim 16, wherein said individual is a woman.
20. The method of claim 16, wherein said individual is an organ transplant recipient.
21. The method of claim 16, wherein said individual is an organ transplant donor.
22. The method of claim 16, wherein said individual is a child younger that 1 year.

23. The method of claims 17-22, further comprising administering a boosting vaccine comprising attenuated live or inactivated HCMV virus.

24. The method of claim 23, wherein said attenuated virus is the Towne strain of HCMV.

25. A vaccine composition comprising a DNA molecule comprising at least one DNA sequence derived from a highly conserved viral gene, wherein said virus causes a persistent or a latent infection.

26. The vaccine composition of claim 25, wherein said virus is selected from the group consisting of herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses.

27. The vaccine composition of claim 26, wherein said virus is human cytomegalovirus.

28. The vaccine composition of claim 27, wherein said DNA molecule comprises at least two DNA sequences derived from at least two highly conserved viral genes.

29. The vaccine composition of claim 27, wherein said DNA molecule comprises at least three DNA sequences derived from at least three highly conserved viral genes.

30. The vaccine composition of claims 27-29, wherein said highly conserved viral genes are selected from the group consisting of gB, UL54, and UL105.

31. A kit comprising a first vaccine composition of any of claims 25-30, and a second vaccine composition comprising an attenuated live or an inactivated virus.

32. The kit of claim 31, wherein said first vaccine composition comprises a DNA molecule comprising at least one DNA sequence derived from a highly conserved human cytomegalovirus gene and said second vaccine composition comprises attenuated live HCMV.

33. A method of eliciting a CD8+ T-cell response in an individual, comprising administering to said individual a DNA molecule comprising at least one DNA sequence derived from a highly conserved viral gene.

34. The method of claim 33, wherein said virus causes a persistent or a latent infection.

35. The method of claim 33 or 34, wherein said virus is selected from the group consisting of herpesviruses, retroviruses, hepatitis viruses, and papillomaviruses.

36. The method of claim 33 or 34, wherein said virus is a cytomegalovirus.

37. The method of claim 33 or 34, wherein said virus is human cytomegalovirus.

38. The method of any of claims 33-37, wherein said DNA molecule is purified plasmid DNA.

39. The method of any of claims 33-38, further comprising administering a boosting vaccine comprising an attenuated live or an inactivated virus.

40. The method of claim 39, wherein said virus is chemically inactivated.

41. The method of claim 40, wherein said chemical inactivation is formalin inactivation.

42. The method of claim 39, wherein said virus is attenuated.

43. The method of claim 40, wherein said virus is HCMV and said attenuated virus is the Towne strain of HCMV.

44. The method of claims 33-43, wherein said DNA molecule comprises at least two DNA sequences derived from at least two highly conserved viral genes.

45. The method of claims 33-43, wherein said DNA molecule comprises at least three DNA sequences derived from at least three highly conserved viral genes.

46. The method of claim 33-43, wherein said DNA molecule comprises at least four DNA sequences derived from at least two highly conserved viral genes.

47. The method of claim 33-43, wherein said DNA molecule comprises 5 to 10 DNA sequences derived from 5 to 10 highly conserved viral genes.

48. The method of claims 33-47, wherein said highly conserved viral genes are selected from the group consisting of CMV genes mouse gB, M54, M105, human gB, UL54, and UL105.

Figure 1

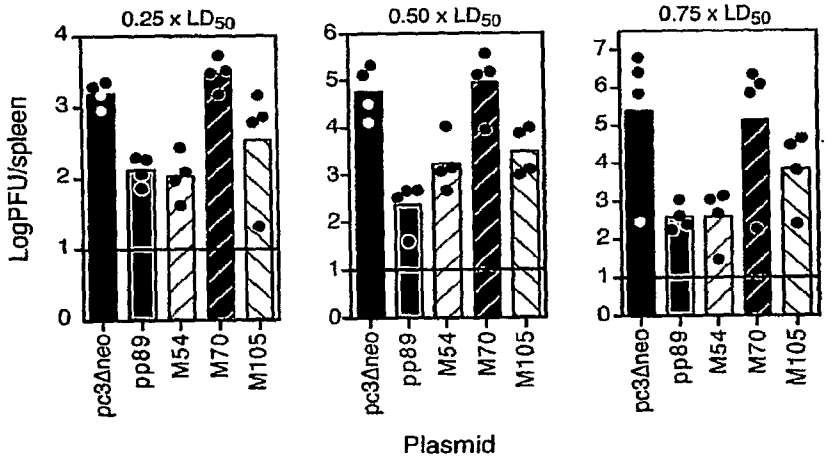
0.25 x LD50
0.50 x LD50
0.75 x LD50
LogPFU/spleen
pc3Δneo
pp89
M54
M70
M105
Plasmid

Figure 2

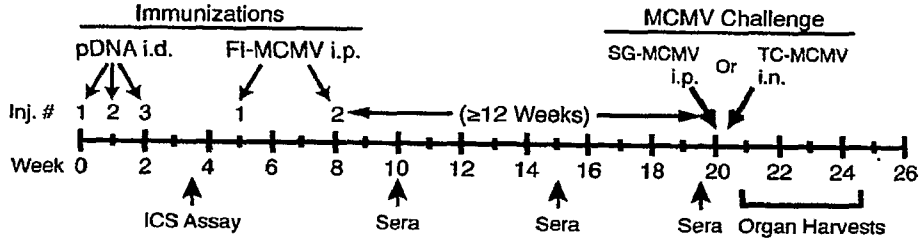
Immunizations
pDNA i.d.
FI-MCMV i.p.
MCMV Challenge
SG-MCMV i.p.
Or
TC-MCMV i.n.
Inj. #
1 2 3
1
2
(≥12 Weeks)
Week
0 2 4 6 8 10 12 14 16 18 20 22 24 26
ICS Assay
Sera
Sera
Sera
Organ Harvests

Figure 3

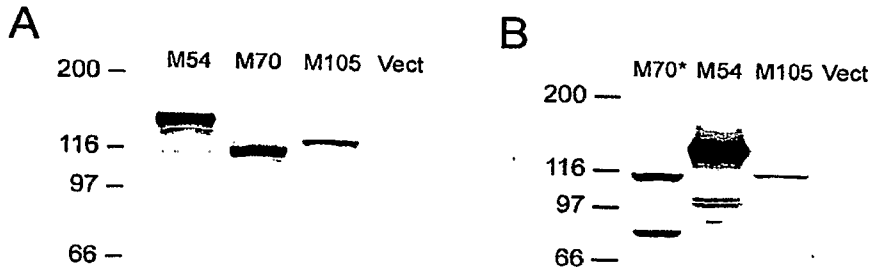
A
200 –
116 –
97 –
66 –
M54
M70
M105
Vect
B
200 —
116 —
97 —
66 —
M70*
M54
M105
Vect

Figure 4

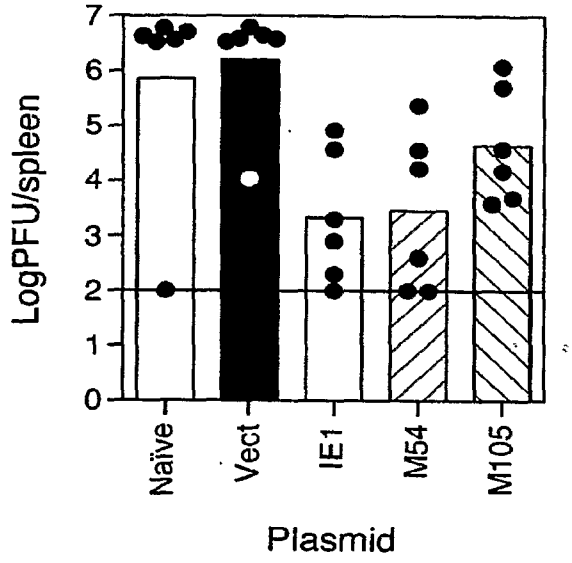

Figure 5

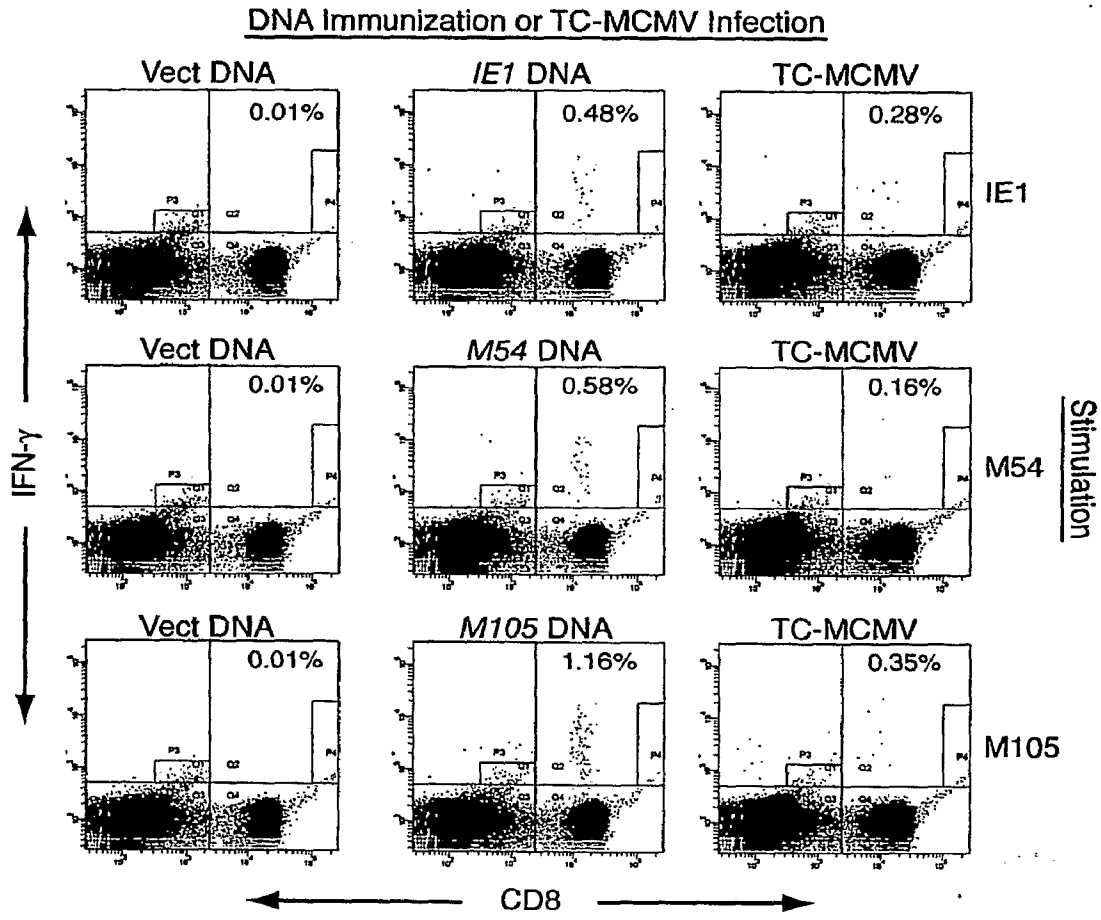
DNA Immunization or TC-MCMV Infection
Vect DNA
IE1 DNA
TC-MCMV
0.01%
0.48%
0.28%
IE1
Vect DNA
M54 DNA
TC-MCMV
0.01%
0.58%
0.16%
M54
Vect DNA
M105 DNA
TC-MCMV
0.01%
1.16%
0.35%
M105
IFN-γ
CD8
Stimulation

Figure 6

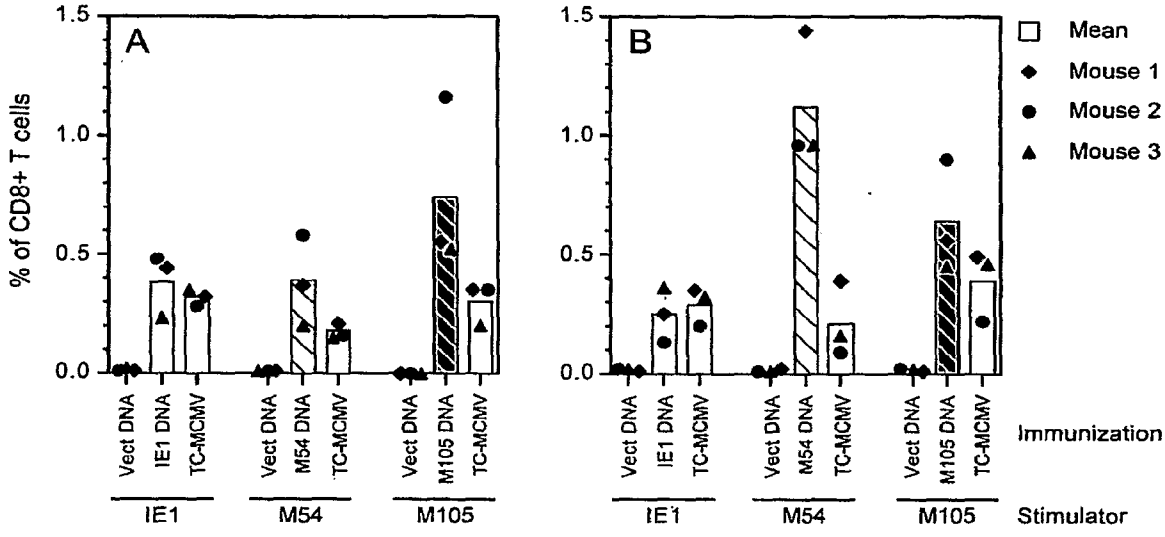
A
B
% of CD8+ T cells
1.5
1.0
0.5
0.0
Vect DNA
IE1 DNA
TC-MCMV
M54 DNA
M105 DNA
IE1
M54
M105
Mean
Mouse 1
Mouse 2
Mouse 3
Immunization
Stimulator

Figure 7

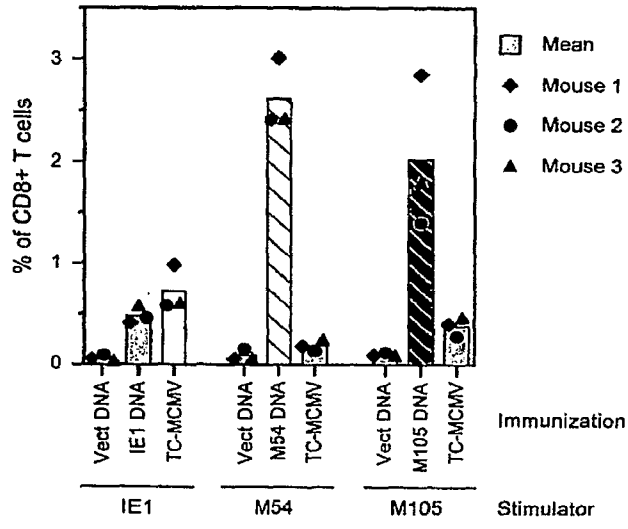
% of CD8+ T cells
0
1
2
3
Vect DNA
IE1 DNA
TC-MCMV
Vect DNA
M54 DNA
TC-MCMV
Vect DNA
M105 DNA
TC-MCMV
IE1
M54
M105
Stimulator
Immunization
Mean
Mouse 1
Mouse 2
Mouse 3

Figure 8

SEQ HCMV UL44
KEYWORD PROTEIN
SEQ ID NO: 1

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1       MDRKTRLSEP PTLALRLKPY KTAIQQLRSV IRALKENTTV TFLPTPSLIL QTVRSHCVSK
61      ITFNSSCLYI TDKSFQPKTI NNSTPLLGNF MYLTSSKDLT KFYVQDISDL SAKISMCAPD
121     FNMEFSSACV HGQDIVRESE NSAVHVDLDF GVVADLLKWI GPHTRVKRNV KKAPCPTGTV
181     QILVHAGPPA IKFILTNGSE LEFTANNRVS FHGVKNMRIN VQLKNFYQTL LNCAVTKLPC
241     TLRIVTEHDT LLYVASRNGL FAVENFLTEE PFQRGDPFDK NYVGNSGKSR GGGGGGGSLS
301     SLANAGGLHD DGPGLDNDLM NEPMGLGGLG GGGGGGGKKH DRGGGGGSGT RKMSSGGGGG
361     DHDHGLSSKE KYEQHKITSY LTSKGGSGGG GGGGGGGLDR NSGNYFNDAK EESDSEDSVT
421     FEFVPNTKKQ KCG
```

KEYWORD DNA (NC_001347 REGION: 56142..57443)
SEQ ID NO: 2

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      1 ctagccgcac ttttgcttct tggtgttagg gacgaactcg aacgttacag aatcctcgct
     61 gtcgctctcc tctttcgcgt cgttgaagta attgccggag ttgcgatcca aaccgccgcc
    121 tcctcctcct ccgccgccgc ccgatccacc tttggacgtc aggtagctgg tgatcttgtg
    181 ctgctcgtat ttttccttgg aggaaagacc gtggtcgtga tcaccgccgc cgccaccgct
    241 gctcattttc cgcgtaccgg aaccaccgcc gccaccgcgg tcgtgcttct tgccgccacc
    301 gccgccacct cctcccagac cgccgagacc catgggctcg ttcatgagat cgttatccag
    361 acccgggccg tcgtcatgca gaccgccggc attggccagc gaagagaggc tgccgccacc
    421 accgccgccg ccacgcgact tgccgctgtt cccgacgtaa tttttgtcga agggatcgcc
    481 acgctggaaa ggttcctcgg tgagaaaatt ctccacggcg aacagaccgt tgcggctggc
    541 cacgtacaac agcgtgtcgt gctccgtaac tatacgcaac gtgcacggca gtttggtgac
    601 ggcgcaattg agcagcgtct ggtagaagtt cttcagctgc acgttgatac gcatgttttt
    661 cacgccgtgg aaactgacgc ggttattggc tgtgaattcc agctcgctgc cgttggtcag
    721 gataaacttg atggccggtg gaccggcgtg caccagaatc tgcacggtgc ccgtagggca
    781 gggcgctttt ttaacgttac gcttgacgcg ggtatgcggc ccgatccact taagcaggtc
    841 ggccaccacg ccgaaatcta gatccacgtg cacggccgaa ttctcgcttt cgcgcacaat
    901 gtcttggccg tgcacgcagg ccgagctgaa ctccatattg aaatcgggcg cgcacatgga
    961 gatcttggcc gacaggtccg agatgtcctg cacgtagaac ttggtcaggt ccttgctgga
   1021 agtcaggtac atgaaattac ccagcagcgg cgtggaattg ttaatggtct tgggctgaaa
   1081 cgacttgtca gtgatgtaga ggcatgagct gttaaaagtg atttttgaca cgcagtgact
   1141 gcgtaccgtt tgcaagataa gcgacggcgt gggcaagaag gtaaccgtgg tgttctcctt
   1201 gagcgcacgg atcacagatc gcagctgctg gatagccgtc ttgtacggct tcagccgcag
   1261 cgccagcgtc ggcggctccg agaggcgcgt cttgcgatcc at
```

SEQ HCMV UL50
KEYWORD PROTEIN
SEQ ID NO: 3

```
1       MEMNKVLHQD LVQATRRILK LGPSELRVTD AGLICKNPNY SVCDAMLKTD TVYCVEYLLS
61      YWESRTDHVP CFIFKNTGCA VSLCCFVRAP VKLVSPARHV GEFNVLKVNE SLIVTLKDIE
121     EIKPSAYGVL TKCVVRKSNS ASVFNIELIA FGPENEGEYE NLLRELYAKK AASTSLAVRN
181     HVTVSSHSGS GPSLWRARMS AALTRTAGKR SSRTASPPPP PRHPSCSPTM VAAGGAAAGP
241     RPPPPPMAAG SWRLCRCEAC MGRCGCASEG DADEEEEELL ALAGEGKAAA AAAGQDVGGS
301     ARRPLEEHVS RRRGVSTHHR HPPSPPCAPS LERTGYRWAP SSWWRARSGP SRPQSGPWLP
361     ARFATLGPLV LALLLVLALL WRGHGQSSSP TRSAHRD
```

KEYWORD DNA (NC_001347 REGION: 73000..74193)
SEQ ID NO: 4

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     61 agccagcacc agcagaagag ccagcaccag cgggcccaga gtcgcaaagc gcgcgggcag
    121 ccacggccca gactgcggtc gcgatggccc ggagcgcgct cgccaccacg atgacggtgc
    181 ccaacgataa ccagtccgct ccaaggacgg cgcgcacggc ggagacggcg gatgacggtg
```

```
 241 atgggtcgac acccctcgcc gacgactcac gtgctcctcc agaggccgac gcgcggaccc
 301 tccgacgtcc tggcccgccg ctgccgctgc cgccttccct tctcccgcca gagccagcaa
 361 ctcctcctcc tcttcatcag cgtctccctc gcttgcgcat ccgcatcgtc ccatacaggc
 421 ctcacaacga cacagccgcc acgaccccgc cgccatgggt ggcggcggcg gccgaggccc
 481 ggcagcggcg ccgccagcgg cgaccatggt gggagagcaa ctcggatgac gaggaggagg
 541 agggggagat gcggtccgag aggaccgctt tcccgccgtt cgcgtaagcg cggccgacat
 601 gcgggcgcgc cacagggacg gaccgctgcc gctgtgactg cttacggtga cgtggttccg
 661 gaccgccaac gacgtcgacg cggctttctt ggcgtacagc tcgcgcagca gattctcgta
 721 ctcgccctcg ttttcgggtc cgaaggcgat gagctcgatg ttgaagaccg acgccgaatt
 781 ggatttgcgc accacgcact tcgtcagcac tccgtaggcc gagggcttga tctcctcgat
 841 gtccttgagc gtgacgatga gcgactcgtt caccttaagc acattgaact cacctacgtg
 901 gcgcgccggc gaaacgagct tgacgggcgc tcgtacaaaa cagcagaggg agacggcgca
 961 gccagtgttt ttaaagataa aacaaggcac gtggtctgtg cggctctccc agtagctgag
1021 tagatactcg acacaataga ccgtgtctgt cttgagcatg gcgtcgcaca ccgagtaatt
1081 ggggttttta cagatgaggc cggcatcggt gacgcgcagc tcgctgggac ccaacttgag
1141 gatacgccgc gtggcctgca ccagatcctg atggagaacc ttgttcatct ccat
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SEQ HCMV UL51
KEYWORD PROTEIN
SEQ ID NO: 5

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1   MSWAKQRVPF LDDDDGEEEN DVQDDVDSPV PTRPLVIDED AEPAAGTSGG LEGGGGDDED
61  GEDGHALPDL DDDLLLQFEP MLPRVYDLLL PSLDARLNFV NAGQKYAAFL KYVHGDCATC
121   SHGEILREKT QLLTAIVSKL MDINGILEGK DESAPGK
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KEYWORD DNA (NC_001347 REGION: 74215..74688)
SEQ ID NO: 6

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 121 cgcgcagtcg ccgtgcacgt acttgaggaa ggcggcgtac ttctgacccg cgttcacgaa
 181 atttaagcgc gcgtccagag agggcagcaa cagatcgtag acgcgcggca gcatcggctc
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 361 gtcgatcacc agcggtcgcg tcggcaccgg agaatccacg tcatcctgca cgtcgttttc
 421 ctcctctccg tcgtcatcgt ccagaaacgg cacccgctgc ttagcccagg acat
```

SEQ HCMV UL52
KEYWORD PROTEIN
SEQ ID NO: 7

```
1   MNPSTHVSSN GPTTPPHGPH TTFLPPTSPA PSTSSVAAAT LCSPQRQAVS RYSGWSTEYT
61  QWHSDLTTEL LWHAHPRQVP MDEALAAAAA ASYQVNPQHP ANRYRHYEFQ TLSLGTSEVD
121 ELLNCCAEET TCGGTQSTVL TNATNTTSCG GAVAGSSNVG PAGASAACDL DAELAGLETS
181 AADFEQLRRL CAPLAIDTRC NLCAIISICL KQDCDQSWLL EYSLLCFKCS YAPRAALSTL
241 IIMSEFTHLL QQHFSDLRID DLFRHHVLTV FDFHLHFFIN RCFEKQVGDA VDNENVTLNH
301 LAVVRAMVMG EDTVPYNKPR RHPQQKQKNN PYHVEVPQEL IDNFLEHSSP SRDRFVQLLF
361 YMWAGTGVMS TTPLTELTHT KFARLDALST ASEREDARMM IEEEEDEEGG EKGGDDPGRH
421 NGGGTSGGFS ESTLKKNVGP IYLCPVPAFF TKNQTSTVCL LCELMACSYY DNVVLRELYR
481 RVVSYCQNNV KMVDRIQLVL ADLLRECTSP LGAAHEDVAR CGLEAPTSPG GDSDYHGLSG
541 VDGALARPDP VFCHVLRQAG VTGIYKHFFC DPQCAGNIRV TNEAVLFGRL HPHHVQEVKL
601 AICHDNYYIS RLPRRVWLCI TLFKAFQITK RTYKGKVHLA DFMRDFTQLL ESCDIKLVDP
661 TYVIDKYV
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KEYWORD DNA (NC_001347 REGION: 74727..76733)
SEQ ID NO: 8

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 181 cagtggcact cggacttgac aactgagctg ctatggcacg cgcacccgcg tcaagtacct
 241 atggacgaag cgctggccgc cgcggcggcc gcctcatacc aggtaaatcc tcaacacccc
 301 gccaaccgtt accgtcatta cgaattccag acgctcagcc tcggcacctc ggaggtagac
```

```
 361 gaactgctca actgttgtgc ggaagaaacc acgtgcggcg gcacgcaatc caccgtactc
 421 accaatgcga ccaacaccac tagctgcggc ggagccgtcg ccggcagtag caacgtagga
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 661 gagtacagct tgctgtgctt caaatgcagt tacgcgcccc gtgcggcgct cagcacgctc
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 961 cgccacccgc aacagaagca aaaaaacaac ccttatcacg tcgaagtgcc gcaagaactg
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1201 atagaagaag aggaggatga agaaggagga gaaaaaggag gagacgatcc gggccgtcac
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1621 gtcgacggcg cactggcgcg acccgacccg gtattttgcc acgtcctgcg tcaggcaggc
1681 gtcacgggca tctacaagca ctttttctgc gacccgcagt gcgccggcaa catccgcgtc
1741 accaacgagg ccgtgctctt cggacgcctg caccccccacc acgtccagga ggtgaaactg
1801 gccatctgtc acgacaatta ctatataagt cgacttccgc gacgtgtgtg gctctgcatc
1861 acactcttca aggcctttca gattacaaaa cgcacctaca aaggcaaagt gcacctggcg
1921 gactttatgc gcgatttcac gcagctgttg gagagttgcg acatcaagct ggtggacccc
1981 acgtacgtga tagacaagta tgtctag
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SEQ HCMV UL53
KEYWORD PROTEIN
SEQ ID NO: 9

```
1       MSSVSGVRTP RERRSALRSL LRKRRQRELA SKVASTVNGA TSANNHGEPP SPADARPRLT
61      LHDLHDIFRE HPELELKYLN MMKMAITGKE SICLPFNFHS HRQHTCLDIS PYGNEQVSRI
121     ACTSCEDNRI LPTASDAMVA FINQTSNIMK NRNFYYGFCK SSELLKLSTN QPPIFQIYYL
181     LHAANHDIVP FMHAEDGRLH MHVIFENPDV HIPCDCITQM LTAAREDYSV TLNIVRDHVV
241     ISVLCHAVSA SSVKIDVTIL QRKIDEMDIP NDVSESFERY KELIQELCQS SGNNLYEEAT
301     SSYAIRSPLT ASPLHVVSTN GCGPSSSSQS TPPHLHPPSQ ATQPHHYSHH QSQSQQHHHR
361     PQSPPPPLFL NSIRAP
```

KEYWORD DNA (NC_001347 REGION: 76726..77856)
SEQ ID NO: 10

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 121 acgtcggcca acaaccacgg cgaaccgccg tcgccggccg acgcgcgccc gcgcctcacg
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 241 atgatgaaga tggccatcac gggcaaagag tccatctgct tacccttcaa tttccactcg
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 541 ctgcacgccg ccaaccacga catcgtgccc tttatgcacg ccgaggacgg ccggttgcac
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 661 ctcacggcgg cgcgcgaaga ctacagcgtc acgctcaaca tcgtgcgcga ccacgtcgtt
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1081 ccccagtcac caccgccgcc gctgtttctc aacagcattc gtgcgccttg a
```

SEQ HCMV UL54
KEYWORD PROTEIN
SEQ ID NO: 11

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1    MFFNPYLSGG VTGGAVAGGR RQRSQPGSAQ GSGKRPPQKQ FLQIVPRGVM FDGQTGLIKH
61   KTGRLPLMFY REIKHLLSHD MVWPCPWRET LVGRVVGPIR FHTYDQTDAV LFFDSPENVS
121  PRYRQHLVPS GNVLRFFGAT EHGYSICVNV FGQRSYFYCE YSDTDRLREV IASVGELVPE
181  PRTPYAVSVT PATKTSIYGY GTRPVPDLQC VSISNWTMAR KIGEYLLEQG FPVYEVRVDP
241  LTRLVIDRRI TTFGWCSVNR YDWRQQGRAS TCDIEVDCDV SDLVAVPDDS SWPRYRCLSF
301  DIECMSGEGG FPCAEKSDDI VIQISCVCYE TGGNTAVDQG IPNGNDGRGC TSEGVIFGHS
361  GLHLFTIGTC GQVGPDVDVY EFPSEYELLL GFMLFFQRYA PAFVTGYNIN SFDLKYILTR
421  LEYLYKVDSQ RFCKLPTAQG GRFFLHSPAV GFKRQYAAAF PSASHNNPAS TAATKVYIAG
481  SVVIDMYPVC MAKTNSPNYK LNTMAELYLR QRKDDLSYKD IPRCFVANAE GRAQVGRYCL
541  QDAVLVRDLF NTINFHYEAG AIARLAKIPL RRVIFDGQQI RIYTSLLDEC ACRDFILPNH
601  YSKGTTVPET NSVAVSPNAA IISTAAVPGD AGSVAAMFQM SPPLQSAPSS QDGVSPGSGS
661  NSSSSVGVFS VGSGSSGGVG VSNDNHGAGG TAAVSYQGAT VFEPEVGYYN DPVAVFDFAS
721  LYPSIIMAHN LCYSTLLVPG GEYPVDPADV YSVTLENGVT HRFVRASVRV SVLSELLNKW
781  VSQRRAVREC MRECQDPVRR MLLDKEQMAL KVTCNAFYGF TGVVNGMMPC LPIAASITRI
841  GRDMLERTAR FIKDNFSEPC FLHNFFNQED YVVGTREGDS EESSALPEGL ETSSGGSNER
901  RVEARVIYGD TDSVFVRFRG LTPQALVARG PSLAHYVTAC LFVEPVKLEF EKVFVSLMMI
961  CKKRYIGKVE GASGLSMKGV DLVRKTACEF VKGVTRDVLS LLFEDREVSE AAVRLSRLSL
1021 DEVKKYGVPR GFWRILRRLV QARDDLYLHR VRVEDLVLSS VLSKDISLYR QSNLPHIAVI
1081 KRLAARSEEL PSVGDRVFYV LTAPGVRTAP QGSSDNGDSV TAGVVSRSDA IDGTDDDADG
1141 GGVEESNRRG GEPAKKRARK PPSAVCNYEV AEDPSYVREH GVPIHADKYF EQVLKAVTNV
1201 LSPVFPGGET ARKDKFLHMV LPRRLHLEPA FLPYSVKAHE CC
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KEYWORD DNA (NC_001347 REGION: 77834..81562)
SEQ ID NO: 12

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   1 tcaacagcat tcgtgcgcct tgacactgta cggcagaaaa gccggctcca agtgcaagcg
  61 ccgcggcagc accatgtgca aaaacttgtc cttgcgcgcg gtttcgccgc cgggaaagac
 121 gggcgacagc acgttagtta cagccttgag aacctgctca aagtacttgt cggcgtgaat
 181 gggcacgccg tgctcgcgca cgtagctcgg atcttcggct acctcgtagt tgcacacggc
 241 cgacggtggt ttccgcgccc tcttctttgc cggctctcct cctctcctgt tgctctcctc
 301 taccccgccg ccgtcagcgt cgtcgtccgt gccatcaatc gcgtccgacc gggaaaccac
 361 gccggcggtt acagaatcac cgttgtcgga ggaaccctgc ggcgccgtcc ggacaccggg
 421 cgccgtcaga acgtaaaaga cccgatcccc gaccgagggt agctcctcag aacgggccgc
 481 caatcgctta atgacggcaa tgtgcggcag gttagattga cggtacagcg agatgtcctt
 541 agagagcacc gacgaaagca ccaggtcctc gacacgcaca cggtgcaggt acagatcgtc
 601 gcgggcctgc accaagcggc gtaagatacg ccagaaaccg cgtggcacgc cgtacttctt
 661 gacttcatcg agtgagaggc gcgacaggcg cacggctgct tccgagacct cgcgatcctc
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 781 caccagatcc acgcccttca tgctcagacc cgaggcgccc tccactttgc cgatgtaacg
 841 tttcttgcag atcatcataa gagagacgaa gacctttca aactccagct tgacgggctc
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1081 gctctcctcc gaatcccct cccgcgttcc cactacatag tcttcctgat taaaaaaatt
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1321 gagcagcata cggcgcacag ggtcttgaca ctcgcgcatg cattcgcgca cggcacgccg
1381 ctgcgaaacc cacttgttga gcagttccga gagcaccgag acgcgcaccg aagcacgcac
1441 aaagcggtgg gtcacgccgt tctctagcgt gacgctgtat acgtcggcgg ggtccacagg
1501 gtactcgcca cccggcacca gcagggtgga gtagcagagg ttgtgggcca tgatgatgga
1561 agggtagagg ctggcaaagt cgaacacggc cacggggtcg ttgtagtaac ccacctcggg
1621 ctcaaacacc gtggcgccct ggtacgaaac cgccgcagta ccgccggcgc cgtgattgtc
1681 gttggaaacg ccgacgccgc cactactgcc ggagccgacg ctgaaaacgc cgacgctgct
1741 actactgtta ctgccggagc cgggtgaaac gccgtcctga ctggacggcg cagattgcaa
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1801 gggcggcgac atctgaaaca tagccgccac agaacccgcg tcgccgggca cagcggcggt
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2101 ggcgtcctgc agacagtaac ggcctacctg ggcgcggccc tcggcattag ccacgaaaca
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2461 gtactcgaga cgcgtgagga tgtacttcaa gtcaaaagag ttgatgttgt aaccggtcac
2521 aaaggccggc gcgtaccgtt gaaagaaaag cataaagccc agcagcagct cgtattcgga
2581 agggaactcg tagacgtcca cgtctgggcc cacctgcccg caggtgccga tcgtaaagag
2641 atgaagaccc gagtgcccaa agatcacacc ctccgaagtg cagccccgac catcgttccc
2701 gtttgggatc ccctgatcca cggcggtgtt tccccccgtc tcgtagcaca cgcacgagat
2761 ctgaatgaca atgtcatcgg acttctcggc gcagggaaaa ccaccctcgc cgctcatgca
2821 ctcgatatcg aaggacaggc atcgatagcg cggccacgag ctgtcgtcgg gcacagccac
2881 caggtcagag acatcgcagt ctacctcgat atcacaagtc gacgcgcgac cctgctgccg
2941 ccagtcgtaa cgattcacgg agcaccagcc gaacgtggtg atccgccgat cgatgaccaa
3001 acgcgtcagc ggatccacac ggacctcgta cacgggaaaa ccctgctcca gcagatactc
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3421 ggtgtgaaaa cgaataggtc ccaccacgcg acccaccagg gtctcgcgcc aaggacacgg
3481 ccaaaccatg tcatgactca acaaatgttt aatctctcga tagaacatga gaggcagccg
3541 tcccgtctta tgcttgatca accccgtctg accgtcgaac atgacacctc gcggcacgat
3601 ctgcaaaaac tgtttctgtg gcggccgctt gcccgagccc tgcgcggagc cgggctgcga
3661 acgctgacgc cggccacccg cgaccgcacc gccggtcacg ccgccgctca gatacgggtt
3721 gaaaaacat
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SEQ          HCMV UL55 (Gb)
KEYWORD        PROTEIN
SEQ ID NO:  13
1         MESRIWCLVV CVNLCIVCLG AAVSSSSTSH ATSSTHNGSH TSRTTSAQTR SVYSQHVTSS
61        EAVSHRANET IYNTTLKYGD VVGVNTTKYP YRVCSMAQGT DLIRFERNII CTSMKPINED
121       LDEGIMVVYK RNIVAHTFKV RVYQKVLTFR RSYAYIYTTY LLGSNTEYVA PPMWEIHHIN
181       KFAQCYSSYS RVIGGTVFVA YHRDSYENKT MQLIPDDYSN THSTRYVTVK DQWHSRGSTW
241       LYRETCNLNC MLTITTARSK YPYHFFATST GDVVYISPFY NGTNRNASYF GENADKFFIF
301       PNYTIVSDFG RPNAAPETHR LVAFLERADS VISWDIQDEK NVTCQLTFWE ASERTIRSEA
361       EDSYHFSSAK MTATFLSKKQ EVNMSDSALD CVRDEAINKL QQIFNTSYNQ TYEKYGNVSV
421       FETSGGLVVF WQGIKQKSLV ELERLANRSS LNITHRTRRS TSDNNTTHLS SMESVHNLVY
481       AQLQFTYDTL RGYINRALAQ IAEAWCVDQR RTLEVFKELS KINPSAILSA IYNKPIAARF
541       MGDVLGLASC VTINQTSVKV LRDMNVKESP GRCYSRPVVI FNFANSSYVQ YGQLGEDNEI
601       LLGNHRTEEC QLPSLKIFIA GNSAYEYVDY LFKRMIDLSS ISTVDSMIAL DIDPLENTDF
661       RVLELYSQKE LRSSNVFDLE EIMREFNSYK QRVKYVEDKV VDPLPPYLKG LDDLMSGLGA
721       AGKAVGVAIG AVGGAVASVV EGVATFLKNP FGAFTIILVA IAVVIITYLI YTRQRRLCTQ
781       PLQNLFPYLV SADGTTVTSG STKDTSLQAP PSYEESVYNS GRKGPGPPSS DASTAAPPYT
841       NEQAYQMLLA LARLDAEQRA QQNGTDSLDG QTGTQDKGQK PNLLDRLRHR KNGYRHLKDS
901       DEEENV

KEYWORD      DNA (NC_001347 REGION: 81703..84423)
SEQ ID NO:  14

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       61 cagccggtct agcaggttag gcttctgtcc cttgtcctgc gtgccagtct gtccgtccaa
      121 agaatctgta ccgttctgct gcgctcgctg ctctgcgtcc agacgggcca gggccagaag
      181 catctggtaa gcctgctcgt tggtgtaagg cggagccgcc gtggatgcat cagacgacgg
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 241 tggtcccggt cctttgcgac cagaattata aacactttcc tcgtaggaag gcggagcctg
 301 taacgacgtg tctttggtgc tgcccgacgt cacggtggtc ccgtcggcgg acaccagata
 361 gggaaagagg ttctgcagcg gctgcgtgca cagacgccgc tgtcgagtat agatcaaata
 421 agtgataatg actacggcta tggccacgag gatgatggtg aaggctccga aggggttttt
 481 gaggaaggtg gcaacgcctt cgaccacgga ggccaccgcg ccacccacgg ccccaatggc
 541 tacgccaacg gcctttcccg cggcgcccag gccgctcatg aggtcgtcca gacccttgag
 601 gtagggcggt agcgggtcga ctaccttgtc ctccacgtac tttacccgct gcttgtacga
 661 gttgaattcg cgcatgatct cttcgaggtc aaaaacgttg ctggaacgca gctctttctg
 721 cgagtaaagt tccagtaccc tgaagtcggt attttccagc gggtcgatat ccagggcgat
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2041 cacgtaacgg gtactgtggg tgttggaata atcgtcggga attaattgca tggttttgtt
2101 ttcataactg tccctatgat atgccacgaa aaccgtgcct cctataacgc ggctgtagga
2161 actgtagcat tgagcaaact tgttgatgtg atgaatctcc cacataggag gcgccacgta
2221 ttccgtattg ctgcccagca gataagtggt gtagatgtaa gcgtagctac gacgaaacgt
2281 caaaaccttt tggtagaccc gtaccttaaa ggtgtgcgcc acgatgttgc gcttgtagac
2341 caccatgatg ccctcatcca agtcttcatt gataggcttc atcgaggtgc agatgatatt
2401 acgttcaaag cgaataagat ccgtaccctg ggccatagaa cacacgcgat aggggtactt
2461 ggtagtgttg actcccacca catctccgta cttgagggta gtgttgtaga tagtctcgtt
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2581 agcagacgtc gtacgagaag tatggcttcc attgtgagta gaagaagttg catgggaagt
2641 actagaagag gaaaccgcag cacccagaca gacgatacac aggttaacgc agactaccag
2701 gcaccagatc ctggattcca t
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SEQ          HCMV UL56
KEYWORD      PROTEIN
SEQ ID NO:   15
1        MEMNLLQKLC VVCSKCNEYA MELECLKYCD PNVLLAESTP FKRNAAAIVY LYRKIYPEVV
61       AQNRTQSSLL TLYLEMLLKA LHEDTALLDR ALMAYSRQPD RAAFYRTVLR LDRCDRHHTV
121      ELQFTDNVRF SVSLATLNDI ERFLCKMNYV YGILAPEAGL EVCAQLLELL RRLCGISPVA
181      RQEVYVEGTT CAQCYEELTI IPNQGRSLNK RLQGLLCNHI AVHRPSSQSD VNIQTVEQDL
241      LDLTTRIPHL AGVLSALKSL FSSSSAYHSY IQEAEEALRE YNLFTDIPER IYSLSDFTYW



301      SRTSEVIVKR VGITIQQLNV YHQLCRALMN GISRHLYGED VEDIFVLGEK ALDGEERMFV
361      GSVFAAPNRI IDLITSLSIQ AFEDNPVFNK LHESNEMYTK IKHILEEIRR PLPDGTGGDG
421      PEGEAIHLRG REAMSGTGTT LMTASNSSNS STHSQRNNGG GGRARGGGKK VVGGGVNGQD
481      GDGSENGLRV RNCDEHEALD LVDARSRIHN VTREVNVRKR AYLQKVSEVG YGKVIRCIKT
541      QERLTSKLID VNLVGPLCLD FISKLMNGFL YRSQYHQDQD VVDVGDQFTY DEHLYVVNNL
601      IHKSLPVESL PLLGQQIYEL CNGPLFTHCT DRYPLSHNVD MAYACDNAGV LPHVKDDLVK
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661       CAEGTVYPSE WMVVKYMGFF NFSDCQDLNV LQKEMWMHVR ELVLSVALYN ETFGKQLSIA
721       CLRDELHPDR DVILTYNKEW PLLLRHEGSL YKSKDLYLLL YRHLSRPDES GDVPTAPVAK
781       PSTLTAAAAV SGVFREPDRP WLPSPYPSSS TAGVSRRVRA TRKRPRRASS LLDLARDEHG
841       IQDLVPGSLR

KEYWORD      DNA (NC_001347 REGION: 84386..86938)
SEQ ID NO:   16

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       121 agtcgaggag gagggatacg gacttggcag ccaaggtcgg tccggctccc tgaagacacc
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       721 cgggagggat tccacaggca gactcttgtg gatcaggtta ttgaccacat acaggtgctc
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      1021 gacgttgtgg atgcgggagc gcgcgtccac caagtcgaga gcctcgtgtt cgtcgcagtt
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      1561 gccgttcatg agcgccccggc acagctggtg atacacattt agctgctgga tggtgatgcc
      1621 cacccgcttg acgataacct ccgaggtacg ggaccagtag gtaaaatccg acaaggaata
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      2161 gctgaaacgg acgttgtccg taaactggag ctccacggtg tgatggcgat cgcagcgatc
      2221 caaacggagg acggtacggt agaaggccgc ccggtccggc tggcgcgagt aggccatcag
      2281 cgcccgatcc agcaaagccg tatcctcgtg cagcgccttc agcagcatct ccaggtagag
      2341 cgtcagcaac gaactctgcg tacgattctg cgccaccacc tccgggtaga tcttccggta
      2401 cagatacact atagccgccg cgtttctctt gaacggcgtg gactccgcca gtaacacgtt
      2461 cggatcgcag tactttagac actccagctc catggcgtat tcgttgcatt tcgaacacac
      2521 tacgcatagt ttctgtaaca aattcatctc cat

SEQ          HCMV UL57
KEYWORD      PROTEIN
SEQ ID NO:   17
1         MSHEELTALA PVGPAAFLYF SRLNAETQEI LATLSLCDRS SSVVIAPLLA GLTVEADFGV
61        SVRTPVLCYD GGVLTKVTSF CPFALYFHHT QGIVAFTEDH GDVHRLCEDA RQKYALEAYM
121       PEADRVPTDL AALCAAVGCQ ASETTVHVVV GNGLKEFLFA GQLIPCVEEA TTVRLHGGEA
181       VRVPLYPPTL FNSLQLDAEA DEVSLDARSA FVEARGLYVP AVSETLFYYV YTSWCQSLRF
241       SEPRVLIEAA LRQFVHDSQQ SVKLAPHKRY LGYMSQRLSS LEKDHLMLSD AVVCELAFSF
301       ASVFFDSAYQ PAESMLFSEW PLVTNATDHR DLIRALTELK LHLSTHVAAL VFSANSVLYQ
361       HRLVYLQSSA RHPSAGGTAS QETLLKAIQF TNGLSAACED VYNDARKVLK FQGAPLKDER
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421      YGPQHLALVC GTCPQLVSGF VWYLNRVSVY NTGLSGSSTL TNHLVGCAAG LCEACGGTCC
481      HTCYQTAFVR VRTRLPVVPK QPKKEPCVIT VQSRFLNDVD ILGSFGRRYN VDAKDGGLDG
541      KGDDGVPGGG AGGGGGRDVS GGPSDGLGGG RGGGGGGDSG GMMGRGGRML GASVDRTYRL
601      NRILDYCRKM RLIDPVTGED TFSAHGKSDF VAVFSALNKF VDDEALGFVS EVRLKSSRDE
661      VAGATQAFNL DLNPYAVAFQ PLLAYAYFRS VFYVIQNVAL ITATSYIVDN PLTTNLVSKW
721      MTQHFQSIHG AFSTTSSRKG FLFTKQIKSS KNSDHDRLLD FRLYAQGTYA VVPMEIKLSR
781      LSVPTLIMVR VKNRPIYRAG KGNAGSVFFR RDHVPRRNPA KGCLGFLLYR HHERLFPECG
841      LPCLQFWQKV CSNALPKNVP IGDMGEFNAF VKFLVAVTAD YQEHDLLDVA PDCVLSYVES
901      RFHNKFLCYY GFKDYIGSLH GLTTRLTTQN HAQFPHVLGA SPRFSSPAEF ALHVKGLKTA
961      GVPAPMAATV ARESLVRSVF EHRSLVTVPV SVEKYAGINN SKEIYQFGQI GYFSGNGVER
1021     SLNVSSMSGQ DYRFMRQRYL LATRLADVLI KRSRRENVLF DADLIKNRVM LALDAENLDC
1081     DPEVMAVYEI LSVREEIPAS DDVLFFVDGC EALAASLMDK FAALQEQGVE DFSLENLRRV
1141     LDADAQRLTD AAGGEVHDLS ALFAPSGVGA ASGVGGGGLL LGESVAGNSI CFGVPGETGG
1201     GCFLVNAGED EAGGVGGSSG GGGGSGLLPA KRSRL
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KEYWORD DNA (NC_001347 REGION: 87505..91212)
SEQ ID NO: 18

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     121 gccgggcacg ccgaagcaaa tggagttgcc cgcgacggac tcgccgagaa gaagaccgcc
     181 acccccgacg ccggacgccg cgccgacgcc actgggcgcg aagagcgccg acaggtcgtg
     241 cacctccccc ccggcggcgt ccgttaatcg ctgggcgtcg gcgtccagca cgcgtcgcaa
     301 gttctccagc gaaaagtcct ccacgccctg ctcctgcaac gcggcaaact tgtccatcag
     361 cgacgcggcc agcgcctcgc agccatccac gaagaagagc acatcgtcgg acgcggggat
     421 ctcctcgcgc acgctcagaa tctcgtacac ggccatcact tcggggtcgc aatccaagtt
     481 ctcggcgtcc agcgccagca tgacgcggtt ttttataaga tccgcgtcaa aaagcacgtt
     541 ctcgcggcgc gagcgtttga tgagcacgtc ggccagacgc gtagccaaga ggtagcgctg
     601 gcgcatgaaa cgataatctt ggccgctcat agagctcacg ttaaggctgc gttccacacc
     661 gttgcccgaa aagtagccga tctgcccaaa ctgatagatc tccttgctgt tgttgatacc
     721 cgcatatttt tccacgctca cgggcacggt caccaaggaa cgatgctcaa aaacgctccg
     781 taccaacgat tcacgcgcca cagtggcggc catgggcgcc ggcacgcctg cggtcttcaa
     841 gcccttgaca tgcaacgcaa attcggcggg cgacgagaac cgcggactag cacctaacac
     901 gtgaggaaac tgcgcgtggt tctgcgtcgt taagcgcgtc gtcaacccgt gcagcgagcc
     961 gatgtagtct ttgaagccat aatagcagag gaatttgtta tggaaacggc tttccacgta
    1021 actcagcaca cagtctggcg ccacatccag cagatcgtgc tcctgatagt cagccgtcac
    1081 agccaccaga aatttgacga aagcattgaa ctcgcccatg tcacctatgg gcacattctt
    1141 gggcaacgcg ttggaacaga ccttctgcca aaactgtaag caggggagac cacattcagg
    1201 aaagagtcgc tcgtgatgtc gatacagcag aaatcccaag cagcccttag ccggattacg
    1261 acgcggaacg tgatcgcggc gaaaaaacac gctacccgcg ttgcccttgc ccgcgcggta
    1321 gatgggtcgg tttttcaccc gcaccatgat caacgtgggt accgacagcc gcgagagctt
    1381 gatctccatg ggcaccacgg cgtacgtgcc ctgcgcgtac agcctaaagt ccagcaggcg
    1441 gtcgtgatcc gaattcttgg acgacttgat ctgcttggtg aagagaaagc ccttgcgcga
    1501 cgacgtggtg gagaacgcgc cgtgaatgga ttgaaaatgc tgcgtcatcc atttggatac
    1561 caagttggtg gtcaacggat tgtccacaat gtatgaggta gcggtaataa gcgccacgtt
    1621 ctggatcacg taaaagacgg atctgaaata ggcgtaggct agcagcggct ggaaggccac
    1681 ggcgtaggga ttcagatcca ggttgaaggc ctgcgtggcg cccgccacct cgtcgcggct
    1741 gctcttgagg cgcacctccg aaacgaaacc cagggcctcg tcgtccacaa acttgttgag
    1801 cgccgaaaag acggccacaa agtcgctttt gccgtgcgcg ctaaaggtat cctcgcccgt
    1861 cacggggtcg atgagccgca tcttgcggca gtaatccaag atgcgattga gccgataggt
    1921 acggtccacg ctagcgccca acatgcgacc gccgcgcccc atcattcccc cggaatcccc
    1981 accacccccа ccaccacgac cgccacccag accgtcgctc gggcccccgc tcacgtctcg
    2041 tccaccaccc ccgccagcac cgccgcccgg aaccccgtcg tcacctttgc cgtccaaacc
    2101 cccgtccttg gcgtcgacgt tgtaacgccg accgaagctg cccaaaatat ccacgtcgtt
    2161 gagaaaacgc gactgcacgg tgatcacgca gggctccttc ttgggctgct tgggcaccac
    2221 gggcaagcgg gtgcgcaccc gcacgaaggc cgtctgataa cacgtgtggc aacaagtacc
    2281 cccacaggcc tcgcacagcc ccgcggcgca gcccaccagg tgattcgtga gcgtcgacga
    2341 acccgacaag cccgtgttgt acaccgagac acgattcaga taccagacga agcccgaaac
    2401 tagctgcgga cacgtgccac acaccaacgc caaatgctgc ggcccatagc gttcgtcctt
    2461 gagcggcgcg ccctgaaact tgagcacctt gcgcgcgtcg ttgtagacgt cttcgcaggc
    2521 cgccgacaac ccgttggtga actgaatagc cttgagcaac gtctcctgac tggccgtacc
    2581 gccggcgctg ggatgccgcg ccgacgactg gagatacacc agcctgtgct ggtagagcac
```

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2641 cgaattagcg ctgaagacca aggcggccac gtgcgtcgag agatgcaact tgagctcggt
2701 cagcgcgcgg atcagatcgc ggtgatcggt tgcgttggtc actaaaggcc actcggaaaa
2761 gagcatagat tcggcaggtt ggtaagccga atcgaaaaat accgaggcaa aactgaaggc
2821 caactcgcaa accaccgcgt cactcagcat cagatgatcc ttttccagac tgctgagtcg
2881 ctggctcatg taccccaagt agcgcttatg tggcgccagc ttcaccgact gctgactgtc
2941 gtgcacaaac tgccgcaacg ccgcctcgat cagcacacgc ggctccgaga agcgcagcga
3001 ttgacaccat gacgtgtaca cgtagtagaa aagcgtctcg cttacggccg gcacgtagag
3061 ccctcgcgcc tccacaaaag cgctgcgcgc atccagcgag acctcgtcgg cttcggcgtc
3121 aagctgcaac gaattaaaga gcgtaggcgg gtacaacggc acgcgcaccg cctcgccgcc
3181 gtgcagtcgc accgtggtcg cctcctccac gcatggaatc agctgaccgg caaagagaaa
3241 ctccttcaag ccgttgccca ccaccacgtg cacagtcgtc tcggacgcct gacagcccac
3301 cgccgcgcac aacgccgcca gatcggtagg cacgcgatcc gcctcgggca tgtaagcctc
3361 caacgcgtac ttctggcggg cgtcctcgca cagccgatgc acgtctccgt gatcctcggt
3421 aaaagccacg atgccttgcg tatgatgaaa gtagagcgca aaaggacaga aggacgtgac
3481 tttcgtgagc accccgccgt cgtaacaaag cacaggcgtg cgcacagaga cgccgaaatc
3541 cgcctccacc gtgagccccg ccaacaaagg agcgatcacc acgctcgagg aacggtcgca
3601 tagcgagaga gtggccagaa tctcctgcgt ttctgcgttc aacctgctga agtagagaaa
3661 agccgcgggc cccaccggcg ctagcgcggt tagttcctcg tggctcat
```

SEQ HCMV UL70
KEYWORD PROTEIN
SEQ ID NO: 19

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1   MTLVLFATEY DSAHIVANVL SQTPTDHCVF PLLVKHQVSR RVYFCLQTQK CSDSRRVAPV
61  FAVNNETLQL SRYLAARQPI PLSALIASLD EAETQPLYRH LFRTPVLSPE HGGEVREFKH
121 LVYFHHAAVL RHLNQVFLCP TSPSWFISVF GHTEGQVLLT MAYYLFEGQY STISTVEEYV
181 RSFCTRDLGT IIPTHASMGE FARLLLGSPF RQRVSAFVAY AVARNRRDYT ELEQVDTQIN
241 AFRERARLPD TVCVHYVYLA YRTALARARL LEYRRVVAYD ADAAPEAQCT REPGFLGRRL
301 STELLDVMQK YFSLDNFLHD YVETHLLRLD ESPHSATSPH GLGLAGYGGR IDGTHLAGFF
361 GTSTQLARQL ERINTLSESV FSPLERSLSG LLRLCASLRT AQTYTTGTLT RYSQRRYLLP
421 EPALAPLLER PLPVYRVHLP NDQHVFCAVA SETWHRSLFP RDLLRHVPDS RFSDEALTET
481 VWLHDDDVAS TSPETQFYYT RHEVFNERLP VFNFVADFDL RLRDGVSGLA RHTVFELCRG
541 LRRVWMTVWA SLFGYTHPDR HPVYFFKSAC PPNSVPVDAA GAPFDDDDYL DYRDERDTEE
601 DEDGKEDKNN VPDNGVFQKT TSSVDTSPPY CRCKGKLGLR IITPFPACTV AVHPSVLRAV
661 AQVLNHAVCL DAELHTLLDP ISHPESSLDT GIYHHGRSVR LPYMYKMDQD DGYFMHRRLL
721 PLFIVPDAYR EHPLGFVRAQ LDLRNLLHHH PPHDLPALPL SPPPRVILSV RDKICPSTEA
781 NFIETRSLNV TRYRRRGLTE VLAYHLYGGD GATAAAISDT DLQRLVVTRV WPPLLEHLTQ
841 HYEPHVSEQF TAPHVLLFQP HGACCVAVKR RDGARTRDFR CLNYTHRNPQ ETVQVFIDLR
901 TEHSYALWAS LWSRCFTKKC HSNAKNVHIS IKIRPPDAPV PPATAV
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KEYWORD DNA (NC_001347 REGION: 101464..104304)
SEQ ID NO: 20

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   1 tcagacggcg gtcgccggcg gcacgggcgc gtcgggcggt ctgattttga tggaaatgtg
  61 gacgtttttg gcgttggagt gacacttttt ggtgaaacag cggctccaga ggctggccca
 121 gagcgcgtag ctgtgctcgg tgcgcaggtc gatgaacacc tgcacggtct cttgcgggtt
 181 gcggtgcgtg tagttgagac agcgaaaatc ccgcgtgcgc gcgccgtcgc gccgcttgac
 241 ggccacgcag caggcgccgt ggggctgaaa gaggaggacg tggggcgcgg taaactgctc
 301 gctgacgtgc ggttcgtagt gttgcgtgag gtgctcgagc agcggcggcc acacgcgggt
 361 gacgacgagc cgctgcaagt ccgtgtcgga aatcgcagcg gcagtggcgc cgtcgccacc
 421 gtacaggtga taggcgagca cctcggtgag accgcggcgt cgataacgcg tcacgttaag
 481 cgagcgcgtc tcgataaagt tggcttcggt cgaggggcag attttgtcgc gtacgctgag
 541 aatgacgcgt ggcggcggcg acaggggcaa cgcgggcagg tcgtgcggcg ggtggtggtg
 601 aagcaggtta cgcagatcca gttgggcgcg cacaaagcct agcgggtgtt cgcggtaggc
 661 gtcgggcacg atgaacagcg gcaacagacg gcgatgcatg aaatagccgt cgtcttggtc
 721 cattttatac atgtagggca gacgtacaga gcgtccatgg tggtagatgc ctgtgtctag
 781 gctgctctcg ggatgcgaga tggggtccag cagcgtgtgc agttcggcgt cgagacagac
 841 ggcgtgattg agcacctgcg ccacggcgcg taaaacgctg gggtgtacgg cgacggtgca
 901 ggcggggaac ggcgtgatga tgcgcagccc cagtttgccc ttgcagcggc agtaaggggg
 961 tgacgtgtca acggaggacg ttgtttttg gaaaacgccg ttatccggga cgttattttt
1021 atcctctttc ccgtcttcgt cttcctctgt gtcgcgctcg tcccggtaat cgagatagtc
```

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1081 gtcgtcatcg aaaggcgcgc cggccgcgtc cacgggcacg ctgttgggtg ggcacgcgct
1141 tttgaagaaa tagaccgggt gccggtcggg gtgcgtgtag ccaaagaggc tcgcccatac
1201 ggtcatccag acgcgtcgta gtccgcgaca tagctcaaag acggtgtgtc gcgccagacc
1261 ggagacgccg tcgcgcagcc gtaaatcaaa gtcggccaca aaattgaaga cgggcagacg
1321 ttcgttgaag acttcgtgtc gcgtgtagta gaactgtgtc tcggggctgg tgctggccac
1381 gtcgtcgtcg tgtagccaca cggtctcggt cagggcctcg tccgagaaac ggctgtcggg
1441 tacgtgacgg agcaggtcac gcggaaagag gctgcgatgc caggtttcgg aggccacggc
1501 gcagaagacg tgctggtcat tgggcaggtg tacgcggtag acgggcagcg gtcgctccag
1561 cagcggtgcc agcgcgggct cgggtagcag gtagcgacgt tgcgagtaac gcgttagcgt
1621 gccggtggtg taagtctggg ctgtgcgtag cgaggcgcat agacgtaaca agccggacag
1681 ggagcgttcc agcggggaga agacagactc ggaaagcgtg ttgatgcgtt cgagctggcg
1741 cgccagctgc gtggaggtgc cgaagaagcc cgccaggtgc gtgccgtcga tgcggccgcc
1801 gtagccggcc agccccaagc cgtgcgggct ggtcgccgag tgggggggatt cgtcgagacg
1861 cagtaggtgc gtctccacgt agtcgtgtag aaagttgtcg agcgagaagt atttttgcat
1921 gacgtccagc agctcggtgg aaagccggcg gcccagaaaa cccggttcgc gcgtgcactg
1981 cgcttcgggc gccgcgtcag cgtcgtaagc caccacgcgc cggtactcga gcaaccgcgc
2041 gcgtgccagc gccgtgcggt aggccaggta gacgtagtgc acgcagaccg tgtcgggcag
2101 acgcgcacgt tcgcggaacg cgttgatctg cgtgtccacc tgctctagct cggtgtagtc
2161 gcggcggttg cgcgcgacgg cgtacgccac gaaagcggac acgcgctgac ggaagggcga
2221 gcccagtagc agacgcgcga actcgcccat ggaggcgtgc gtggggatga tggtgcccag
2281 gtcgcgcgtg cagaagctgc gcacgtactc ctccacggtg gagatggtgc tgtactggcc
2341 ctcgaatagg tagtaggcca tggtcagcag cacctggccc tcggtgtgcc cgaagacgct
2401 gatgaaccac gagggcgagg tggggcagag gaagacctgg ttgagatgac gtagcacggc
2461 cgcgtggtga aagtacacca ggtgcttgaa ttcgcgcacc tcgccgccgt gttcgggcga
2521 gagcacgggc gtgcggaaaa gatgccggta gagcggttgc gtctcggcct cgtccagact
2581 ggcgatgagc gccgagaggg ggatgggctg gcgcgcggcc aggtagcgcg agagctgcag
2641 cgtttcgttg ttcacggcga agacgggcgc cacccgccgc gagtccgagc acttttgcgt
2701 ctgtaggcag aagtaaacac gtcgcgagac ctggtgtttg accagcaggg ggaagacgca
2761 gtggtccgtc ggtgtctgcg agagtacgtt ggcgactata tgagcagaat catactctgt
2821 tgcgaacaga acgagcgtca t
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SEQ HCMV UL71
KEYWORD PROTEIN
SEQ ID NO: 21

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1   MQLAQRLCEL LMCRRKAAPV ADYVLLQPSE DVELRELQAF LDENFKQLEI TPADLRTFSR
61  DTDVVNHLLK LLPLYRQCQS KCAFLKGYLS EGCLPHTRPA AEVECKKSQR ILEALDILIL
121 KLVVGEFAMS EADSLEMLLD KFSTDQASLV EVQRVMGLVD MDCEKSAYML EAGAAATVAP
181 LTPPAVVQGE SGVREDGETV AAVSAFACPS VSDSLIPEET GVTRPMMSLA HINTVSCPTV
241 MRFDQRLLEE GDEEDEVTVM SPSPEPVQQQ PPVEPVQQQP QGRGSHRRRY KESAPQETLP
301 TNHEREILDL MRHSPDVPRE AVMSPTMVTI PPPQIPFVGS ARELRGVKKK KPTAAALLSS
361 A
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KEYWORD DNA (NC_001347 REGION: 104320..105405)
SEQ ID NO: 22

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1   atgcagctgg cccagcgcct gtgcgagctg ctgatgtgcc gtcgcaaagc cgcgcctgtg
61  gccgattacg tgctgctgca gcctagcgag gacgtggagc tgcgcgagct gcaggcgttt
121 ctggacgaga actttaagca gctggagatc accccggccg acctgcgaac cttttctcgc
181 gacacggacg tggtgaacca cctgctgaag ctgctgccgc tctataggca atgccagagc
241 aagtgcgcgt tcctcaaggg ctatctctcg gagggctgtt tgcctcacac gcggccggcg
301 gccgaggtgg agtgcaagaa atcgcagcgt atcctagagg ccctggacat tctcatcctc
361 aaactggtgg tgggcgagtt tgccatgtcc gaggccgaca gcctggagat gttgctggac
421 aagttctcca cggatcaggc ctcgctggtg gaggtgcagc gcgttatggg cctggtggac
481 atggactgcg agaaaagcgc gtacatgctc gaggccggcg cggctgcgac ggttgcgcca
541 ctgacgccac cggcggtcgt tcaggggaa agcggcgtcc gcgaggacgg ggaaacggtt
601 gccgccgtgt cggcctttgc ctgtccctcg gtttcggact cgctgatccc cgaggaaacg
661 ggggtcacgc gtcctatgat gagtttggct cacattaaca ccgtctcctg tcctaccgtt
721 atgaggttcg accagcggct gctggaagag ggcgacgagg aggatgaagt gaccgtgatg
781 tcgccgtcac ccgagcccgt gcaacagcag ccgccggtcg agcccgtgca gcagcagccc
841 cagggacgcg ggtctcaccg tcggcgctac aaggagtcgg cgccgcaaga gacgctgcct
901 acgaatcacg aacgcgagat tttggatctc atgcgacaca gccccgacgt gcctcgggag
961 gcggtgatgt caccgaccat ggtcaccata cctcctcccc agataccctt tgtgggttcc
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1021 gcgcgtgaac tcaggggcgt gaagaaaaag aaacccacgg cggcggcctt gctgtcctcc
1081 gcgtga

SEQ HCMV UL77
KEYWORD PROTEIN
SEQ ID NO: 23
1 MSLLHTFWRL PVAVFFEPHE ENVLRCPERV LRRLLEDAAV TMRGGGWRED VLMDRVRKRY
61 LRQELRDLGH RVQTYCEDLE GRVSEAEALL NQQCELDEGP SPRTLLQPPC RPRSSSPGTG
121 VAGASAVPHG LYSRHDAITG PAAAPSDVVA PSDAVAASAA AGASSTWLAQ CAERPLPGNV
181 PSYFGITQND PFIRFHTDFR GEVVNTMFEN ASTWTFSFGI WYYRLKRGLY TQPRWKRVYH
241 LAQMDNFSIS QELLLGVVNA LENVTVYPTY DCVLSDLEAA ACLLAAYGHA LWEGRDPPDS
301 VATVLGELPQ LLPRLADDVS REIAAWEGPV AAGNNYYAYR DSPDLRYYMP LSGGRHYHPG
361 TFDRHVLVRL FHKRGVIQHL PGYGTITEEL VQERLSGQVR DDVLSLWSRR LLVGKLGRDV
421 PVFVHEQQYL RSGLTCLAGL LLLWKVTNAD SVFAPRTGKF TLADLLGSDA VAGGGLPGGR
481 AGGEEEGYGG RHGRVRNFEF LVRYYIGPWY ARDPAVTLSQ LFPGLALLAV TESVRSGWDP
541 SRREDSAGGG DGGGAVLMQL SKSNPVADYM FAQSSKQYGD LRRLEVHDAL LFHYEHGLGR
601 LLSVTLPRHR VSTLGSSLFN VNDIYELLYF LVLGFLPSVA VL

KEYWORD DNA (NC_001347 REGION: 111838..113766)
SEQ ID NO: 24

1 atgagtctgt tgcacacctt ttggcggcta cccgtcgccg tcttcttcga accgcacgag
61 gaaaacgtgc tgcgctgccc cgagcgcgtg cttcggcggt tgctggagga cgcggcggtg
121 acaatgcgcg gcgggggctg gcgcgaggac gtgctcatgg accgggtgcg caaacggtat
181 ctgcgtcagg agctcaggga tctgggtcac agggtgcaga cttactgcga ggatctcgaa
241 gggcgcgtgt ccgaggcgga ggcgctgttg aaccagcagt gcgagctcga cgaaggaccg
301 tcgccgcgga cgctgctaca accaccgtgt cgtccgcgtt cttcgtcccc agggaccggc
361 gtggcaggag cttctgccgt cccacacggt ctttatagtc ggcacgatgc catcacggga
421 cccgccgccg ccccgtctga cgtggtcgcc ccgtctgacg cggtcgccgc gtcagcggcc
481 gccggtgctt cttctacctg gctggcgcag tgcgccgagc ggccgttgcc cgggaacgta
541 cctagctact ttggaatcac gcagaacgat ccctttatcc gctttcacac cgattttcgc
601 ggcgaggtgg tcaacaccat gttcgagaat gcctctactt ggactttctc ctttggtatc
661 tggtactatc ggctcaagcg ggggttgtac acgcaaccac ggtggaaacg agtgtaccat
721 ctggcgcaga tggacaactt ttccatttcg caggagctgc tgctcggcgt ggtcaacgct
781 ttggaaaacg tgacggtgta tccgacgtac gactgtgtac tctccgattt ggaagccgcc
841 gcctgtctgc tggccgccta cggacatgcg ctttgggagg gccgcgatcc gccggactcc
901 gtggcgacgg tgttgggtga gctccctcag ctgttgccgc gtctggccga cgacgtgagt
961 cgtgagattg ccgcttggga aggccccgtc gccgcgggta acaactatta cgcgtatcgc
1021 gactcgcccg atctacgcta ctacatgccc ctaagcggtg gtcgtcacta tcacccgggc
1081 acttttgatc gtcacgtgct ggtgcggctt ttccacaaac gcggcgttat tcagcatttg
1141 ccgggctacg ggacgataac ggaggagctg gtgcaagagc gtctgtcggg ccaggtgcgc
1201 gacgacgtgc tttctctctg gagtcgacgt ctgctggtcg gcaagctggg tcgcgacgtg
1261 cccgtctttg tgcacgaaca gcaatatctg cgttcgggcc tgacctgcct ggctggcctg
1321 ctgttgttgt ggaaggtgac caacgcggat agcgtcttcg ctccgcgcac gggcaaattt
1381 acgttggccg acctgctggg ttcggatgcc gtagccggcg gcgggttgcc cgggggcgc
1441 gcgggcggcg aagaggaggg ctacgggggа cggcacgggc gggtacgtaa ctttgagttt
1501 ctggtacggt actacatcgg gccgtggtac gcgcgcgacc ccgcggtcac gctgtcgcag
1561 ctctttcccg gcctggctct gttggccgtg accgagagcg tgcgcagcgg ctgggatccc
1621 tcacgtcgcg aggacagcgc cggaggtggc gacggcggcg gcgccgtgct catgcagctc
1681 agcaagagca accccgtggc cgactacatg ttcgcgcaga gctccaaaca gtacggcgat
1741 ttacgtcgct tagaggtaca cgatgccctg ctctttcact acgaacacgg gctagggcgg
1801 ctgttgtcag tgaccctgcc gcgtcaccgt gtgtccactc tgggctcgtc cctctttaac
1861 gtcaacgata tttacgaact gttgtacttt ttagtgttgg ggtttcttcc gagcgtggcg
1921 gtgttgtaa

SEQ HCMV UL79
KEYWORD PROTEIN
SEQ ID NO: 25
1 MMARDEENPA VPRVRTGKFS FTCANHLILQ ISEKMSRGQP LSSLRLEELK IVRLICVLLF
61 HRGLETLLLR ETMNNLGVSD HAVLSRKTPQ PYWPHLYREL RQAFPGLDFE AAVFDETRAA
121 RLSQRLCHPR LSGGLLTRFV QRHTGLPVVF PEDLARNGNI LFSLGTLYGH RLFRLAAFFT
181 RHWGAEAYEP LIRIICQKMW YFYLIGTGKM RITPDAFEIQ RSRHETGIFT FIMEDYRTFA

241 GTLSRHPHRP HPQQQQHHHP GPPHPPLSHP ASSCLSPEAV LAARALHMPT LANDV

KEYWORD DNA (NC_001347 REGION: 115205..116092)
SEQ ID NO: 26

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   1 tcacacgtcg ttagccagcg tcggcatatg aagggcgcgg gcggccagta cggcctctgg
  61 gctgagacag gacgaggcag ggtgagaaag aggaggatgg gggggaccgg ggtggtggtg
 121 ctgctgctgt tgtgggtgcg gacggtgcgg gtgccgggac agcgtgccgg cgaacgttct
 181 gtaatcttcc ataataaaag taaaaatgcc cgtctcgtgt cgactccgct ggatctcgaa
 241 ggcgtcgggg gtaatgcgca tcttgccggt gccgatgaga taaaagtacc acatttttg
 301 acagatgatg cgaatcaagg gttcgtacgc ttcggcaccc cagtggcgcg tgaagaaggc
 361 cgccagacga aacaagcggt gtccgtagag cgtgcctagg gagaagagga tgttgccgtt
 421 gcgcgccagg tcttcgggga aaacgaccgg caggccggtg tggcgctgca caaagcgcgt
 481 cagcagtccg ccgctcaagc gcgggtgaca caggcgctgg ctgagacggg cggcgcgcgt
 541 ttcatcgaac acggccgcct caaagtccag ccccgggaag gcctggcgca gttcgcggta
 601 cagatgaggc cagtagggtt gcggcgtctt gcgactaagc acggcgtggt ccgagacacc
 661 caggttgttc atggtttcgc gcagtagcag cgtttcgaga ccgcggtgaa agaggaggac
 721 gcagatgagg cgtacgatct tgagttcttc caaacgcagc gagctcagcg gctgtccgcg
 781 cgacatcttc tcgctaatct gtaatattag atgattggcg caagtaaagg agaatttgcc
 841 cgtgcggacc cgcgggacgg cggggttctc ttcgtcgcgg gccatcat
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SEQ HCMV UL87
KEYWORD PROTEIN
SEQ ID NO: 27

```
1   MAGAAPRRLG CDALIVVGGS AMPRRVLHVP VHVRACNLTQ ELSTGEDARF CRPRPVNVER
61  VRAVFAALYR ACPIHVRTEP ERVKLVLGRL LLGPVAVPCF CDGEVEGHGE HLVPTTQFCR
121 GPLLYVHRRC CCGSVTAGRA LSYHVLENHV ATHVLRGLLS LTEWNRELPS LFCDCPGGGG
181 ASGTEERYAM ACLPRDLSLH LDDYPYLMVE IGRVLSVSEV DDYVTAVSGY LGEAAAPRIQ
241 VHYKLLFGLN VRPQAPCALD ATRDFFLLEL QKLWLGVEYH HEVTSEFFGR VLAQLHRDRA
301 RVMMALRLPE QTVCHLSTFV LSRFKRQVLY FKLQVSYGKC RTGHADRSGG GGNGGNQGHH
361 NLLCYRRLSV TFADTDTVWR NLFYVYYELA RDLGSHGTED RPVSRGYGVS CASRTSRLSP
421 SESTVVSANG HALSSTALPT TSAGHKLSLP RDPAADRVRR YVCIISRLMY ARYGERWRKH
481 CQRRSETGEE EEEETLESGE TDATPPFDFT GQQLRRAYQE HRRRKHLAVQ RYAPCRRKLI
541 GGMEFAEVTG VSLDRIAVNA FNTNRVINMK AALSSIAASG LGVRAPRLPK NMTHSFVMYK
601 HTFKEPACTV STFVSNDAVY INSLNVNIRG SYPEFLYSLG VYRLHVNIDH FFLPAVVCNS
661 NSSLDVHGLE DQAVIRSERS KVYWTTNFPC MISHTNNVNV GWFKAATAIV PRVSGADLEA
721 ILLKELSCIK NMRDVCIDYG LHRVFTQLEL RNSYQIPFLA KQLVLFLRAC LLKLHGREKR
781 LQLDRLVFEA AQRGLFDYSK NLTAHTKIKH TCALIGSRLA NNVPKILARN KKVKLDHLGR
841 NANVLTVCRH VEAHKIPRTR LKVLVEVLGA LQSISGTPHT REVIHQTLFR LCSAAAATSG
901 LCSSPPPLCV SSSSSVPSVP TSVSVDGSSE PTSPRARFAS R
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KEYWORD DNA (NC_001347 REGION: 129286..132111)
SEQ ID NO: 28

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   1 atggccggcg ctgcgccgcg ccgcctcggc tgtgacgctc taatagtcgt tggcggctcc
  61 gctatgccgc gccgggtttt acacgtcccc gtgcacgttc gcgcctgcaa cctcacccaa
 121 gagctatcga cgggcgagga cgcccgcttt tgtcgtccgc gacccgttaa cgtcgaacgg
 181 gtgcgcgctg tttttgcggc tctctaccgt gcctgtccga tacacgtgag gaccgagccc
 241 gagcgtgtca agctggtact gggtcgtctg ttactgggac ccgtggccgt accctgtttt
 301 tgcgacggtg aagtggaggg ccacggtgaa catctggtac ctacgacgca gttttgtcgc
 361 gggccgctgc tctacgtgca ccgacgttgt tgttgcggat ccgtgaccgc cgggcgcgcg
 421 ctgtcctacc acgttctcga aaaccacgtg gccacgcatg tgctacgcgg attgctctcg
 481 ctgacggaat ggaatcgaga attgccgagc ctcttttgcg actgtcctgg cggcggtggc
 541 gcctcgggaa ccgaggaacg ctacgctatg gcctgcctgc cgcgcgacct cagcctgcac
 601 ctggacgact atccttacct gatggtggaa atcggacgcg tactcagtgt cagcgaggta
 661 gacgactacg taaccgccgt ctccggctac ctgggcgagg ccgcggcgcc gcgcatccag
 721 gttcactaca agctgctctt tggactcaac gtgcgtccgc aagcgccgtg cgcgttggac
 781 gctacacgcg acttttttct gctggagctg caaaagcttt ggctgggcgt tgaatatcac
 841 cacgaagtca cgtcggagtt tttcggtcgc gtactggctc agctgcatcg cgaccgcgcc
 901 cgcgtcatga tggcgcttcg cttgcccgag cagacggtgt gccacctgag caccttcgtt
 961 ctcagtcgct tcaagcgaca ggtactgtac ttcaagctac aggtgagcta cggcaagtgc
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1081 aacctactgt gttatcgacg ccttagcgtc acatttgccg acacagacac ggtgtggaga
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1201 cgacccgtaa gccgcggtta cggtgtttct tgcgcttcga ggacgtcgcg actgtcaccg
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1321 acgagcgcgg gtcacaagct gtcactgccg cgcgacccgg ccgcagatcg cgttcgacgt
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1441 tgtcaacggc ggtcggagac gggagaagag gaggaggaag agacgctgga atcgggggag
1501 actgacgcca cgccgccatt tgactttacg gggcagcagc tgcgccgggc ctatcaggaa
1561 caccgacgtc gtaaacatct agccgtgcag cgttacgcgc cgtgccgtcg taagctcatc
1621 ggcgggatgg agtttgccga ggtgacgggc gtgagtctag accgcatcgc cgtcaacgct
1681 ttcaacacca accgcgttat caatatgaag gctgcgctct cgtccatcgc cgcgtcgggt
1741 ctcggcgtac gcgcgccgcg gcttcccaag aacatgaccc acagttttgt gatgtacaag
1801 cacaccttta aggagcccgc ttgcaccgtc agcacttttg tttccaacga cgccgtctac
1861 atcaactcgc tcaacgtcaa tattcgcggt tcctaccccg agtttctgta ctcgctgggc
1921 gtgtaccggc tgcacgttaa tatcgatcac ttttttctgc cggccgtggt gtgcaacagc
1981 aactcctcgc tggacgtgca tgggctggag gaccaggcgg tgattcgctc ggagcgcagc
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2101 ggctggttca aagcggctac ggccattgtg ccgcgcgtct cgggcgccga cctggaagcc
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2221 ctgcaccgtg ttttcacgca actagagctg cgcaattcgt accagatccc cttcctggcc
2281 aagcagttag tgctgtttct gcgtgcttgc ctgctcaagc tgcacggtcg agagaagcgg
2341 ctgcagttgg accgcctagt atttgaggcg gcacagcggg gtctctttga ctacagcaag
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2461 aacaacgtgc ccaagatcct ggcccggaac aaaaaagtca aattggatca cctgggccgg
2521 aacgccaacg tgctgacggt gtgtcggcac gtggaagccc acaagatccc tcgcacgcgc
2581 ctcaaagtgt tagtcgaggt gctgggcgcg ttgcagagta tcagcggtac gccgcacacg
2641 cgcgaagtga tccaccagac gttgtttcga ttgtgctcgg cggccgcagc cacatcgggc
2701 ctgtgttcat cccctccccc attgtgtgtg tcctcatctt cctccgtccc ttctgtccca
2761 acctccgtca gcgttgacgg cagttctgaa cccacgtcgc cgcgagcgcg gtttgcatca
2821 cgatga
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SEQ HCMV UL89
KEYWORD . PROTEIN
SEQ ID NO: 29

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1    MLRGDSAAKI QERYAELQKR KSHPTSCIST AFTNVATLCR KRYQMMHPEL GLAHSCNEAF
61   LPLMAFCGRH RDYNSPEESQ RELLFHERLK SALDKLTFRP CSEEQRASYQ KLDALTELYR
121  DPQFQQINNF MTDFKKWLDG GFSTAVEGDA KAIRLEPFQK NLLIHVIFFI AVTKIPVLAN
181  RVLQYLIHAF QIDFLSQTSI DIFKQKATVF LVPRRHGKTW FIIPIISFLL KHMIGISIGY
241  VAHQKHVSQF VLKEVEFRCR HTFARDYVVE NKDNVISIDH RGAKSTALFA SCYNTNSIRG
301  QNFHLLLVDE AHFIKKEAFN TILGFLAQNT TKIIFISSTN TTSDSTCFLT RLNNAPFDML
361  NVVSYVCEEH LHSFTEKGDA TACPCYRLHK PTFISLNSQV RKTANMFMPG AFMDEIIGGT
421  NKISQNTVLI TDQSREEFDI LRYSTLNTNA YDYFGKTLYV YLDPAFTTNR KASGTGVAAV
481  GAYRHQFLIY GLEHFFLRDL SESSEVAIAE CAAHMIISVL SLHPYLDELR IAVEGNTNQA
541  AAVRIACLIR QSVQSSTLIR VLFYHTPDQN HIEQPFYLMG RDKALAVEQF ISRFNSGYIK
601  ASQELVSYTI KLSHDPIEYL LEQIQNLHRV TLAEGTTARY SAKRQNRISD DLIIAVIMAT
661  YLCDDIHAIR FRVS
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KEYWORD DNA (NC_001347 REGION: 133394..139320)
SEQ ID NO: 30

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1    ctagctgacc ctgaaacgga tggcgtgtat atcgtcacac aggtaggtgg ccatgatgac
61   ggcgatgata agatcgtccg agatacgatt ctggcgcttg gccgagtaac gcgccgtcgt
121  gccttcggcc agcgtgacgc ggtgcaggtt ctgaatctgc tccagaagat actcgatggg
181  gtcgtggctc agcttgatgg tgtaggagac gagctcttgc gaggctttga tgtagcccga
241  gttgaaacgc gagatgaact gttccacggc cagcgccttg tcgcggccca tgaggtagaa
301  gggctgttcg atgtggttct ggtcgggcgt gtggtagaag agcacgcgga tgagcgtgct
361  gctctgcacg ctctgtcgga tgaggcaggc gatgcgcacg gccgccgcct ggttggtgtt
421  gccctccacg gcgatgcgca gttcgtccag gtaagggtgc aggctcagca ccgagatgat
481  catgtgcgcc gcgcactcgg cgatggctac ctcagaactc tcggagaggt cgcgcaaaaa
541  gaaatgctct aggccgtaaa tgagaaactg gtgtcggtag gcgcctacgg ccgccacgcc
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 601 cgtgcccgag gccttgcggt tggtggtgaa ggccgggtcc agatacacgt aaagcgtctt
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 721 gcggctctgg tccgtgatga gcacggtgtt ctgcgagatt ttattggtac cgccgatgat
 781 ctcgtccatg aaagcgcccg gcataaacat gttggccgtc ttgcgcactt gcgagttgag
 841 gctgatgaag gtgggcttgt gcagtcggta gcaaggacac gccgtggcgt cgcccttctc
 901 cgtgaagctg tgcaggtgct cttcgcacac gtaagagacc acgttgagca tgtcaaaggg
 961 cgcattgtta aggcgcgtca agaaacacgt ggagtcactg gtagtgttgg tggacgatat
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1741 cagttacact cgctctacgc gtgcacgcgc tgctttcgca cgcacctgtg tgatctgggc
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1981 cacgccggcc gttacgccga cgtgatccag gaggtggtcg agcgcgaccg cctcaaaaag
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2101 aaccgtattt cggtgcccgt catcagccaa ctttttattc agcttatcat cggtatctac
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4201 tgagcttcgg aggtcctttg ggtccagcca gcatcgattt cttgccaagc tttagccagg
4261 tgaccagcag tatgacgtgc gatggtatta cgcccgacgt gatttacgag gtctgcatgt
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4321 tggtgcccca ggatgaagcc aagcgtatcc tggtcaaggg tcacggtgcc atggacctga
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4561 gcagcttttg cacggatcac gagggacacg tagatcccac tggcaattac gtgggttgca
4621 cccccgatat gggccgctgt ctttgttacg tgccctgtgg gcccatgacg cagtcgctca
4681 tccacaacga ggaacccgcg actttttttct gtgagagcga tgacgccaag tacctatgcg
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5341 gagaggaagt cgatctggaa ggcgtggatg aggtactgca gcacgcgatt ggccagcacg
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5461 tcgagtcgga tggcttttgc gtcgccctcg acggcggtac tgaagccgcc gtcgagccac
5521 tttttaaagt cggtcatgaa gttgttgatc tgctgaaact gcggatcgcg gtagagctcg
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5821 gccacattgg tgaaggccgt ggagatgcag gaggtggggt ggctcttgcg cttctgcagc
5881 tccgcgtagc gctcctggat cttggcggcc gagtctccgc gcaacat
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SEQ HCMV UL92
KEYWORD PROTEIN
SEQ ID NO: 31

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1   MCDASGACDM RHVQNAFTEE IQLHSLYACT RCFRTHLCDL GSGCALVSTL EGSVCVKTGL
61  VYEALYPVAR SHLLEPIEEA ALDDVNIISA VLSGVYSYLM THAGRYADVI QEVVERDRLK
121 KQVEDSIYFT FNKVFRSMHN VNRISVPVIS QLFIQLIIGI YSKQTKYDAC VIKVSRKKRE
181 DALLKQMRSE YGNAPVFGSG V
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KEYWORD DNA (NC_001347 REGION: 135071..135676)
SEQ ID NO: 32

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1 atgtgcgacg cctcgggcgc ctgtgacatg aggcacgtcc agaacgcgtt taccgaggag
61 atccagttac actcgctcta cgcgtgcacg cgctgctttc gcacgcacct gtgtgatctg
121 ggcagcggct gcgcgctcgt ctccacgctc gagggctccg tctgcgtcaa gacgggcctg
181 gtatacgagg ctctctatcc ggtggcgcgt agccacctgt tggaacccat cgaggaggcc
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301 acgcacgccg gccgttacgc cgacgtgatc caggaggtgg tcgagcgcga ccgcctcaaa
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421 gtcaaccgta tttcggtgcc cgtcatcagc caacttttta ttcagcttat catcggtatc
481 tactcaaagc agaccaagta cgacgcgtgt gtcatcaagg ttagtcgtaa gaagcgcgag
541 gacgcgcttc tgaaacagat gcgttccgaa tatggaaacg cacctgtatt cggatctggc
601 gtttga
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SEQ HCMV UL95
KEYWORD PROTEIN
SEQ ID NO: 33

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1   MMAAAVVRAE VRRQRREERK KMAAARTTED PPENHVVADV ARGTGAVTRS SSSSLVVSSS
61  SASGSDESSS ASPLSFPVSS PSTAVRSPGS AGVSTSLCSV ERMVELSAQS PAADFSVSEA
121 WRFEEAVNMA LVACEAVSPY DRFRLIETPD ENFLLVTNVI PRESAEVPVL DSSSSGGDSG
181 PEDKKKNVGN KTAGEKNGGG SRAKRRRRRR APKNDAATPS FLRRHDVLER FAAAAKPLPS
241 LCVRDYALRN ADRVTYDGEL IYGSYLLYRK AHVELSLSSN KVQHVEAVLR QVYTPGLLDH
301 HNVCDVEALL WLLYCGPRSF CARDTCFGRE KNGCPFPALL PKLFYEPVRD YMTYMNLAEL
361 YVFVWYRGYE FPAPTPQATT AGGGGGSGGG GGAGACAVET SASAGRVDDA GDEVHLPLKP
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421 VSLDRLREVL QAVRGRFSGR EVPAWPASSR TCLLCALYSQ NRLCLDLARD EARTVSYSPI
481 VIQDCAAAVT DVTLSHILPG QSTVSLFPVY HVGKLLDALS LNDAGLITLN L

KEYWORD DNA(NC_001347 REGION: 139319..140914)
SEQ ID NO: 34

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121 gctcgtggga cgggcgccgt cactcgttcg tcttcgtcgt ccctagtggt gtcgtcttcc
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961 tgcgcgcgtg acacttgttt cggtcgcgaa aagaacggtt gtcctttccc cgcgttgttg
1021 cccaaactct tttacgaacc cgtgcgggac tatatgacct acatgaatct ggctgagctg
1081 tacgtctttg tttggtatcg cggctacgaa ttccctgcgc cgacgccgca ggcgacgacg
1141 gcgggtggtg gtggtggtag tggtggcggc ggcggggccg gcgcttgtgc ggtcgagacg
1201 agcgcgtcag caggccgggt cgatgacgcc ggcgacgagg tgcatttgcc tttaaagccc
1261 gtctcgctgg accgtctcag agaggtgttg caggcggtgc gcggccgctt ctcggggcgc
1321 gaggtgcccg cctggccggc ctcgtcgcgc acctgtttgt tgtgcgcgct ctacagtcag
1381 aaccgtctct gtttagatct cgcgcgtgac gaggcgcgga ccgtgagtta tagccccatc
1441 gttatccaag actgcgccgc ggctgtcacc gacgtcactt tgagccacat cttgcccggc
1501 cagagcaccg tctcgctttt ccccgtctac cacgtcggca agttgctgga cgctctctcg
1561 ctgaacgacg cgggtctcat cacgttgaat ctatga

SEQ HCMV UL98
KEYWORD PROTEIN
SEQ ID NO: 35
1 MWGVSSLDYD DDEELTRLLA VWDDEPLSLF LMNTFLLHQE GFRNLPFTVL RLSYAYRIFA
61 KMLRAHGTPV AEDFMTRVAA LARDEGLRDI LGQRHAAEAS RAEIAEALER VAERCDDRHG
121 GSDDYVWLSR LLDLAPNYRQ VELFQLLEKE SRGQSRNSVW HLLRMDTVSA TKFYEAFVSG
181 CLPGAAAADG SGGGGSHYTG SRAGVSPGIQ FGIKHEGLVK TLVECYVMHG REPVRDGLGL
241 LIDPTSGLLG ASMDLCFGVL KQGSGRTLLV EPCARVYEIK CRYKYLRKKE DPFVQNVLRR
301 HDAAAVASLL QSHPVPGVEF RGERETPSAR EFLLSHDAAL FRATLKRARP LKPPEPLREY
361 LADLLYLNKA ECSEVIVFDA KHLSDDNSDG DATITINASL GLAAGDGAGG GADHHLRGSP
421 GDSPPPIPFE DENTPELLGR LNVYEVARFS LPAFVNPRHQ YYFQMLIQQY VLSQYYIKKH
481 PDPERIDFRD LPTVYLVSAI FREREESELG CELLAGGRVF HCDHIPLLLI VTPVVFDPQF
541 TRHAVSTVLD RWSRDLSRKT NLPIWVPNSA NEYVVSSVPR PVSP

KEYWORD: DNA (NC_001347 REGION: 143632..145386)
SEQ ID NO: 36

1 atgtggggcg tctcgagttt ggactacgac gacgatgagg agctcacccg gctgctggcg
61 gtttgggacg atgagcccct cagtctgttt ctcatgaaca ccttttgct gcaccaggag
121 ggcttccgta atctgccctt tacggtgctg cgtctgtctt acgcctaccg catcttcgcc
181 aagatgctgc gggcccacgg tacgccagta gccgaggact ttatgacgcg cgtggccgcg
241 ctggctcgcg acgagggtct gcgcgacatt ttgggtcagc ggcacgccgc cgaagcttcg
301 cgcgccgaga tcgccgaggc cctggagcgc gtggccgagc ggtgcgacga ccggcacggc
361 ggctcggacg actacgtgtg gctcagccgg ttgctggatt tagcgcccaa ctatcggcag

```
 421 gtcgagctct tccagttgct ggaaaaggaa tcgcgcggac agtcgcgcaa ctcggtgtgg
 481 catctgttgc gtatggacac ggtctcggcc accaagttct acgaggcctt cgtcagcggc
 541 tgtctgccgg gcgccgcggc ggcggacggt tcgggtggcg gcggctcgca ctacacgggt
 601 tcgcgcgccg gcgtctcgcc gggcatccag ttcggtatca aacacgaggg cttagtcaaa
 661 acgctggtgg aatgttacgt gatgcacgga cgcgagccgg tgcgcgacgg cctcggtctg
 721 ctcatcgacc ccacgtcggg gctgctgggc gcttccatgg acctgtgctt cggcgtgctc
 781 aagcagggta gcggtcgcac cttgctggtg gaaccgtgtg cgcgcgtcta cgagatcaag
 841 tgccgctaca aatatttgcg caaaaaggag gacccctttg tgcagaacgt gctgcggagg
 901 cacgacgcgg cggccgtggc ctcgctgttg cagtcacacc cggtgccggg cgtggagttt
 961 cgcggtgaac gcgagacccc gtcggcacgc gagtttctgc tttcgcacga cgcggcgctc
1021 ttcagggcca cgctcaagcg cgcgcgcccg ctcaagccgc ccgaaccgct gcgcgagtac
1081 ctggccgatc tgctgtatct caataaggcc gagtgttcgg aagtgatcgt gtttgacgcc
1141 aagcacctga gtgacgacaa cagcgacggg gacgccacga tcactattaa cgcgagtctc
1201 ggcctagccg cgggcgacgg cgctggcggc ggcgctgatc accacctgcg gggcagcccg
1261 ggcgattcgc cgccgccgat acctttcgag gacgaaaaca cgcccgagct gctgggccgg
1321 ctcaacgtgt acgaggtagc gcgcttttca ctgccggctt ttgtcaatcc gcgtcaccag
1381 tattactttc agatgctcat tcagcagtac gtgctcagcc aatactatat aaagaagcat
1441 ccggacccgg agcggatcga tttccgcgac ctgcctaccg tctacctggt ctcggccatc
1501 ttccgcgagc gcgaggaaag cgaactgggc tgcgagttgc tggccggcgg tcgcgttttc
1561 cactgcgacc acatcccgct cctgctcatc gtcacgcccg tggtctttga ccctcagttt
1621 acgcgccatg ccgtctctac cgtgctagac cgttggagtc gcgacctgtc ccgcaagacg
1681 aacctaccga tatgggtgcc gaactctgca aacgaatatg ttgtgagttc ggtaccacgc
1741 ccggtgagcc cctga
```

```
SEQ          HCMV UL100
KEYWORD      PROTEIN
SEQ ID NO:   37
1         MAPSHVDKVN TRTWSASIVF MVLTFVNVSV HLVLSNFPHL GYPCVYYHVV DFERLNMSAY
61        NVMHLHTPML FLDSVQLVCY AVFMQLVFLA VTIYYLVCWI KISMRKDKGM SLNQSTRDIS
121       YMGDSLTAFL FILSMDTFQL FTLTMSFRLP SMIAFMAAVH FFCLTIFNVS MVTQYRSYKR
181       SLFFFSRLHP KLKGTVQFRT LIVNLVEVAL GFNTTVVAMA LCYGFGNNFF VRTGHMVLAV
241       FVVYAIISII YFLLIEAVFF QYVKVQFGYH LGAFFGLCGL IYPIVQYDTF LSNEYRTGIS
301       WSFGMLFFIW AMFTTCRAVR YFRGRGSGSV KYQALATASG EEVAVLSHHD SLESRRLREE
361       EDDDDDEDFE DA

KEYWORD      DNA (NC_001347 REGION: 146157..147275)
SEQ ID NO:   38
```

```
   1 ttaagcgtcc tcgaagtctt catcatcgtc gtcgtcctct tcttcgcgga ggcgacggct
  61 ttccaagctg tcgtggtgac tgagcacagc gacttcttcg ccggaggctg tggccagcgc
 121 ctggtacttg acactgccgc taccgcgtcc gcgaaagtag cggacggcgc gacacgtcgt
 181 aaacatggcc catatgaaaa agagcatgcc gaacgaccag ctgatgccgg tgcggtattc
 241 gttgctgagg aaggtatcgt actgcacgat ggggtagatg aggccgcaga gtccaaagaa
 301 ggcgcccagg tggtagccga attgcacctt gacgtattga aaaaagacgg cctcgatcag
 361 taaaaagtag atgatggaga tgatagcgta gaccacgaag acggctaaca ccatgtggcc
 421 tgtacgcacg aaaaagttgt ttccgaagcc gtagcacagg gccatggcta ccacggtggt
 481 gttgaaacca agcgctacct ctaccaggtt gacgatgagc gtgcggaact gcaccgtacc
 541 tttgagcttg gggtgcagac gcgagaagaa aaagagtgag cgtttgtagc tgcggtactg
 601 cgtgaccatg ctcacgttga aaatggtcag gcagaaaaag tgcacggcgg ccatgaaggc
 661 gatcatgctg ggcagccgaa atgacatggt cagtgtgaat agttggaacg tgtccatgct
 721 gagaatgaag aggaaggctg tgaggctgtc gcccatgtac gaaatgtcgc gtgtcgactg
 781 gtttaggctc atgcctttgt ccttgcgcat gctgatcttg atccagcata ccaggtagta
 841 gatggtcacg gctaaaaaga cgagctgcat gaacacggcg tagcacacca actgcaccga
 901 gtctaagaaa agcataggcg tgtgcaggtg cattacgttg taggccgaca tgttgagcct
 961 ttcaaagtcc acgacgtgat agtagacgca ggggtagccc aggtgcggaa aattgctcag
1021 cactagatgc acgctgacgt tgacaaaagt cagcaccatg aaaacgatag aagcgctcca
1081 tgtccgtgta ttcaccttat ccacgtgcga gggggccat
```

```
SEQ          HCMV UL102
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KEYWORD PROTEIN

SEQ ID NO: 39

```
1    MTAQPPLHHR HHPYTLFGTS CHLSWYGLLE ASVPIVQCLF LDLGGGRAEP RLHTFVVRGD
61   RLPPAEVRAV HRASYAALAS AVTTDADERR RGLEQRSAVL ARVLLEGSAL IRVLARTFTP
121  VQIQTDASGV EILEAAPALG VETAALSNAL SLFHVAKLVV IGSYPEVHEP RVVTHTAERV
181  SEEYGTHAHK KLRRGYYAYD LAMSFRVGTH KYVLERDDEA VLARLFEVRE VCFLRTCLRL
241  VTPVGFVAVA VTDEQCCLLL QSAWTHLYDV LFRGFAGQPP LRDYLGPDLF ETGAARSFFF
301  PGFPPVPVYA VHGLHTLMRE TALDAAAEVL SWCGLPDIVG SAGKLEVEPC ALSLGVPEDE
361  WQVFGTEAGG GAVRLNATAF RERPAGGDRR WLLPPLPRDD GDGENNVVEV SSSTGGAHPP
421  SDDATFTVHV RDATLHRVLI VDLVERVLAK CVRARDFNPY VRYSHRLHTY AVCEKFIENL
481  RFRSRRAFWQ IQSLLGYISE HVTSACASAG LLWVLSRGHR EFYVYDGYSG HGPVSAEVCV
541  RTVVDCYWRK LFGGDDPGPT CRVQESAPGV LLVWGDERLV GPFNFFYGNG GAGGSPLHGV
601  VGGFAAGHCG GACCAGCVVT HRHSSGGGGS GVGDADHASG GGLDAAAGSG HNGGSDRVSP
661  STPPAALGGC CCAAGGDWLS AVGHVLGRLP ALLRERVSVS ELEAVYREIL FRFVARRNDV
721  DFWLLRFQPG ENEVRPHAGV IDCAPFHGVW AEQGQIIVQS RDTALAADIG YGVYVDKAFA
781  MLTACVEVWA RELLSSSTAS TTACSSSSVL SSALPSVTSS SSGTATVSPP SCSSSSATWL
841  EERDEWVRSL AVDAQHAAKR VASEGLRFFR LNA
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KEYWORD DNA (NC_001347 REGION: 147453..150074)

SEQ ID NO: 40

```
   1 atgaccgctc agccgccgct gcaccaccgc caccacccgt acaccctgtt cgggaccagc
  61 tgtcatctca gctggtacgg ccttctagag gcctcggtgc ctatcgtaca atgtctgttt
 121 ttggatctgg gtggcggccg tgccgagccg cggcttcaca cgttcgtggt gcgcggtgac
 181 cgtctaccgc cggctgaggt gcgtgctgtg catcgcgcca gctacgctgc gctggcctcg
 241 gccgtgacta cggacgccga tgagcgtcgg cgcggcctag agcagcgtag cgccgtgttg
 301 gcgcgcgtgt tgctagaagg cagcgcgtta atccgcgtgt tggcgcgcac cttcacgccg
 361 gtgcagattc agacggacgc tagtggcgtg gagattttgg aggccgcacc ggcactgggc
 421 gtggaaaccg cagcgctgtc gaacgcgctt agtcttttcc acgtagccaa gctagtggtc
 481 atcggctcgt atcccgaagt gcacgagccg cgtgtggtca cgcataccgc ggaacgcgtc
 541 tccgaagagt atggcaccca cgcgcacaaa aaattgcgtc gcggttacta cgcctacgat
 601 ttggccatgt cgtttcgcgt cggcactcac aagtatgtgc tggagcgcga cgacgaggcc
 661 gtcctggcac gcctctttga ggtgcgcgag gtgtgttttt tgcgcacctg tctgcgtctg
 721 gtcacgcctg tcggtttcgt ggccgtggca gtgaccgacg agcagtgttg tttattgctg
 781 cagtcggcct ggactcacct ttacgacgtg cttttccgtg gtttcgctgg gcagccgccg
 841 ctacgcgact acctggggcc ggacctcttt gagacgggcg ccgcccgttc tttctttttt
 901 cccggtttcc cgcccgtgcc cgtctacgcg gtccacggtc tgcacacgtt aatgcgcgag
 961 acggcgttgg acgcggcggc tgaggtgctc tcgtggtgcg gcctgcccga catcgtgggc
1021 tcggccggca agctggaggt ggaaccctgc gcgctctcgc tcggcgtgcc cgaggatgag
1081 tggcaggtct tcggtaccga ggccggcggc ggcgccgtgc gtctcaatgc cacggctttt
1141 cgcgagcgac cggccggcgg cgatcgtcgc tggctgttgc cgccgctgcc acgtgacgac
1201 ggcgacggtg aaaacaacgt cgtggaagtc agcagcagca ccggcggtgc gcacccgccg
1261 agcgacgacg ccactttcac cgtgcacgtt cgcgacgcca cgctacatcg agtgctcatc
1321 gtggatttgg tcgagcgcgt gctggccaag tgtgtacgcg cgcgcgactt caatccctac
1381 gtgcgttata gtcatcgact ccacacttat gcggtttgtg aaaagtttat tgagaatctg
1441 cgttttcgct cgcgacgcgc tttctggcag atccagagtc tgctgggcta catctccgag
1501 cacgttacgt cagcctgcgc ttcggccggc cttttgtggg ttctgtcgcg cggccaccgc
1561 gagttttatg tctacgacgg ctattcgggt cacggacccg tctcggccga agtgtgcgtg
1621 cggactgtgg tcgactgtta ttggcgcaaa ctttttggcg gcgacgatcc gggtcccacc
1681 tgtcgtgttc aagagagcgc gcccggcgtg ctgttggtct ggggcgacga gcggttggtg
1741 ggtcccttca acttcttcta cggcaacggc ggcgccggtg gtagtccgct ccacggggtg
1801 gtgggtggtt tcgcggcggg acattgcggt ggcgcttgtt gcgcgggctg cgtcgtcact
1861 caccgccatt ctagcggcgg cggtggtagt ggcgtgggcg acgcggacca cgcgagtggc
1921 ggcggtctag atgccgctgc cgggagtggt cataacggcg gtagtgatcg ggtttctccc
1981 tccacgccgc ccgcggcgtt aggtggctgt tgctgcgcag ccggtggcga ctggctctcg
2041 gccgtgggtc atgtcctggg ccggctgccg gcgctgttac gggagcgcgt gagcgtgtcc
2101 gagctggaag ccgtgtaccg cgagatcctc tttcgtttcg tggctcgccg caacgacgtg
2161 gacttttggt tactgcgctt ccagcccggt gaaaacgaag taaggccgca cgctggggtg
2221 attgactgcg cgcccttcca cggcgtgtgg gccgagcagg gccagatcat cgtacagtca
2281 cgcgatacgg cgttggcggc cgatatcggc tacggcgtct atgtggacaa ggcctttgcc
2341 atgctcacgg cttgcgtgga ggtctgggcg cgagagttat tgtcgtcctc caccgcttcc
```

```
2401 accaccgctt gttcttcttc ttccgttctc tcctccgcct tgccgtccgt cacttcgtcc
2461 tcttcgggca cggcgacggt gtctcctccg tcttgttctt cttcgtcggc gacttggctc
2521 gaggagcgcg acgagtgggt gcgctcgctg gcggttgacg cgcaacacgc tgctaagcgg
2581 gtggcttccg agggcctgcg gtttttccgg ctcaacgctt aa
```

SEQ HCMV UL104
KEYWORD PROTEIN
SEQ ID NO: 41

```
1   MERNHWNEKS SGAKRSRERD LTLSTIRSIL AADERLRIKA SSYLGVGRGV DDEAVIDIFP
61  TGQTMSFLRL LHGFLGTCRG QSMHQVLRDP CVLRKQLLYG VCKTLFDTIT VRRVAEEWKL
121 HAALFPYRAL DEEDLEQYLL VWSASLRQSV QTGVLGGLRD ILYQYADNDD YGLYVDWCVT
181 VGLVPLLDVK TKPSEAAERA QFVRAAVQRA TETHPLAQDL LQANLALLLQ VAERLGAVRV
241 ANAPEVRVFK KVRSERLEAQ LRGKHIRLYV AAEPLAYERD KLLFTTPVAH LHEEILRYDG
301 LCRHQKICQL LNTFPVKVVT ASRHELNCKK LVEMMEQHDR GSDAKKSIMK FLLNVSDSKS
361 RIGIEDSVES FLQDLTPSLV DQNRLLPARG PGGPGVVGPG GAVVGGPAGH VGLLPPPPGP
421 AAPERDIRDL FKKQVIKCLE EQIQSQVDEI QDLRTLNQTW ENRVRELRDL LTRYASRRED
481 SMSLGARDAE LYHLPVLEAV RKARDAAPFR PLAVEDNRLV ANSFFSQFVP GTESLERFLT
541 QLWENEYFRT FRLRRLVTHQ GAEEAIVYSN YTVERVTLPY LCHILALGTL DPVPEAYLQL
601 SFGEIVAAAY DDSKFCRYVE LICSREKARR RQMSREAAGG VPERGTASSG GPGTLERSAP
661 RRLITADEER RGPERVGRFR NGGPDDPRRA GGPYGFH
```

KEYWORD DNA (NC_001347 REGION: 150936..153029)
SEQ ID NO: 42

```
1    ctagtgaaat ccgtatggac ctccagcacg ccgcggatca tcagggcctc catttcgaaa
61   tcggccgaca cgctctgggc cgcgccgctc ctcgtctgcc gtgatcaagc ggcgcggcgc
121  ggacctttca agtgttcctg ggccgccgct cgaggcagtt ccccttttctg gcactccgcc
181  cgccgcttcg cggctcattt ggcgccgacg cgccttctcg cggctgcaaa tcagctccac
241  gtatcggcaa aacttgctgt cgtcgtaggc ggcggccacg atctcgccga aggagagctg
301  caggtaggcc tcgggtacgg ggtccagcgt gcccagcgcc aggatgtgac acagataggg
361  cagggtcacg cgctctaccg tgtaattgga gtagacgatg gcctcttcgg ccccttgatg
421  cgtgaccaga cgccgtaggc gaaaggtacg gaaatactcg ttttcccaca actgcgtgag
481  gaagcgttcc agcgactcgg tgccgggcac gaactgcgag aagaagctgt tggccaccag
541  gcggttgtct tccaccgcca gcggacggaa gggcgccgcg tcgcgcgcct tgcgcacggc
601  ctccaacacg ggcaggtggt agagttcggc gtcgcgcgcg cccaggctca tggagtcctc
661  gcgccgcgag gcgtagcgcg tgagcaggtc gcgcagttcg cgcacgcgat tctcccaggt
721  ctggttaagc gtgcgcaggt cctggatctc gtccacctgc gactggatct gctcctccag
781  gcacttgata acctgcttct taaacaggtc gcggatgtcc cgctcgggcg ccgccgggcc
841  gggtggcggc ggcagcagcc cgacgtggcc cgcgggtcct cccaccacgg cgccgccggg
901  tcccaccacg ccgggtccgc ccggaccacg cgcgggtagt agacggtttt ggtccaccag
961  cgaggggtc aggtcctgca gaaaggactc gacgctgtcc tcgatgccga tgcgcgattt
1021 gctgtccgag acgttaagca aaaacttcat aatggacttt ttggcgtcgc tgccccggtc
1081 gtgctgctcc atcatctcca ccagcttctt gcagttgagc tcgtggcggc tggcggtcac
1141 cactttcaca ggaaaggtat tgagcaactg gcagatcttt tggtggcggc agagcccgtc
1201 gtagcgcaga atctcctcgt gcaggtgtgc caccggcgtg gtgaacagca gcttgtcgcg
1261 ctcataagcc agcggttcgg ccgccacgta caagcggatg tgcttgccgc gcagctgcgc
1321 ctccagccgc tccgagcgca ccttcttgaa gacgcgtacc tcgggcgcgt tggctacgcg
1381 cacggcgccc aggcgctcgg ccacctgcag cagcagcgcc aggttagcct gcagcaggtc
1441 ctgcgccagc gggtgtgtct cggtggcccg ctgcacggcc gcgcgtacaa attgcgcccg
1501 ctcggccgcc tcgctcggct tggtcttcac gtccagcagc ggtaccagtc ccaccgttac
1561 gcaccaatcc acgtagagac catagtcgtc gttatcggcg tactgatata aaatgtcgcg
1621 gaggccgccc agcacgcccg tttgcacgct ctggcgcaac gaggcgctcc acaccaacag
1681 atactgctcc aggtcctctt cgtccagcgc gcggtaggga aatagcgccg cgtgcaactt
1741 ccactcctcg gccacgcgcc gcaccgtgat ggtgtcaaag agcgttttgc acactccgta
1801 gagcagctgc ttgcgcagca cgcacgggtc gcgcagcacc tggtgcatgc tttggccgcg
1861 acacgtcccc agaaagccgt gcagcaaccg caggaagctc atcgtctgcc ccgtggggaa
1921 aatgtcgatg acggcctcgt catccacgcc gcggcccacg cccaagtacg acgacgcctt
1981 gatcctcaac ctctcgtcgg ccgccaagat cgaacggatc gtcgacaagg tcaagtccct
2041 ctcgcgcgag cgctttgcgc ccgaggattt ttcgttccag tggtttcgct ccat
```

SEQ HCMV UL105

KEYWORD PROTEIN
SEQ ID NO: 43

```
1       MSMTASSSTP RPTPKYDDAL ILNLSSAAKI ERIVDKVKSL SRERFAPEDF SFQWFRSISR
61      VERTTDNNPS AATTAAATTT VHSSASSSAA AAASSEAGGT RVPCVDRWPF FPFRALLVTG
121     TAGAGKTSSI QVLAANLDCV ITGTTVIAAQ NLSAILNRTR SAQVKTIYRV FGFVSKHVPL
181     ADSAVSHETL ERYRVCEPHE ETTIQRLQIN DLLAYWPVIA DIVDKCLNMW ERKAASASAA
241     AAAAACEDLS ELCESNIIVI DECGLMLRYM LQVVVFFYYF YNALGDTRLY RERRVPCIIC
301     VGSPTQTEAL ESRYDHYTQN KSVRKGVDVL SALIQNEVLI NYCDIADNWV MFIHNKRCTD
361     LDFGDLLKYM EFGIPLKEEH VAYVDRFVRP PSSIRNPSYA AEMTRLFLSH VEVQAYFKRL
421     HEQIRLSERH RLFDLPVYCV VNNRAYQELC ELADPLGDSP QPVELWFRQN LARIINYSQF
481     VDHNLSSEIT KEALRPAADV VATNNSSVQA HGGGGSVIGS TGGNDETAFF QDDDTTTAPD
541     SRETLLTLRI TYIKGSSVGV NSKVRACVIG YQGTVERFVD ILQKDTFIER TPCEQAAYAY
601     SLVSGLLFSA MYYFYVSPYT TEEMLRELAR VELPDVSSLC AAAAATAAAP AWSGGENPIN
661     NHVDADSSQG GQSVPVSQRM EHGQEETHDI PCLSNHHDDS DAITDAELMD HTSLYADPFF
721     LKYVKPPSLA LLSFEETVHM YTTFRDIFLK RYQLMQRLTG GRFATLPLVT YNRRNVVFKA
781     NCQISSQTGS FVGMLSHVSP AQTYTLEGYT SDNVLSLPSD RHRIHPEVVQ RGLSRLVLRD
841     ALGFLFVLDV NVSRFVESAQ GKSLHVCTTV DYGLTSRTAM TIAKSQGLSL EKVAVDFGDH
901     PKNLKMSHIY VAMSRVTDPE HLMMNVNPLR LPYEKNTAIT PYICRALKDK RTTLIF
```

KEYWORD DNA (NC_001347 REGION: 152857..155727)
SEQ ID NO: 44

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   1 atgtcgatga cggcctcgtc atccacgccg cggcccacgc ccaagtacga cgacgccttg
  61 atcctcaacc tctcgtcggc cgccaagatc gaacggatcg tcgacaaggt caagtccctc
 121 tcgcgcgagc gctttgcgcc cgaggatttt tcgttccagt ggtttcgctc catcagtcgc
 181 gttgaacgaa cgacagataa caacccctct gccgcaacta ccgccgcggc aacgacgacc
 241 gttcactcct ccgcctcctc ttctgccgcc gctgccgctt cgtccgaggc cggcggcacg
 301 cgcgtgccct gcgtcgaccg ttggcccttc tttcccttcc gcgcgctgct cgtcaccggc
 361 acggcgggcg ccggcaagac ttccagcatc caggtgctgg cggccaatct agattgcgtg
 421 atcaccggta ccacggtgat cgccgcgcag aacctcagcg cgatcctcaa ccgcactcgc
 481 tcggcgcagg tcaagaccat ctaccgcgtc ttcggcttcg tcagcaagca cgtgccgctg
 541 gctgacagcg ccgttagcca cgagacgctg gaacgctacc gcgtgtgcga gccgcacgag
 601 gagaccacca tccagcgcct gcagatcaac gatctgctcg cctactggcc ggtcatcgcc
 661 gacatcgtgg acaaatgctt aaatatgtgg gagcgcaagg ccgcttcggc ctccgccgcg
 721 gccgcagccg ccgcctgcga ggacctctcg gagctgtgcg agagcaatat catcgtcatc
 781 gacgagtgcg gccttatgct gcgctacatg ctgcaggtgg tggtgttttt ttactacttt
 841 tacaacgccc tgggcgacac gcgactttac cgcgaacgcc gcgtgccctg catcatctgc
 901 gtcggttcgc ccacgcagac cgaggcgctg gagagccgct acgaccacta cacgcaaaac
 961 aagagcgtgc gcaagggcgt tgacgtgctc tcggcgctga ttcagaacga ggtgctcatc
1021 aactactgcg acatcgccga caactgggtc atgtttattc acaacaagcg ttgcaccgac
1081 ctggactttg gcgacctgct caagtacatg gagttcggta tcccgctcaa ggaggagcac
1141 gtggcctacg tggatcgctt cgtgcggccg cccagctcca tccgcaaccc ctcgtacgcc
1201 gccgagatga cgcggctttt tctctcacac gtcgaggtgc aggcttactt caagcggctg
1261 cacgagcaga tccgcctgag cgagcgccac cgtctctttg atctgcccgt ctactgcgtg
1321 gtcaacaacc gcgcgtacca ggagctctgc gagctggccg acccgctggg cgactcgccg
1381 cagcccgtcg agctctggtt ccgccagaac ttggcgcgca tcattaacta ctcgcagttt
1441 gtcgaccaca acctctccag cgagatcacc aaggaggcgc tgcgccccgc ggccgacgtc
1501 gttgccacca acaactcctc cgtccaggct cacggagggg gaggatctgt aatcgggagc
1561 accggcggca acgacgagac ggcgtttttc caggacgatg ataccaccac tgcgcccgat
1621 agccgtgaga cgctgctcac cttgcgcatt acctacatca agggcagttc ggtgggagtc
1681 aactctaagg tgcgggcctg tgttatcgga taccagggca cggtcgaacg tttcgtggac
1741 atcttgcaaa aggacacgtt tatcgaacgc acgccctgcg agcaggcggc ctacgcctac
1801 tcgttagttt cgggcctgct cttctcggcc atgtactact tctacgtgtc gccctacacg
1861 accgaggaga tgttgcgtga gctggcgcgc gttgagctgc ccgacgtgag ttcgctctgc
1921 gccgctgccg ccgccacggc cgccgctccc gcttggagcg ggggagagaa tccgataaat
1981 aatcacgtcg acgcggattc ttctcagggc ggccagagcg tgccggtatc tcaacggatg
2041 gaacatggcc aagaggagac ccacgacatc ccctgcctgt ccaaccacca tgacgactcg
2101 gacgccatca cggacgccga actcatggat cacaccagtc tgtacgcgga tccctttttt
2161 ctcaaatacg tcaagccacc tagcctggcg ctgctttctt tcgaggagac ggtgcacatg
2221 tacactacct tccgcgacat ttttctcaag cgctaccagc tcatgcagcg tctcacgggc
2281 ggtcgcttcg ccacgttgcc gctcgttacc tacaatcgcc gtaacgtggt gttcaaggcc
```

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2341 aactgtcaga tcagctcgca gaccggctcc ttcgtgggca tgctttcgca tgtgtcgccg
2401 gcgcagacgt acacgctcga gggctacacc agcgacaacg tgctcagtct gcccagtgac
2461 cgccaccgca tccaccccga ggtggtgcag cgcggccttt cgcggctggt gctacgcgat
2521 gcgcttgggt tcctctttgt gctcgacgtt aacgtttcgc gcttcgtcga gtcggcgcag
2581 ggcaagagtc tgcacgtgtg caccaccgtg gactacggcc tcacttcgcg cacggccatg
2641 accatcgcca agagtcaggg cctgtcgctc gagaaggtgg ccgtggactt tggggaccat
2701 cccaagaacc tcaagatgag ccacatctac gtggccatgt cgcgagtcac ggaccccgaa
2761 cacctcatga tgaacgttaa cccgttgcga ctgccctatg agaagaacac cgctatcacc
2821 ccctatatct gtcgcgcgct caaagacaaa cgcaccacgc ttatttttg a
```

```
SEQ          HCMV UL114
KEYWORD      PROTEIN
SEQ ID NO:   45
1        MALKQWMLAN IADNKGSLLT PDEQARVFCL SADWIRFLSL PDHDTVLLRD TVAAVEGARQ
61       LEMVYPAPEH VHRWSYLCPP EQVRVVIVGQ DPYCDGSASG LAFGTLAGRP PPPSLNNVFR
121      ELARTVDGFQ RPASGCLDAW ARRGVLLLNT VFTVVHGQPG SHRHLGWQTL SNHVIRRLSE
181      RREHLVFMLW GADAHTCEYL IDRRRHLVLK SCHPSPRNTT RAFVGNDHFI LANAYLDTHY
241      RETMDWRLCG
```

```
KEYWORD      DNA (NC_001347 REGION: 163901..164653)
SEQ ID NO:   46
```

```
   1 tcacccacag agtcgccagt ccatggtctc tcggtaatgc gtgtccagat acgcgttggc
  61 cagtataaaa tggtcgttgc ccacgaaggc gcgggtggtg ttgcgcggcg acgggtggca
 121 ggacttgagt accaagtgcc gccgtcggtc gatcaggtac tcgcaggtgt gcgcgtcggc
 181 gccccacagc atgaacacca gatgctcccg gcgctctgac agcctccgga tcacatggtt
 241 actcagcgtc tgccagccta agtgacggtg agatccaggc tgtccgtgca ccacggtgaa
 301 cacggtgttg agcagcagca cgccgcgtcg cgcccaggcg tccaggcaac ccgaggccgg
 361 acgctgaaac ccgtccaccg tacgcgccag ttcgcgaaac acgttgttga gggagggcgg
 421 cggcggtcgg cccgccagcg tgccgaaggc caggccgctg gcgctgccgt cgcagtacgg
 481 gtcctggccc acgatcacca cgcgcacctg ctcgggcgga cacagatagc tccagcggtg
 541 tacgtgctcg ggtgccgggt acaccatctc gagttgccgc gcgccctcca ccgccgccac
 601 cgtgtcgcgc agcagcaccg tgtcgtggtc gggcaagctg aggaagcgga tccagtcggc
 661 gctcagacaa aacacgcgag cctgctcgtc gggggttaac agagagcctt tattatcagc
 721 aatgttagcg agcatccact gcttgagggc cat
```

```
SEQ          MCMV M44
KEYWORD      PROTEIN
SEQ ID NO:   46
1        MEGGRKVREH EPPTLAFRLK SYKTAIQQLR CVVRSLKENT TVSFLPTPAL IVQTVKNQFI
61       AKIVFNSSCL YITDKSFSAK TINNSIPLLG NLMYMTSSRD LTKFTVQDTS DLSAKVCMSA
121      PDYNMEFSSA CVHNQDIIRE TGDSAARVDL DSAVVGELIR WIAPNIRPKR NSKKQSTSSS
181      TVQITLHANP PTVKFSLGCN SELEFTASNR IAFHEVKNLR ITVQAKNLHQ ALCNCVVTKL
241      ACTLRVMTDH ETMLYVASKN ANFTIENFLS EEPFVRGDVG FDRMPVANSN NYQNSSSSAG
301      DDFAACVDQV IDNCTKKHER VSRKAGGGGG GGGGVVVNDD HQGGGGSGKD NKYDQHKITS
361      FMVSKGAVGG GAGGGGSDRG GYFNDTKEES DSEDSVTFEY TPNTKKQKCA A
```

```
SEQ          MCMV M50
KEYWORD      PROTEIN
SEQ ID NO:   47
1        MEIDKNVGAD LISNTRRILR LDENELRITD TALICKNPNY SLCDAMLTTD IVYPVEYLLS
61       YWECRSGRTA CFVFKNTGCR VSLSCYIGFP ERLKDLKRVC DFNFLSVNEA LVVTLADIER
121      IKPCDKGVLT NCVVRKSNSG MSYNIEVVAF GPDNEAEYQA LLRDIYARRM TSVPTDCGSL
181      ICRRARCLAA APPRRPPPPP PPGQRWGSLR KHGPVLTRRY AGGGGAAKNQ PAAASPTSTS
241      TSSPAAPSRD QDQTQRPPPA GDTNVTAAET TYSERTISFL TRHANAIHCA LILAAAIALV
301      LLWLLYWHAA RSAGHP
```

SEQ MCMV M51
KEYWORD PROTEIN
SEQ ID NO: 48

```
1    MLTIAHRLQR ESISSGRHSS RISAVFSSPI RASSESRSQH AASSSSSIVS RPESVDEDEE
61   EDGVWPSVTS GGVLVGCACS NSSLTRNESI VVSEGSQALY IASAATAMNG DSVRRRGGDA
121  PDDDEAAGAA PVPAEECNLD ALFERFFGDG GADAIRFEPM LPRVYELTLP SIDSRLNFIN
181  VGRRHAAFLR HVYGGCDRCE HAAVLNEKMK LFTAVITKLL DVNGILERRE TTD
```

SEQ MCMV M52
KEYWORD PROTEIN
SEQ ID NO: 49

```
1    MYRAWDPSLT TIDSFLVNEL LLHAHPTKTP PEVTEGQTPS SSSSSSTDSG RETMLEEEEA
61   ACCDLDSELA RIGDENTAEI RELCLPLEID SRCNLCAIVS ICLRRDPQQK WLLDYCFLCH
121  KCAAAPRTAM ATLIVATEFL HLMKLHFRDI AFDNIFKERI VTIFDFHAHF FINRCYTQRD
181  EHPVMVENIT LAHMAVTRAL LTDDDAVPYT KRRKIQYKLP KKPAPAEPEE LRLLDKYRRA
241  TEGSFARVLF YIWSGTNVMF NTTLTDLAIK KSKALKALKT RQSEIEPSVG PVFLSPIPTF
301  RLRNATTTVC LLCELMACSY RDNVFLQQLR ERITNYSRNN LKIIDRTQLT MAEILSHGRN
361  SEFPQQLKNK DVSIYVTSSP ETLAAASRPG TEEPFELSAL TYLVLRQVGV IGVYKHLFAD
421  PLCAANMRST DPNILFFDVP NEYLNEAKLA ICSTNAYPSR VERDFWLYAH MFKAFQIIKR
481  NFKTKTQLSD FLRDFSQVLE SHDFSLVDPS FTVEKYV
```

SEQ MCMV M53
KEYWORD PROTEIN
SEQ ID NO: 50

```
1    MFRSPEGEER DAADREEEEG GEARRRSRMM MSPRRVKRAR HRPAGSGLRT PLRSPSACRC
61   SSPSPERQWQ QRRRAEKRST TPTDPPPPPK RSAASAAAGA AAPESEYLNV KLSELHDVFQ
121  RHPDLEQKYL KIMKLPITGK ESIRLPFDFK SHRQHTCLDL SPYGNDQVSR SACTTCKETT
181  RLPTASDSMV AFINQTSNVM KHRKFYFGFR KNMELLKMAA NQPQLFQIYY IVQSCVQEIV
241  PLIYYDREMA HMQLIFEKET VHIPSQCIEQ ILTVAKDAYG VSLDIAHQRI TLTARCLRLE
301  SSSLRIDVLM LQRKVDELEI PNETNEKFES YSL
```

SEQ MCMV M54
KEYWORD PROTEIN
SEQ ID NO: 51

```
1    MDTCVETFFN PYLRRKPRRD WRRCEDNNKN FLQVVPRGVL YDGATGLIKV QSGMEPRMFY
61   AEKEYVLNPD KPWPTLRTRG WCRGPYSDEL RFHTYDQVVN LVLADSDEQI SPRWKHHVVP
121  AGNVIRMFGA TDEGVSVCVN VFGQKAYFYC ERMQSEDLKN TVYDIADKVP EPCSPFSVSI
181  SPVTKSSFYG YGLGHIPNLY RLSFNNWNMC RKIGKRMLEE GRKVYELGVD PLARFLIDRK
241  IPSFGWCLAR RYSVRAAGYV SRAQLEIDCD VADILPIEEQ SNWPFYRCLS FDIECMSGTG
301  AFPAAENVDD IIIQISCVCF GVGEMVHHAY DVHADLSTPA VPENHLFTIG PCAPIPDVKI
361  YTFPSEYEML RGFFIFLSWY SPEFITGYNI NGFDIKYILT RAEKLYKMDV GQFTKLRRGG
421  RMFVFSPEKG KAGFGTSNTV KVFWSGSIVL DMYPVCTAKA SSPNYKLDTM AEIYLKKKKD
481  DLSYKEIPVQ FSAGDEGRAR VGKYCLQDAV LVRELFEMLA FHFEAAAAIAR LARIPLRKVI
541  FDGQQIRIYT CLLEECSGRD MILPNMPSLG HEAAAAIEEA AAGGEGDETS EGENSNNSRT
601  VGYQGATVLE PECGFHHVPV CVFDFASLYP SIIMSNNLCY STLLVEGSPE VPEKDVLRVE
661  IGDQCHRFVR ENVHRSLLAE LLVRWLTQRK LVREAMKQCT NEMQRMIMDK QQLALKVTCN
721  AFYGFTGVAA GMLPCLPIAA SITKIGRDML LATAGHIEDR CNRPDFLRTV LGLPPEAIDP
781  EALRVKIIYG DTDSVFAAFY GIDKEALLKA VGALAANVTN ALFKEPVRLE FEKMFVSLMM
841  ICKKRYIGKV HGSQNLSMKG VDLVRRTACG FVKAVVSDVL HMVFNDETVS EGTMKLSRMT
901  FDDLKKNGIP CEFGPVVSRL CRARDDLHLK KVPVPELTLS SVLSQELSCY KQKNLPHLAV
961  IRRLAARKEE LPAVGDRVEY VLTLPDGCKK NVPNYEIAED PRHVVEAKLS INAEKYYEQV
1021 VKAVTNTLMP VFPRDMPKRE KFFSLVVPQR IYIPDQFLHL CGNVNELARG GDDSDGGDSE
1081 KENMDTERSS SHEAMET
```

SEQ MCMV M55 (gB)
KEYWORD PROTEIN
SEQ ID NO: 52

```
1    MSRRNERGCR SSSWYAMSTA LAVTIWCLLA CTSEVIAAAS TPGTTPKAKT DTSSETASAE
61   TETATSGAAT GKKEATPTQA SKITGTTIVP FVNETENMVS VDIDKYPYRV CMSVSTDLVR
121  FGKSIDCINH TPKTPVQEGI MIVYKQNIVA HTFEVITYHK DAIFQRSYAD TTTNYFLGTS
181  VTKMAFPVWE LDEVNRNNRC YSAASRILNG EVYVAYHEDS YRNYTMVLVE DDYRSKNSKR
241  YVTTKSRYHK GAWTWRYTES CNMNCVVVVT KARSNTPYEF FVLSSGEVVE ISPFYDGENS
301  EPFEEDTRNF WIRKNYTMKT YFGELAAPKK VVPLMAFLER EDMTIGWEIF PKQNVTCDWK
361  KWQTVSRAIR TDTNTSYHFV SKSLTATFVA SKHKIDYNTT TEGKNYNTFR CVYDEFVEEV
421  NRVFEDEYNE THVKDGELEM YRTTGGLIVL WQGLKAKSLH NLEKFAALNN VSVGTVSPPV
481  TSATENGTTA ASVAARRKRS LDHIDDVVTD ITYAQLQFTY DVLKDYINDA LRNIMDAWCR
541  DQKRTAEMLK ELSKINPSNI LSAIYERPVT AKLAGDVIAM SECVKVDQSS VKVLKDMRIF
601  QDGKVVNCYS RPLVVFQFIN STKLESGQLG ENNEIMLGTF RTENCDTNSR KIFVVGTVGY
661  EYRDYRFRNV TSLEHIQLVD TLIGLDIEPL ENTDFKVLEL YSKGELRASN VFSLDEIMRE
721  YNSQKQHIRT LSAKVNDNTP SYLLGLDTFM QGLGVAGKGI GVAIGAVGGA VSSVVNAVTG
781  FLTNPFGGFT TILLVIGVLA VVYLIFTRQR SAAARPVEYF FPYATQTAVQ YAPPGGAHGG
841  LESGPPGAPG LHRRVNAGGS DDSGKAWTSD KKGLERTYTE QDALLILRAL KQLDDSQRTE
901  KAQQKATRLP TGILDRLKGN DTSGYQRLPA EDSDFEY
```

SEQ MCMV M56
KEYWORD PROTEIN
SEQ ID NO: 53

```
1    MAMNTLQKLC VVCSKCNECA MDVECLKYCD PNIVSMDSTA FRRNGVMVIH LYRTLYPALV
61   SQNAVQTSVL TLYMEMLLQG LYDTMREIDM ALTDFGTHRD RQRYYRRVLK LDSCNRHESI
121  TITFAPELAL TIDLATLNDV ERLLCKINCV YGAVDASQGV AVCRRLLSLL ARLCDICPVA
181  GPEIYRETVT CFQCYEELMA VPNQGRSINR RMQGLLCDHI TIKKVLVQLD MDAQTVEQDM
241  GDIAIRAPSV KGIIRAIKSL ASFSPASYAY INDAEEALRG YNLFSEIPDR IYSLSDYTYW
301  SKTSEAIVRH VGITMRQLNV SHSLWKTLRT ELSRYHYGED LEDVFTLGEG RFGGDERIYV
361  GSIFAAPGKV VDMITSMSIK SFENNPLFNR LHESNEIYAK IKSLIEEIRG VGDGPAAGAA
421  ASRAEAASGA GAGGEEGAGA AAGRGNTGGD EGAGTTTAMS SALECGDPLL RVHDVNKEVN
481  VRKRAYLKKV SEMGYNKVMA CIRNQEHLVT KLVNVNLVGT VCLEAVSKIM NGFLSRQRSI
541  TEAETYPDVA ESLGYDEHLY VINNLVHKRL PSELLPQLGQ QIYRFINGPM FTHYLDRHPL
601  PYNVNMAYAC DNAGILPHVK EDLVRCADGT VVPSDWMTVG YMGFFRFADI RELNDLQKMV
661  WAHIRELVLS VALYNETFGK QLALWRVEDG DEIGDGIILT YNPESPLILR RGDRSYRSRD
721  LYLLLYKHLS VDSETLADAG SRASVADLCQ VERPGPIAEQ RSSTQNVKKK RKRMSLLELV
781  RDVDGAGGDD LVPPCLYK
```

SEQ MCMV M57
KEYWORD PROTEIN
SEQ ID NO: 54

```
1    MADDDLSSLA PVAPAVWMFF LKKTRELADI VAAMSLCDKA TPVVIAPLLI DLTVDRDFCG
61   AVRTPMSTYE GGVLTKVTSF CPFAFFFHNT DEILDVVEDH GDVVHLCDDA RRRFGVQAFS
121  PLANRDRTDV DVLCDELGIA PAEYTGHVVC GNGLKELLYA GQLIPCPEEA VKVQVGAVDG
181  VKVPLYPYTL FSGGADAAHA DGASAAVACD DPWVLEHGFY DPALSEALFY FMFTSWGQSL
241  RVCETSRLIE AGLQQFVEDT QQTVKLTPFK KYHGYTSQKL TAVERDQLMT VDAVCSELAF
301  SYASIYLDSV YEFSTASNFL EWPLVKNAKT HADLLDNLRD FQLHLAKHIA ALIFSSNSIL
361  YQTRIVFVPS AGKGANSNPS AQDSLLKSIR FFNGLTGMYD DILNDAKKTI RFEGAVGRDE
421  KYSPHHLAYF CGTSPQLFST LMWFFNRMSI YSTGVTSGDT VFSHIVNAGS KLCGACGGRC
481  CHTCYATSFI RVNTRLPGIP KQIKKEPVVV TLLSRAFADA DLLGNYGKRY GLESREAGDG
541  GGGGAGGRTD EVAAGPPAGG ASGLNFVSVD RMKYLGQVLD YCKKNSLIDA ITGEDIINVR
601  SKRDFVATVT ALNQTIDDAV CRFAMDVRRS GHGRDEISGS TQSFNLDLSP YATAFSPVLS
661  FQYYRTMFSI IQNLALINAA SYVVDNPLTT AQISKWVALH FQSICGAFGT TPLKKGFLNV
721  KDTKNLKSVE FERIMDFRSF QETGRYRKIS TEIKSCKMSV QSLKSCRIKN RPISKTPQSS
781  VFFKKGALQR KNPIKGCLSF LLFRCHEKLF PACGLSCLEF WQRVLQNSLP RSVNVGKVED
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841       FDNLVRFLLT VTDDYDESDV VDIQPDCLLS YVENRFHNKF LYMFGFRDYM STIQGMSTRL
901       TPQNHSQFPC LLKDAPKFVS IAEYVLHFKK MKLDGVKAPQ VATITREPVL KNVFDGRSLV
961       SVSFAVEKYS SSMGTRDVFQ FGQIGYYVGS GVDRSLNTGS MGTQDYRFMR YRYIIATKLV
1021      DVLIRRSRRE NVMYDADVVR SRVLAALDST GLDVDPELAA IAELMEGRDE GDIPEIDDIL
1081      FYVDQQEYIA RSMYRKMRSL AERGVTDFSL ASLREATATN ATAAGSAAGG GGSATEGGGG
1141      AAAADESGPM YDFSALFSRR DEAEDVNAGL INGDDVRGDD EFELPSKRSR L
```

SEQ MCMV M70
KEYWORD PROTEIN
SEQ ID NO: 55

```
1         MTVVLFATEY DTPNIVVNML SETPTEHHLF PLMIKYKPSN RIEFVLQTQR CPDSTRVRPV
61        FICDARRLSL SEYVSTNTPL PARVICAGID ADATRELYEH LFDRKKDETG HDEENGSAGG
121       DLFSDLTSTL KCLVHYNRSA ILRYLNNTFL SPTSPSWFLS TYGTHEGTLI LTMSYYLFER
181       QYSTIQTTRD YTKCFTADPG RNLFTYINMR DFMATMNGSR FRKQTARFAA FAKARNARDR
241       RELEYVDAKI NAFREESRLA ADSCVYYVYL AYRTALCREK FLQYCEHTAY DKNLPDDQQC
301       AAEENYLGRS LDAELISIMN TYFSVEGYFG SYIHVDRAKL SPPHSYRGYD WNTEADTMVG
361       YSSTATNLAI SLRKLNSTCE SLFSPLPPTL MGLLKLCASD RYVPRAEKSR KRTSGGREKE
421       DETRVCRRNY LLNDTSRPIG PMPVFRVEMP EKRHVFCAVS AENWTRRLLP KDLMKNLPSE
481       YVSDECLTDA VWLREDIAAS CEVGEQLYRT RHEMFNENLP VFNFVGDVDL KLREDLQGLS
541       RQEVFDLCRA LRRTLIGAWR HLFPEVDPDS HPVFFFKSAC PQNAAGAADE AMLYGGGGYD
601       EDDDPRPEHA AAVVDYGDAV RRPPFCVCRR KLGLRVIIPF PPRTAAIGAQ TLKRLAGILD
661       HTLCLDRDLV CKLNAISHPG ECFDTGIYSH GRSIRMPLMY KLDEASGLML HSRLNPIFIV
721       PAGYRDRPAE FVLQQLCPQN LTHHGRPPRR DGSADQLTEV VLHITDRACA DSDGNFLQSR
781       ARRAMSRRRL PLGPLLRAHL SLESGQSAPS LPTLVGRGGG GEGGASSDYE EERAVGSDEE
841       EDDDDVENLQ AFARRIAWPA LLRHTRNHYR EEVQQQLEAA TVFTAVGRTC VAVKRGLYGR
901       ARDFSCLARE HYTRQETVQV FLDIRGDQRR NVWATLWSRC FTRRCNSNAK QTHLSLKISL
961       PSQY
```

SEQ MCMV M71
KEYWORD PROTEIN
SEQ ID NO: 56

```
1         MMMTDFGGGG TGTSNARGGV GGAIAAADDD AGAAPPSCWR RMLDFALCRR TIRDGSEYIV
61        LRADEDVDMA ELEGFLKDNF GNLGVSSADL SEIDRESEVT KHLLRLLPVY KRCVRRQTRL
121       DRLLANQCRP HLRNAAEIEC QKSKRVMQAL DIVILKLLVG EFTLSDEDSV ERLLEKFSVD
181       QSTLCEVGRI VRLIDMDREN TQRLVDGREE PAPPLCDLNG VPSSSSSSSY AATTTISSAS
241       DLLLRELDNA PAAPDHLPGE IDEILLRDEA TSGTGRLHNV GRRRDLEEQK QQHQQMAAL
```

SEQ MCMV M77
KEYWORD PROTEIN
SEQ ID NO: 57

```
1         MSRLKTFHDV PCIVAFEAHR ENVLVFPREK LARLRDESAL RLRQYADDLG HDARLRRRAG
61        EDLESLGKEL RNECERFRGR IDQAEQLLSG PMSDILGGGE GTEVAGTAGD GGSVDNASQK
121       NKRKKAGGGA SASSCSATGD GGGSGVGDDD DSRQQCLWVT PNDPPISYST DFRGELVETI
181       FNVSQAWTFS FGSWYYRLKR WLYNQPRWRR VYRLTQIESL SVSQELLMGV LNAVEQVTVY
241       PGHDTVVSDL EVAACLLAAY QAALDPRAAV PTTVEGVLRD SGRVLRALSD DIAAEIARRP
301       SGGNAFAYKD PPGLRFYAPV QQGRRYAAGT FDENALVAVL LRRGAIAQVP GGATGVAAAA
361       SGGPGSSAAA AVASREVMSR LSGAVSDDVL ALWTLRLFGK RLSGVVPNLL QEQHYLRSGL
421       TAVLCLLFLW KLLNSESVFS GRAGKFSLRD VFPDLCGGRD APPPVEREEG FAGGCVKNFE
481       FMMERYVVPW YSRDPAVTVS QLWPGLVLLL YCESHRSGWD LSRRPFEHAT ADGVSSAAGV
541       LHVQASRFNP LVDYMLLQQT AAPDKDVDRL AAHDFALFHC ENGIGRLLSI TLPKHRVLTL
601       GQQFFNLQNV YDSMYFFVLG FLPVVSVT
```

SEQ MCMV M79
KEYWORD PROTEIN
SEQ ID NO: 58

```
1       MVKTIRVGRF LHLSDDNHLI LHITTKLLSG QPLSSMRLEE LKIIRLACLL TLGRGIELLI
61      LRETVANNGV SDNTILNRKI SPEFWRKMYE AMRAHVPTET LHRAFSERSA AALSVEITGS
121     RACRALVSHL IRTETGLALS LPDELLSDGN IFFSLGTVYG HRLFRLLRFF NRHWGKEAHE
181     PAIRTICQKV WFFYLIAWKK LTVSPEAFSV QRSDHELGIF SFLIQDYLTF TGTLRRSTPP
241     MDKKEEGVIA DLLSGALE
```

SEQ MCMV M87
KEYWORD PROTEIN
SEQ ID NO: 59

```
1       MMSASDGSPA SLSCLDPALI VKSPTARVKS APVCVNSYNL TREISPFEDS RLSQAVTVDE
61      EHISSIFRTL MAAGPDPGAT DEDKARVVLC RLLMGPVAVP CYCDEWDVDD YLAKCAYRCS
121     GPALYVHRSR CRCGAEGGGT MFTLLHDHYT THVFRGLLSL SEWNVRLTDV FCACNAFRSD
181     RYVMAVLPKH QSVFIEYYPY FLVCLARYLT VPEIDDCANS MTAHLGPAIA ARVGVHYKML
241     FGANARPPRV TEVARRANYD LFLLELQKLW LNVSYRNAVT RDFFETVFSA FHHETGKVML
301     ALRSPGRQPL FPRWISMSRF KKQVLYFELE VRCTKSRKDE LKNALIFRKT SVLFADHDVI
361     WRNLFYTYYA WCAHRGFGGE SRLWGPSGSG GGAATESERG GGVRGRDQAT TASAAAAAAS
421     TDDDASAAST ESGVAVSAPA AAATSAAKAH PHAPAAPTVV GGGQGTAVSS TATQKYVKIV
481     DRLALVRLRF RERRLAAEAA VGSGSGSVEG AVAGGTSGVQ TDVKADEPVA VPSFDFDPYR
541     CLVRHRAAEG VRREGEGSVY GARKIIGGRE FSEMTAVSLN RVAVNAFNTN RVINLKATIV
601     QTPRLSAFYV PRNMTHSFVM YKHTFKEPPY TVSTFVSNDA AHTNSLNVNI RGSYQEFLYA
661     LSVYKLYVNI ENFFLPASVC NSNSSLDVHG IEDQGVIRSE RDKVYWTTNF PCMISNTDNI
721     NVGWFKAATA IIPKVSGVAL ENVLLKELAY VTSIDQLCVD YTLHRVFTVL ETRNCYQIPF
781     LSKQFILFVR IMMLRICGLE HRLAVDRLIF RAIRQGVFDY HKNTVAHTKI KHTCALVGTR
841     LANNVPKVLV KNKKIKLDYL GRNANLLTLC RHVDHACVDA HRLEALIGVL DCLEKLTSID
901     RTKEALTRAR VRLCGGYRPE AATSRR
```

SEQ MCMV M89 Ex2
KEYWORD PROTEIN
SEQ ID NO: 60

```
1       MSIRGQNFNL LIVDEAHFIK KEAFNTILGF LAQNTTKIIF ISSTNTTSDS TCFLTKLTSA
61      PFDMLNVVSY VCEEHIQAFS EKGDATACPC YRLHKPTFIT LNSDVRKTAN MFMPGSFMDE
121     IMGGTNKINE ETVLITDESR EEFDLFRYST TNPQFHPHLG AILSVYVDPA FTSNRRASGT
181     GVAAVGTYRD QFIVYGLEHY FLKDLLDSSE TSIADCVSHM LLSILRLHPF LSQVRVTIEG
241     NSNQAAAVRI ACNIKHNLLS AHAETLFYHS PDQNEIQQPF YLMNRDKRLA VEDFIAKFNS
301     SYIKASQELI SHTIKLSYDP VEYLLDQLRH IQRITLNEYV TYSAKRNNQS DDLVVALIMA
361     VYMCSPERSF NFKPI
```

SEQ MCMV M92
KEYWORD PROTEIN
SEQ ID NO: 61

```
1       MFSHGRDPRT GKPISAAGAR AHARGGGSGK CDGGGGCDMR NLCNPLTQEL NLRNMYVCVR
61      CHRTHLCDLR HDCVVVHTQD GSVCIKTGLT YGSVFPGGCV SALEPVTEPH VDEINVVGVI
121     MSYVYTYLTR NADHYADVIG SVIEGGWFNK PTENAIYFTF NRVFKQHNAL QKVPISVIGQ
181     LFVQLVIGVH ARVTKYDSTV IKVSRRKRED GLLKRMRFEY GNAPSFRTGR
```

SEQ MCMV M95
KEYWORD PROTEIN
SEQ ID NO: 62

```
1       MATAAGGVYA GGEDQQQQRP RATDVSTALC DVEALAAVEE GRVSEADVNR YREAVDAALI
61      ACEASSPRDR FRLIETAGGN FLLVTNALPK DRTEQQPPCV LEGSGRASSN NNYEGIGTPS
121     AGSGNAFDGL LALERGTSGG GLTATVPSAP GYVAKSVNTL SYDGRLLSNS YVLYTKEQLR
```

181 KSLSPDKRAI VERILRFVDT PGILDHNNVQ DVEAVLWLLF CGPQSVCQNP TCFGRDRECE
241 VSYPVLLPPV FYDPITDYSA YINLAELYVY VWYRNYDFDS EPTRCYELGT VAMDRVKKTL
301 QSVRQRFSDR SVPVWPVSSR TCVFCALYNQ NRVCLDLAKS DVDVTSYSPI IIKDCRDAAT
361 NVTLSHVLPG QRVASLFPVY DIGTLLRALC DSNDGEERRK RMRETIDSAL STTDDAV

SEQ MCMV M98
KEYWORD PROTEIN
SEQ ID NO: 63
1 MATTVLPPEA TAMTTIPRRI VDDVVVDDGG GFVTHNIDSA FGGSERNECL VFDQSEQCLA
61 RVFDGLSSES FDIYCLYNLL DIKERVSSVP VCALRLAYFR SVFNKINLTH DGPGLATNFL
121 SIVDREVSNA GGESTVRDAV GGVEGAQFAL ARAIFRLPAR RLLRVMKAIE RDSRGQAANP
181 VWHALRVDTV SATRFHDVLA TRKIAFRKDL DVRHSSEAVR FGMQCESAIA QVLREFVAEG
241 RGGVSDIGLL LDPASGVLGA SLDFCSGLSR DDDGLLVVAP GAAIFEIKCR FKYLRSRDDR
301 AVQGLLDDPG LQSFADFILD HHTPAVEFRH QGQLPTSREC LVSYDRVFRQ SCKRRRTGVV
361 SESLRLWIDG LIKENSEVLS TVFVFDARAA EGETGAATQV GDDDEDFILS AERPPLYLDL
421 FLKAAFAAPV FANPRHPYYC QTLVQHYVLS QYYINAHRDP ERMSPDELPS VYLVSAILRK
481 RDESERGRVI RINGHRSDCD EVPLCVVVTP VRLDPHFARD AVSSVLDVWE GDIGKKTGLA
541 LWVQSAVNSY VAACIPTPRT P

SEQ MCMV M100

KEYWORD PROTEIN
SEQ ID NO: 64
1 MLSLFDPPRR PRTRDTCTMA KAGVMTLSHV DRMNLRTWTM AIACCLLSFV NIVVFSVAAH
61 FPGIGFPCYY PRIIDFDNMN LTMYNAIHHL TPQLFLDPVQ LIVYVIFTEL IFFCVLSYYI
121 VCWVQIYFRS EHGTQVNQST RDINFMGDSA TCFTFVLTMD TFQIFLLSLS FRLPSMVAFS
181 KCMYFMCLTA FVVTLVTHYE SRERSAFALS KIHPKLQGTI RYRTAVVNLT QLILGFATMV
241 LAMSLALGFG NSFFVKTAHV VFGAMVAFAI VACVYFSIIE SVLSRYMKVQ FGYHIGTILG
301 VCGAMYPIIR YEALNASSYA RDINIGITVL LLLCVAFSVI RTVRFLLRRN KRYRALALDN
361 EEIRALRSDA E

SEQ MCMV M102
KEYWORD PROTEIN
SEQ ID NO: 65

1 MERRWRRGLP VHLSIYAFLP EENQAILQCF FCEVADGDRV VTRLFVFPVN IPAEGELRTY
61 LLANYTSAIV SSSLDTIPDS TTAANGSGVG GEVGGGGGSG DECADRVARR SRALAQILMH
121 VGPDFEPLTR FFTPVEIFSD GVEILGSRRW ENVRGIYNSI LQTLAALTVG RIRAIGSYHQ
181 MADAVSIETS TAIQSIIAEG ATTEDAEDEC RYRNTHAYRK LRRGFVSRDI TFSIRIGNKK
241 FMLSEPSAVG AKFSVSDVFV IQDVKWRGKK LRLCFPREFL AFVFSDDQCL VLLRDAMQRL
301 FKEVYGGFSG LYPVFDFFGP NMLRSGGPRS VFFPGFPAVA VYSVPWRYDM NTENGADAIN
361 EIRSLVGLPD IVGVAGKVPL VPEPGNAVDT LDAVRMYDID LHYADMRHFR INARLCVTHD
421 MGDAALDDES SVAHIYVGVG GVCRISIVDL RFAVLRMCLP GPEFPFVLSD VARRVDRMMI
481 DAFLQRLAHS SPRIFRRVRS LENYICKRVM DACEDEGYPW ILVRDDCEIF VRRPVDCDQV
541 NFDTIVRANL ARVWAELFGL QYLCPVCRIT VAMSGVLFAT GKYLLSGFPD EQKYFPTPGW
601 VGATGRLLSE AVFCAFQSPD WGAKDKIIRF MATHMLRLSA RRHETRFWAQ RFAPGRNRVQ
661 QHDGVMDANE FCGIHVCGRM VAVQPLDGAL HDNICYNDYV KKTFEVLRVT LEKVIIVLSQ
721 DQTNTAVVNN STGEIDCVAI KQEVTDDAIV SDTTGSDELD AALRALRETT ANTVGMVVER
781 TDTHNLIEEF NDVFQQTMDF VVERYSAFFS MN

SEQ MCMV M104
KEYWORD PROTEIN
SEQ ID NO: 66

```
1       MWRNQSLYRD SRENRFKASD LTRSTIRSIF EADDIFRTKM LSYLDNPPEP PSDPLFPTDS
61      SLDLFSMING TEGACIGQTI HQILRDPSVF RKQIFYAMMR FLLNGISVGE LSTAWASHRR
121     RFVRAEDEGG AALEQFEIWA DALKHTIVDS IAALLEKLIY TYAADDRYCR YVDWIVSVGV
181     VPIAEVRTAE REKAVDAAQR RFLAEVAECH LLDRPDPLRA RTLRACVSAL MTREVPNVPD
241     IRIHRLKSNG HIECFSGKRR LKRFIYAEPT ILEEERLILT TPLARIRYER KRHNELRIHK
301     KICQLLNTNP IKVVTTSRHE MNTKRIVELM EKRDRQVDAK TSIVKFLLNV SDSKSKIGLE
361     DSVESFLQDL TPSVDQARLL PSRAPLIQPA PSGSGAQDIR ELFRRQVIRC LEDQIQDHVE
421     EIENLKLLNK TWESKTRELR DALDRYESEG RRGRGPPAFD LQTLDTVNAL RRVQGLPTAP
481     VTVDDNRVVC NSFFSQFVPD ERESDERLSR LWEQEYFRCF KFRRNVTNQG AEDSISYSNY
541     TIERVLLPFL TAVIEFPMLD AIPEEYLFLS LSELANVIYE TSKLQRYTDY IRYRETIRVQ
601     AFLEREQATA AAAAAAGAAT AAAPSERIGR APGQVSGPPT KIRRLDETTP GTANYRPQQK
661     TIVTTTPIGL PPPSSPAPEV SPRFRSPQQK LETLRDRNVQ HLNG
```

```
SEQ         MCMV M105
KEYWORD     PROTEIN
SEQ ID NO:  67
1       MEKRSSDESV GNKGSDGGSG GLSRYDNIFV LNMSSASKIE RIVDRVKSLA LKRFSRESLY
61      KDWFRHMLDP CAGLVAPELG DDGSSEGGGN AAMIVGDREL ARRPPFLPFS CLLITGTAGA
121     GKTSSVQVLA ANLDCVITGS TVISSQALSS ALNRSRSAQI KTIFRTFGFN SRHVALADRV
181     HLRRRDDVAF DGDVDPICQQ QWRDLSTYWP VVSDIAIRAL DGGKGRKDTD DLCRSNIIVI
241     DECGVILRHM LHVVVFFYYF YNALNDSELY RQRAAPCIVC VGSPTQSEAL ESRYDHRTQN
301     RDVQRGMDVL SALISDPVLS EYCDVAHNWV MFINNKRCLD LEFGDLLKHI EFGLPLKSEH
361     VEYLDRFVRP AGLIRDPAHA IDVTRLFISH AEVKRYFTAL HDRVRIYSQH LIFEVPVYCV
421     LNNSAFHEYC ASMCTGEPTP RPETWFRKNL ARISNYSQFT DHNLSEDIQV EELAQSCGGG
481     GAGGDDDGFD LEEEMINETL LTCRITFIRD SAVGVTAKTK ACVVGYTGTF DDFAEILQKD
541     LFIERTPCEQ AVYAYSLISG LLFSAMYLFY SSPLTTPEIL RDLSEIPLPD IPTLVIGANG
601     GDGARDSDDN DEYEEDLEGG GCFDGVSGGG SGNGGGEKYR RRLTSDDEDD FYDLSYVDRG
661     RQPEPPQLQP PPQPQPQPRL TMSAALPPRQ IDEEISDVEM LCYSDIYTDK FFLKYSIPPP
721     VSSISFEEIV HIYTIFRDIF LARYRIMQKH TKGAFGKTRL VTYNRRNVWR RKNCEIESQT
781     GSFVGMLTFV SPSNNYVLEG FTNHNVFIMD AERNRIHRRI LEKGLPRLIV RDACGFLLIL
841     DYNVSKFSDV IDGKSVHICT MVDYGVTSRM AMTIAKSQGI GLESVAIDFG DNPKNLKMSQ
901     IYVGISRVVD PDRLVLNTNP VRNTYENNTF ITPFIRRALQ NKDTTLVF
```

```
SEQ         MCMV M114
KEYWORD     PROTEIN
SEQ ID NO:  68
1       MALRQWMLRH IAVHDVGAAA AGADVSADVI HQQAEALGIH EAWMSFLKLS ATQASQLVRI
61      TDRVDQERRM CTIYPEKSDV HRWSRLCFPY DVRVVILGQD PYHDGSACGL AFGTVRDRPA
121     PPSLVTVFKE LRRSIPEFSM PKCGCLDAWC REGVLLINTV FTVVKGQPGS HEALGWQILS
181     DRVLQALSEQ REGLVFLLWG LQAQKKEYLI DPRKHLILRS SHPSPRAQGA RNPFVGNNHF
241     VLANEYLSRR GERVDWNVLC SK
```

Figure 9

SEQ HSV-2 UL5
KEYWORD PROTEIN
SEQ ID No: 69

```
1       MAASGGEGSR DVRAPGPPPQ QPGARPAVRF RDEAFLNFTS MHGVQPIIAR IRELSQQQLD
61      VTQVPRLQWF RDVAALEVPT GLPLREFPFA AYLITGNAGS GKSTCVQTLN EVLDCVVTGA
121     TRIAAQNMYV KLSGAFLSRP INTIFHEFGF RGNHVQAQLG QHPYTLASSP ASLEDLQRRD
181     LTYYWEVILD ITKRALAAHG GEDARNEFHA LTALEQTLGL GQGALTRLAS VTHGALPAFT
241     RSNIIVIDEA GLLGRHLLTT VVYCWWMINA LYHTPQYAGR LRPVLVCVGS PTQTASLEST
301     FEHQKLRCSV RQSENVLTYL ICNRTLREYT RLSHSWAIFI NNKRCVEHEF GNLMKVLEYG
361     LPITEEHMQF VDRFVVPESY ITNPANLPGW TRLFSSHKEV SAYMAKLHAY LKVTREGEFV
421     VFTLPVLTFV SVKEFDEYRR LTQQPTLTME KWITANASRI TNYSQSQDQD AGHVRCEVHS
481     KQQLVVARND ITYVLNSQVA VTARLRKMVF GFDGTFRTFE AVLRDDSFVK TQGETSVEFA
541     YRFLSRLMFG GLIHFYNFLQ RPGLDATQRT LAYGRLGELT AELLSLRRDA AGASATRAAD
601     TSDRSPGERA FNFKHLGPRD GGPDDFPDDD LDVIFAGLDE QQLDVFYCHY ALEEPETTAA
661     VHAQFGLLKR AFLGRYLILR ELFGEVFESA PFSTYVDNVI FRGCELLTGS PRGGLMSVAL
721     QTDNYTLMGY TYTRVFAFAE ELRRRHATAG VAEFLEESPL PYIVLRDQHG FMSVVNTNIS
781     EFVESIDSTE LAMAINADYG ISSKLAMTIT RSQGLSLDKV AICFTPGNLR LNSAYVAMSR
841     TTSSEFLHMN LNPLRERHER DDVISEHILS ALRDPNVVIV Y
```

KEYWORD DNA (NC_001798 REGION: 11846..15249)
SEQ ID No: 70

```
   1 tttattgacc gttcgttcgc ccggcggtgc cgtcgccgcg cgcagaggga atatgcaagc
  61 gggcggggtg gggaggaaag aaggtttcag gttccggggg ttgggtctgc gtcgtccagg
 121 gtggggctga tctgaatttc ccgcagaacc tcgaccagta ggtctgttgt gtttgctggg
 181 aactcgcccg ccgttgggga tacgggggcg gggggtgtgg tcgggcggac gtccaggggt
 241 gcgttatcgc acccccgcgc cgcctcgggg gccgtcccgt agatcgttgc ggtgatgtag
 301 atggtgtccg gggtccacac caccgtcagg atgccggccg tcgcactccg gacgctttcg
 361 ccgtgcgatg agctgaccca ggagtcaaag gggtacgcgt acatatgggc gtcccaccag
 421 cgctccagcc tctgggtact agcgcgtcct ataaagcggt atgcgcaaaa ttcggcacga
 481 cagtcgataa tcaccagcag cccgatgggg gtgtgttgta tcaccacgcc tccgcggggc
 541 aggcggtcct ggcgcgctcg accccgcgtc agaaccgcgc gcgtccctga ctcaaacacg
 601 tgcaccacct gtgccgcgtc cggcagcgcg ctcgttagcg acgccctggg gtgatgtagg
 661 ctgtacgcga tggtcgtctg ggggttcccc atgtctcggg ggggtggggg tgaatgtcac
 721 ccggcccggg tgcggtggga acgcgaggga atggagggtt aatagacaat gaccacattc
 781 ggatcgcgta gagcagatag tatgtgctcg ctaatgacgt catcgcgttc gtggcgctcc
 841 cggagcgggt ttagattcat gtgcaggaac tcggatgagg tggtgcggga catggctacg
 901 tacgcgctgt ttaggcgcag gtttccgggc gtgaagcata tggcgacctt gtccagactg
 961 agcccctggg agcgcgtgat ggtcatcgcg agtttggagc tgatgccgta gtcggcgttg
1021 atggccatgg ccagctccgt ggagtcgatc gactcgacaa actcactgat gttggtattg
1081 acgacagaca tgaagccgtg ctggtcccgc aggacgatgt agggcagggg ggactcctcc
1141 aagaactcgg ccacgccggc cgtcgcgtgc cgccgccgca gctcctccgc gaacgcgaac
1201 acccgggtgt acgtgtaccc catcagcgtg tagttgtccg tctgcagggc cacggacatc
1261 agccccccgc gcggcgagcc ggtcagcagc tcgcagcccc ggaaaatgac attgtccacg
1321 taggtgctga agggggcgct ctcaaacacc tccccgaaga gctcccgtag gataaggtat
1381 cgccccagaa aggccctctt caggagccca aactgggcgt ggacggccgc ggtggtctca
1441 ggctcttcga gggcgtagtg gcagtagaac acgtccagct gctgttcgtc cagcccggcg
1501 aagataacgt caaggtcgtc gtcggggaag tcgtccgggc ccccgtcccg cgggcccagg
1561 tgcttaaaat tgaacgcacg ctcccccgga gagcggtcgc tggtgtcggc ggccctggtt
1621 gccgatgcgc cggcggcgtc ccggcgtagc gacaggagtt ctgccgtcag ctcccctagg
1681 cggccgtagg ccagggtcct ctgggtcgcg tccaggccgg ggcgctggag aaagttgtaa
1741 aagtgaatca gcccgccgaa catgagccgc gacaggaacc ggtaggcgaa ctccaccgag
1801 gtctcccccc gggtcttcac gaagctgtcg tcgcgcagca cagcctcgaa ggtccgaaac
1861 gtcccgtcga acccaaacac catctttcgg aggcgcgcgg tcaccgcgac ctggctgttg
1921 aggacgtacg tgatgtcgtt ccgggccacg actagctgtt gcttgctgtg cacctcacag
1981 cgcacgtgcc ccgcgtcctg gtcctgactc tgggagtagt tggtgatgcg actggcgttg
2041 gccgtgatcc acttttccat ggtcagcgtg ggttgctgcg tgagccgtcg atactcgtca
2101 aactctttga ccgacacaaa cgtgagcacg gggagggtaa acacaacaaa ctccccctcg
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2161 cgagtcacct ttaggtaggc gtggagcttg gccatgtacg cgctgacctc cttgtgggac
2221 gagaacagcc gcgtccaccc cggaaggttg gccgggttgg tgatgtaact ttccgggacg
2281 acaaagcggt ccacaaactg catgtgctcc tcggtgatgg gaaggccgta ctccagcacc
2341 ttcatgaggt tcccgaactc gtgctccaca catcgcttgt tgttaatgaa aatggcccag
2401 ctgtgcgaga ggcgcgtgta ctcgcgtagg gtgcggttgc agatgaggta cgtgagcacg
2461 ttttcgctct gccggacgga gcatcgcagt ttttggtgtt cgaaggtgga ctccagcgag
2521 gccgtctggg tcggcgaccc cacgcacacc agcaccggcc gcaggcggcc cgcgtactgg
2581 ggggtgtggt acagggcgtt aatcatccac cagcaataca ccacggtcgt gagtaggtgc
2641 cgccccagga gcccggcctc gtcgatgacg ataatgttgc tgcgggtgaa agccggcagc
2701 gccccgtgtg tgaccgaggc caggcgcgtg agggcaccct ggcccagccc caaagtctgc
2761 tctagggcgg tgagggcgtg gaactcgttt cgcgcgtctt cgcccccgtg cgccgccagg
2821 gcccgcttgg tgatgtcgag gatcacctcc cagtagtacg tcaggtctcg ccgctgcagg
2881 tcttccagcg aggcggggct gctggccagg gtgtacgggt gctgccccag ctgggcctgg
2941 acgtgattcc cgcgaaaccc gaactcgtga aagatggtgt tgatgggtcg actcagaaac
3001 gccccgaga gcttaacgta catgttctgc gccgcgattc gcgtggcgcc cgtgaccacg
3061 cagtccagga cctcgttgag ggtctgcacg cacgtactct ttccggatcc ggcgttgccg
3121 gtgatgagat acgccgcgaa cggaaactcc cggagcggca ggccggtcgg gacctccaag
3181 gccgccacgt cccggaacca ctgcaggcgc ggcacctgcg tgacgtcgag ctgctgctgc
3241 gagagctctc ggatgcgtgc gatgattggt tggaccccgt gcatggacgt aaaatttaaa
3301 aacgcctcgt ccctgaaccg cacggcgggt ctggccccgg gctgctgtgg gggcggacct
3361 ggtgcccgga cgtcccgcga gccctccccg ccggacgccg ccat
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SEQ HSV-2 UL6
KEYWORD PROTEIN
SEQ ID No: 71

```
1       MAAQRARAPA MRTRGGDAAL CAPEDGWVKV HPTPGTMLFR EILLGQMGYT EGQGVYNVVR
61      SSEAATRQLQ AAIFHALLNA TTYRDLEEDW RRHVVARGLQ PQRLVRRYRN AREGDIAGVA
121     ERVFDTWRCT LRTTLLDFAH GVVDCFAPGG PSGPTSFPKY IDWLTCLGLV PILRKTREGE
181     ATQRLGAFLR QHTLPRQLAT VAGAAERAGP GLLDLAVAFD STRMAEYDRV HIYYNHRRGE
241     WLVRDPVSGQ RGECLVLCPP LWTGDRLVFD SPVQRLCPEI VACHALREHA HICRLRNTAS
301     VKVLLGRKSD SERGVAGAAR VVNKALGEDD ETKAGSAASR LVRLIINMKG MRHVGDINDT
361     VRAYLDEAGG HLIDTPAVDH TLPGFGKGGT GRGSRPQDPG ARPQQLRQAF QTAVVNNING
421     MLEGYINNLF GTIERLRETN AGLATQLQAR DRELRRAQAG ALEREQRAAD RAAGGGAGRP
481     AEADLLRADY DIIDVSKSMD DDTYVANSFQ HQYIPAYGQD LERLSRLWEH ELVRCFKILR
541     HRNKQGQETS ISYSSGAIAS FVAPYFEYVL RAPRAGALIT GSDVILGEEE LWEAVFKKTR
601     LQTYLTDVAA LFVADVQHAA LPRPPSPTPA DFRASASPRG GSRSRTRTRS RSPGRTPRGA
661     PDQGWGVERR DGRPHARR
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KEYWORD DNA(NC_001798 REGION: 15248..18163)
SEQ ID No: 72

```
   1 atggccgcac agcgcgcgcg ggcgccggcg atgcggacgc ggggcggcga cgcggcgcta
  61 tgcgcccccg aggacggctg ggtgaaggtt caccccaccc ccgggacgat gttgttccgc
 121 gagattctcc tcgggcagat ggggtacacc gagggtcagg gggtgtacaa cgtcgtccgg
 181 tccagcgagg ccgccacccg acagctgcag gcggcgatct tccacgcgct cctcaacgcc
 241 acgacgtacc gggacctgga ggaggactgg cgccgccacg tggtggcccg cggcctccag
 301 ccgcagcggc tggttcgcag gtaccggaac gcccgggagg gcgatatcgc cggggtggcc
 361 gagcgggtgt tcgacacgtg gcgatgcacg ctcaggacga cgctgctgga ctttgcccac
 421 ggggtggtag actgctttgc gccgggcggc ccaagcggac cgaccagctt ccccaaatat
 481 atcgactggc tgacgtgtct ggggctggtt cccatattgc gcaagacgcg cgaggggggag
 541 gcgacgcagc gcctgggggc gtttctcagg cagcacacgc tgccccggca gctggccacg
 601 gtcgccgggg ccgcggagcg cgccggcccg gggcttctgg atctggccgt cgcgttcgac
 661 tccacgcgca tggcggaata cgaccgcgtg cacatctact acaaccatcg ccgggggggag
 721 tggctggtgc gcgacccggt cagcgggcag cgcggcgagt gcctggtgct gtgccccccc
 781 ctgtggaccg gcgaccgcct ggtcttcgat tcgcccgttc agcggctgtg ccccgagatc
 841 gtcgcgtgcc acgccctccg ggaacacgcg cacatctgcc gtctgcgcaa caccgcgtcc
 901 gtcaaggtgc tgttggggcg caagagcgac agcgagcgcg gggtggctgg cgccgcgcgg
 961 gtcgtcaata aggcgctggg ggaggatgac gagacgaagg ccggctcggc cgcctcgcgt
1021 ctcgtgcggc tcatcatcaa catgaagggc atgcgccacg tgggcgacat caacgacacg
1081 gtacgcgcct acttggacga ggcgggggggg cacctgatcg acacccccgc cgtcgaccac
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1141 accctccctg ggttcggcaa gggcggcacc ggccgcgggt cgcgccccca ggacccgggg
1201 gcgcgaccgc agcagcttcg ccaggcgttt cagacggccg tggtcaacaa catcaacggc
1261 atgctggagg gctatatcaa taatctcttt ggaaccatag aacgcctgcg agagacgaac
1321 gcgggtctgg cgacccagct gcaggcgcgc gaccgcgagc tgcggcgcgc ccaggcgggg
1381 gcgctggagc gggagcagcg cgcggcggac cgggcggccg ggggaggcgc gggccgcccg
1441 gcggaggcgg atcttctccg ggccgactac gacattatcg acgtcagcaa gtccatggac
1501 gacgacacgt acgtggccaa cagtttccag caccagtaca tccccgcgta cggccaggac
1561 ctcgagcgcc tgtcgcgcct ctgggagcac gagctggtgc gctgcttcaa gattctgcgc
1621 caccgcaaca agcagggcca ggaaacgtcg atctcgtact ctagcggggc gatcgcctcc
1681 ttcgtggccc cgtatttcga gtacgtgctt cgcgcccccc gagcgggcgc gctcatcacc
1741 ggctccgatg tcatcctagg ggaggaggag ttatgggagg cggtctttaa gaaaacccgc
1801 ctgcagacgt acctgacaga cgtcgcggcc ctgttcgtgg cggacgtaca gcacgcggct
1861 ctgccccggc ccccctcccc aacccccgcc gatttccggg cgagcgcgtc cccgcggggc
1921 gggtcccggt cccggacccg gacccgatcc cggtcgcccg ggagaacgcc gaggggtgcg
1981 ccggaccagg gctggggcgt cgaacgcagg gatggccgac cccacgcccg ccgatgaggg
2041 aacggccgcc gccatcctca aacaggccat cgccggggac cgcagtctgg tcgaggtggc
2101 ggaggggatc agcaaccagg cgctgctgcg catggcctgc gaggtgcgcc aggtcagcga
2161 tcgccagccg cggtttaccg cgaccagcgt cctgcgcgtt gacgtcaccc ccaggggcg
2221 gttgcggttc gttctggacg ggagttccga cgacgcgtac gtggcgtcgg aggattactt
2281 taagcgctgc ggggaccagc cgacgtatcg cggttttgcg gtcgtcgtcc tcacggccaa
2341 cgaggaccac gtgcacagcc tggccgtgcc ccccctcgtt ctgctgcacc ggctctcctt
2401 gtttcgcccc acggacctcc gggacttcga gctcgtctgc ctgctgatgt acctggagaa
2461 ctgtccccgg agccacgcca cgccctcgct gttcgtcaag gtgtcggcgt ggttgggggt
2521 cgtggcccgc cacgcgtctc ccttcgagcg cgtccgctgc cttctcctcc gcagctgcca
2581 ctggatcctg aacacgctaa tgtgcatggc gggcgtgaag cccttcgacg acgagctagt
2641 cctgccccac tggtacatgg cccactacct gctggccaac aatccgcccc ccgtcctctc
2701 ggccctgttt tgcgccaccc cgcagagctc tgcgttgcag ttgcccgggc ccgtcccccg
2761 cacggactgt gtggcctata acccggccgg cgtcatggga agctgctgga attccaagga
2821 cctgcgttcg gctctggtgt attggtggct ttcggggagc cccaaacgac ggacctcgtc
2881 gcttttctat cggttttgct aactccggaa aataaa
```

SEQ HSV2 UL8
KEYWORD PROTEIN
SEQ ID No: 73

```
1    MEAPGIVWVE ESVSAITLYA VWLPPRTRDC LHALLYLVCR DAAGEARARF AEVSVGSSDL
61   QDFYGSPDVS APGAVAAARA ATAPAASPLE PLGDPTLWRA LYACVLAALE RQTGRWALFV
121  PLRLGWDPQT GLVVRVERAS WGPPAAPRAA LLDVEAKVDV DPLALSARVA EHPGARLAWA
181  RLAAIRDSPQ CASSASLAVT ITTRTARFAR EYTTLAFPPT RKEGAFADLV EVCEVGLRPR
241  GHPQRVTARV LLPRGYDYFV SAGDGFSAPA LVALFRQWHT TVHAAPGALA PVFAFLGPGF
301  EVRGGPVQYF AVLGFPGWPT FTVPAAAAAE SARDLVRGAA ATHAACLGAW PAVGARVVLP
361  PRAWPAVASE AAGRLLPAFR EAVARWHPTA TTIQLLDPPA AVGPVWTARF CFSGLQAQLL
421  AALAGLGEAG LPEARGRAGL ERLDALVAAA PSEPWARAVL ERLVPDACDA CPALRQLLGG
481  VMAAVCLQIE QTASSVKFAV CGGTGAAFWG LFNVDPGDAD AAHGAIQDAR RALEASVRAV
541  LSANGIRPRL APSLAPEGVY THVVTWSQTG AWFWNSRDDT DFLQGFPLRG AAYAAAAEVM
601  RDALRRILRR PAAGPPEEAV CAARGVMEDA CDRFVLDAFG RRLDAEYWSV LTPPGEADDP
661  LPQTAFRGGA LLDAEQYWRR VVRVCPGGGE SVGVPVDLYP RPLVLPPVDC AHHLREILRE
721  IQLVFTGVLE GVWGEGGSFV YPFDEKIRFL FP
```

KEYWORD DNA(NC_001798 REGION: 18393..20665)
SEQ ID No: 74

```
   1 tttattgacc aaattcaggg aaacagaaac cgaatctttt catcgaaagg gtacacaaag
  61 ctcccgccct cgccccacac gccttccaga acccccgtaa acaccagttg aatctcgcgc
 121 aggatctcgc gcaggtgatg ggcgcagtcc acgggggga gcaccaaggg ccgcgggtac
 181 agatccacgg ggacgccgac cgactccccg cccccgggac atacgcgcac gacgcgtctc
 241 cagtattgct ccgcgtccag cagggcgcct ccgcggaagg ccgtttgggg caggggtcg
 301 tcggcctcgc ctgggggggt cagaacgctc cagtactccg cgtccagacg cctcccgaag
 361 gcatccagga caaagcggtc acaggcgtcc tccatgacgc cccgggccgc gcacacggcc
 421 tcctccggcg ggccggcggc cggccgccgg aggattcgtc tcagcgcgtc gcgcataacc
 481 tcggccgccg cggcgtacgc ggccccgcgg agaggaaatc cctgcaggaa gtcggtgtca
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```
 541 tcgcgggagt tccagaacca cgccccggtc tggctccagg tgacgacgtg ggtgtagacg
 601 ccctctggcg ccagggaggg ggcgaggcgc gggcgtatgc cgttggccga aagtacggcg
 661 cgcacggacg cctcgagggc ccggcgggcg tcctggatcg cgccgtgcgc ggcgtccgcg
 721 tccccggggt ccacgttgaa cagcccccag aacgcagccc cggtgccgcc gcagaccgca
 781 aacttcaccg agctggccgt ctgctcgatc tgcaggcaga cggcggccat gaccccgccg
 841 agcagctgcc ggagcgcggg gcaggcgtcg cacgcgtccg gcaccaggcg ctccagcacg
 901 gcccgggccc agggctccga gggggcggcc gccaccagcg cgtccagcct ttccaggccc
 961 gcccgccccc gggcttccgg cagcccggcc tccccgaggc ccgcgagggc ggccaggagc
1021 tgggcctgga gcccggagaa acaaaaccgc gccgtccaga ccggcccgac ggccgccggg
1081 gggtcgagta gttggatggt ggtggccgtg gggtgccacc gcgcgaccgc ttcccgaaag
1141 gcgggcagga ggcggccggc cgcctccgag gccacggccg gccatgcccg cgggggcagg
1201 acgaccctgg cgcccaccgc gggccaggcc cccaggcacg cggcatgggt ggccgcggcg
1261 ccccgcacca ggtcacgcgc cgactcggcg gcggcggcgg ccggcacggt aaacgtgggc
1321 cagcccggaa atcccagcac ggcaaagtat tggacgggcc ctccccggac ctcaaacccg
1381 ggccccagaa aagcgaagac gggggccagg gctccgggggg cggcgtggac cgtggtatgc
1441 cactgccgga agagggcgac cagcgccggg gcggagaacc cgtcgccggc gctcacgaag
1501 tagtcgtagc cgcgcggcag cagcacccgc gccgtgaccc gctgcgggtg tccgcggggc
1561 cgcaggccga cctcgcacac ctcgaccagg tccgcgaagg cgccctcctt cctggtcggc
1621 ggaaacgcca gggtggtgta ttcgcgcgca aaacgcgcgg tcctcgtcgt gatggtgacg
1681 gcgagcgagg cggaggacgc gcactggggg ctgtcgcgaa tggcggccag gcgcgcccac
1741 gccaaccgcg cgccggggtg ctcggcgacg cgcgcggaca gggccagcgg gtcgacgtcg
1801 accttggcct ccacgtccag gagggcggcg cgaggagcgg ccggcgggcc ccacgacgcc
1861 ctttcgaccc tcacgaccag acccgtctgc gggtcccagc ccaggcgcag cgggacgaag
1921 agggcccacc ggcccgtctg gcgctccagg gccgccagaa cgcacgcata cagcgcccgc
1981 cacagggtcg ggtcccccag gggctccagc ggggaggcgg ccggggccgt cgcggcgcgg
2041 gcggccgcga cggccccggg ggccgagacg tcgggggagc cgtagaagtc ctgcaggtcg
2101 gacgaaccaa cggacacctc cgcgaagcgc gcgcgcgcct cccccgcggc gtcgcgacag
2161 accagataca gcagggcgtg gaggcagtcg cgcgtgcgcg ggggcagcca taccgcgtat
2221 agggtaatgg cgctgacgct ctcctccacc caaacgatgc cgggggcttc cat
```

SEQ HSV2 UL15
KEYWORD PROTEIN
SEQ ID No: 75

```
1    MFGQQLASDV QQYLERLEKQ RQQKVGVDEA SAGLTLGGDA LRVPFLDFAT ATPKRHQTVV
61   PGVGTLHDCC EHSPLFSAVA RRLLFNSLVP AQLRGRDFGG DHTAKLEFLA PELVRAVARL
121  RFRECAPEDA VPQRNAYYSV LNTFQALHRS EAFRQLVHFV RDFAQLLKTS FRASSLAETT
181  GPPKKRAKVD VATHGQTYGT LELFQKMILM HATYFLAAVL LGDHAEQVNT FLRLVFEIPL
241  FSDTAVRHFR QRATVFLVPR RHGKTWFLVP LIALSLASFR GIKIGYTAHI RKATEPVFDE
301  IDACLRGWFG SSRVDHVKGE TISFSFPDGS RSTIVFASSH NTNGIRGQDF NLLFVDEANF
361  IRPDAVQTIM GFLNQANCKI IFVSSTNTGK ASTSFLYNLR GAADELLNVV TYICDDHMPR
421  VVTHTNATAC SCYILNKPVF ITMDGAVRRT ADLFLPDSFM QEIIGGQARE TGDDRPVLTK
481  SAGERFLLYR PSTTTNSGLM APELYVYVDP AFTANTRASG TGIAVVGRYR DDFIIFALEH
541  FFLRALTGSA PADIARCVVH SLAQVLALHP GAFRSVRVAV EGNSSQDSAV AIATHVHTEM
601  HRILASAGAN GPGPELLFYH CEPPGGAVLY PFFLLNKQKT PAFEYFIKKF NSGGVMASQE
661  LVSVTVRLQT DPVEYLSEQL NNLIETVSPN TDVRMYSGKR NGAADDLMVA VIMAIYLAAP
721  TGIPPAFFPI TRTS
```

KEYWORD DNA(NC_001798 REGION: 28969..34829)
SEQ ID No: 76

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   1 atgtttggcc agcagctggc gtccgacgtg cagcagtacc tggagcgcct ggagaaacag
  61 aggcaacaga aggtgggcgt cgacgaggcg tcggcgggcc tgacgctcgg cggcgatgcg
 121 ctgcgcgtcc ctttttgga ttttgccacc gcgacgccca agcgccacca gaccgtggtc
 181 ccgggcgtcg ggacgctcca cgactgctgc gagcactcgc cgctcttctc ggccgtcgcg
 241 cggcggttgc tgtttaatag cctggtgccg gcgcaactca gggggcgtga ctttgggggc
 301 gaccacacgg ccaagctgga gttcctggcc cccgagctgg tgcgggcggt ggcgcgcctg
 361 cggtttcggg agtgcgcgcc ggaggacgcc gtgccccaac gcaacgccta ctacagcgtc
 421 ctgaacacgt ttcaggccct gcaccgctcc gaagcctttc ggcagttggt tcacttcgtg
 481 cgggacttcg cccagttgtt gaaaacctcg ttccgggcct ctagtctcgc ggagactacg
 541 ggcccccga agaaacgggc caaggtggac gtggccaccc acgggcagac gtacggcacc
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601 ttggagctct tccagaaaat gatactaatg cacgcgacct actttctggc cgccgtgctg
661 ctcggggacc acgcggagca ggtcaacacg ttcctgcggc tcgtgttcga gatccccctg
721 tttagcgaca cggccgtgcg gcacttccgc cagcgcgcca ccgtgtttct agtccccagg
781 cgccacggaa agacctggtt tttggtgccc ctcatcgcgc tgtcgctcgc gtccttccgg
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901 atcgacgcct gcctgcgggg ctggtttggc tcgtcccggg tggaccacgt caaggggaa
961 accatctcgt tctcgttccc ggacggctcg cgcagcacga tcgtgtttgc ctccagccac
1021 aacacgaacg taagtacgcc ttcctcccgc ggtgcctgtt tccccggtgc cgccctcccc
1081 gagatcgacc gacagacaaa cacagccaga cgcgagtgtg ggacgacacg cccgcagccc
1141 ccccccccgcc atggcggggg ggaagcctta ctgtttattt gtaatcggac gatgaggctc
1201 tggccacggc ccgcgcgacc gcggggcagc tcgttgcaaa caggcggctg gtatacgatg
1261 acagaacgca gaggcgccac ccggcgctgg tcgggcggat gacgctttcc gcgccgtccc
1321 ggcccacgac gacctcgtgc aggtgggccg tgatgcgcgg gcggcgggtc gcctgccgca
1381 ggataaccgc gtccacgggg tgcccgaaga ggagctgaca caggctcgcg tccccccgga
1441 cggccagggt gcgctgggcc atattggacc acatgcacgg ggcgacgcag ggacaggcct
1501 ccgccacggc gggggcgcgc cacagcgcgt tggcggaatc gatgtgggcc gtcggggcgc
1561 aggcgccgcc tcctcccggg gggtcggtaa tcctggatag cagccatcct aaatggcggg
1621 cccggctgcc cgggggacag agcgacccca ggtcatcatc catggcccag cagtatatgc
1681 ggccgccggg gaggtgccac caggcccccg gacccagggc acagcacgcc ccggattcgg
1741 gggccgtgtc cgtgggtacc aggtaggcgc cgtcgagctc gtgggccacg ggctcgtccg
1801 cgagctgttc ggcggcgggg tcgggggttt cctccggggg ggaggcagct tccaggtggc
1861 cgaaggctag ggtgcacagc agcggggtcc gggggtgcgt tacgctgcgg aggtggacgg
1921 tggcgcagta gcggcgctcg cggttaaaga agaaaatggc aaagaacgtg ttcgaaggca
1981 ggcgcagcgc cttgggccgc gtcaggtaca ggaagatctc gcagaaaagg gcacgctcgg
2041 ggtcggggtc cggaagggcc acctggcaca gcggctcggt gaggaccgtg aggcaccgaa
2101 aaatcttaag ccgctcgtcc ccccgaacga cgcgccacac gaagacagag ttggcgatgc
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2221 ggtgacccgg cggggccgcg gctcccgggg ggcctggcgt cgcctgggga cgccagagtg
2281 cccgctgtgc caggttggtg gtggggaagg gaccggagac gcaccaaaag cagaggggcc
2341 agcgcgtgta tgagttgggg ggggggtggg tgagcggtgg aacaaaagca cgcgtcagcg
2401 gacaaggccg ggtcccgtag ccgccccgcg acagaaccgg agtccgacgg cacgcgcgac
2461 ggggtctgcg aggctgaggt acgccgcggt gttaatggta aacgcaaagc ctcccggaaa
2521 gaccactagc ccgcagaggc ggcgattgaa cccaaggcag aggtacgcgt agctctctcc
2581 cggaaggtat tgctcgcaga ccctgtgtgg ggcagtggag gggctgccct ccatgaagcg
2641 acatttactc tgctcgcgtc cattgacgtc accgtcaatc accactgcga ttggacggtt
2701 ggtgaggcgc agcgtgtctc cgctggtgct gtagtagtca aacgcgtagt gggcgtcgga
2761 gtcggcgaag cgggcgggga tgtcgtcgct gagagggacg agccgccgcc gccgcccccg
2821 accgccctgg ccgcccagat gcgccagcac ggccagggcg tacgcggtgt gaaagaacgc
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3001 gatgcgcggg ccgccttgga gcgcggcccg gatagagtgg cccagggccc gcagacacgc
3061 gatctggatg cgcgcgacga aggccacctc ggccgcgatg tcaaagggct gcagcacggg
3121 gcgcgggtgg cgcagggtc cctcgagcgc gggaaagcga cgcagcagcg ccgtctgggc
3181 cgcgggggac agctggtggg ggcgcacgac gcgctcggcg gcacaggcct ccgtcagggc
3241 cgtggccagc tcggaggaca gccgcggggg gcgggcgcgt cgcccgcccc acgccaccga
3301 attctcgtag gagacgacga cgaagcgctg cttggtcccg tagtgatggc gcaggaccac
3361 ggagatggag cgacggctcc acagccagtc gggccggtcg ccgccggcca gagcttccca
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3601 cccgctgacg gcctggtgga ccagggcgcc ctggcggagc cccgaggcga cgccggaggc
3661 cgcgtgcttg gggcgcgcgc ggaccgggtg gcggcgggtg acgtcctgca cggcccgctg
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3781 gtcgcctccc ggggccgtga gctgctcctc cggggagatg gggggtctg gggtgccgac
3841 aacggccggc ccggccccgc ccgagaccga ggacgcctgg ggagtggggg tgccgctttc
3901 ccccatcccc agggacaggt gggccgccgc ctccgtcgcg gcggcgggag ccgcggcccc
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4021 cgcgtatcgc gtgtttggcg ggacgagctc gtcgtaactg aacaggagca cgcgggcaca
4081 ggtcgcccac gggccccacg ccaggcgcag cgccgcgacc gtgtacgggt cgtacacgcc
4141 ttgggcgtcg cacgcgaccg gcagggagac gaacagcccg cccgcgctgg ggacgcgcgg
4201 caggaggtcc gggtgcgccg ggatgacggg ggctaggatc gcccccaccg catccgccgg
4261 cacgtaggcg gcaaacgccg aacgccacgg ggtgcagtcg ccggtcgcgt gggcccgggt

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4321 ctgggtttcg acccggaagt tcgcggccgc cccaccgtcg gggcggccgc gcacgagggc
4381 ggacagcggg acccccgccg ccgccaggca ctcgctggag atgatgacgt gaatcagcga
4441 ggcggggctg ctcgggtccc gggtgagatc gtattggacc tcgttggcaa agtgcgcgtt
4501 catggcccgg ccggcggtgc gagccctccc cggtgccgga aggggcgtgg gtgggggtg
4561 cgtgtgcgcg tcctcggggc ccgcgggcgc acgtgcgctt atacgctgtg tgtttcgtct
4621 gtccccaggg aatccggggc caggacttta acctgctttt cgtcgacgag gccaacttta
4681 ttcgcccgga tgcggtccag acgattatgg gctttctcaa tcaggccaac tgcaagatca
4741 tcttcgtctc gtcgaccaac accgggaagg ccagcacgag ctttttgtac aacctccgcg
4801 gggccgccga cgagctgctc aacgtggtca cctatatatg cgacgaccac atgccgcggg
4861 tggtgacgca caccaacgcc acggcctgtt cctgctatat cctgaacaaa cccgtgttta
4921 tcacgatgga cggcgccgtt cgccggacgg ccgatctgtt tctgcccgac tccttcatgc
4981 aggagatcat cgggggcag gcccgcgaga ccggcgacga ccggcccgtc ctaacaaagt
5041 cggcgggga gcggtttctg ctgtaccgcc cctccaccac caccaacagc ggcctgatgg
5101 cccccgagct gtacgtgtac gtggacccgg cgttcacggc caacacgcgc gcctccggca
5161 ccggcatcgc ggtcgtcggg aggtaccgcg acgatttcat tatcttcgcc ctggagcact
5221 ttttcctccg cgcgctcacg ggatcggccc ccgcggacat cgcccgctgc gtcgtgcaca
5281 gcctcgccca ggtgctggcg ctgcaccccg gggcgtttcg cagcgttcgc gtggcggtcg
5341 agggcaacag cagccaggac tcggccgtgg ccatcgccac acacgtgcat accgagatgc
5401 accgcatcct ggcctcggcg ggggccaacg gcccggggcc cgagctcctc ttctatcact
5461 gcgagccgcc cggcggcgcg gtattgtacc ccttctttct gctcaacaaa cagaagacgc
5521 ccgccttcga atactttatc aaaaagttca actccggggg cgtcatggcg tcccaggagc
5581 tcgtctccgt gacggtgcgc ctgcagaccg acccggtcga gtatctgtcc gagcagctca
5641 acaacctcat cgaaaccgtc tctcccaaca ccgacgtccg catgtactcc ggaaaacgca
5701 acggtgccgc ggacgacctc atggtcgcgg tcatcatggc catttacctg gcggccccga
5761 ccgggatccc cccggccttt tttccgatca cgcgcacgtc ttgagtcttt cttgccgttt
5821 cttttgtttc tctttctttc ccccctctc tccgcaataa a
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SEQ HSV-2 UL17
KEYWORD PROTEIN
SEQ ID No: 77

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1   MNAHFANEVQ YDLTRDPSSP ASLIHVIISS ECLAAAGVPL SALVRGRPDG GAAANFRVET
61  QTRAHATGDC TPWRSAFAAY VPADAVGAIL APVIPAHPDL LPRVPSAGGL FVSLPVACDA
121 QGVYDPYTVA ALRLAWGPWA TCARVLLFSY DELVPPNTRY AADGARLMRL CRHFCRYVAR
181 LGAAAPAAAT EAAAHLSLGM GESGTPTPQA SSVSGGAGPA VVGTPDPPIS PEEQLTAPGG
241 DTATAEDVSI TQENEEILAL VQRAVQDVTR RHPVRARPKH AASGVASGLR QGALVHQAVS
301 GGALGASDAE AVLAGLEPPG GGRFASRGGP RAAGEDVLND VLTLVPGTAK PRSLVEWLDR
361 GWEALAGGDR PDWLWSRRSI SVVLRHHYGT KQRFVVVSYE NSVAWGGRRA RPPRLSSELA
421 TALTEACAAE RVVRPHQLSP AAQTALLRRF PALEGPLRHP RPVLQPFDIA AEVAFVARIQ
481 IACLRALGHS IRAALQGGPR IFQRLRYDFG PHQSEWLGEV TRRFPVLLEN LMRALEGTAP
541 DAFFHTAYAL AVLAHLGGQG GRGRRRRLVP LSDDIPARFA DSDAHYAFDY YSTSGDTLRL
601 TNRPIAVVID GDVNGREQSK CRFMEGSPST APHRVCEQYL PGESYAYLCL GFNRRLCGLV
661 VFPGGFAFTI NTAAYLSLAD PVARAVGLRF CRGAATGPGL VR
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KEYWORD DNA(NC_001798 REGION: 30142..33471)
SEQ ID No: 78

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1 tttatttgta atcggacgat gaggctctgg ccacggcccg cgcgaccgcg gggcagctcg
61 ttgcaaacag gcggctggta tacgatgaca gaacgcagag gcgccacccg gcgctggtcg
121 ggcggatgac gctttccgcg ccgtcccggc ccacgacgac ctcgtgcagg tgggccgtga
181 tgcgcgggcg gcgggtcgcc tgccgcagga taaccgcgtc cacggggtgc ccgaagagga
241 gctgacacag gctcgcgtcc ccccggacgg ccagggtgcg ctgggccata ttggaccaca
301 tgcacggggc gacgcaggga caggcctccg ccacggcggg ggcgcgccac agcgcgttgg
361 cggaatcgat gtgggccgtc ggggcgcagg cgccgcctcc tcccgggggg tcggtaatcc
421 tggatagcag ccatcctaaa tggcgggccc ggctgcccgg gggacagagc gaccccaggt
481 catcatccat ggcccagcag tatatgcggc cgccggggag gtgccaccag gcccccggac
541 ccagggcaca gcacgccccg gattcggggg ccgtgtccgt gggtaccagg taggcgccgt
601 cgagctcgtg ggccacgggc tcgtccgcga gctgttcggc ggcggggtcg ggggtttcct
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781 aaatggcaaa gaacgtgttc gaaggcaggc gcagcgcctt gggccgcgtc aggtacagga
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 841 agatctcgca gaaaagggca cgctcggggt cggggtccgg aagggccacc tggcacagcg
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1141 cggagacgca ccaaaagcag aggggccagc gcgtgtatga gttgggggcg gggtgggtga
1201 gcggtggaac aaaagcacgc gtcagcggac aaggccgggt cccgtagccg ccccgcgaca
1261 gaaccggagt ccgacggcac gcgcgacggg gtctgcgagg ctgaggtacg ccgcggtgtt
1321 aatggtaaac gcaaagcctc ccggaaagac cactagcccg cagaggcggc gattgaaccc
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1621 agggacgagc cgccgccgcc gcccccgacc gccctggccg cccagatgcg ccagcacggc
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1741 gttctccagg agcacgggga agcgccgcgt cacctcccct agccactcgc tctggtgggg
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1861 agagtggccc agggcccgca gacacgcgat ctggatgcgc gcgacgaagg ccacctcggc
1921 cgcgatgtca aagggctgca gcacggggcg cgggtggcgc aggggtccct cgagcgcggg
1981 aaagcgacgc agcagcgccg tctgggccgc gggggacagc tggtgggggc gcacgacgcg
2041 ctcggcggca caggcctccg tcagggccgt ggccagctcg gaggacagcc gcgggggcgg
2101 ggcgcgtcgc ccgccccacg ccaccgaatt ctcgtaggag acgacgacga agcgctgctt
2161 ggtcccgtag tgatggcgca ggaccacgga gatggagcga cggctccaca gccagtcggg
2221 ccggtcgccg ccggccagag cttcccaccc gcggtccagc cactcgacca gcgatcgcgg
2281 cttggcggtc cccggcacga gggtgagcac gtcgttgagg acgtcctcgc ccgcggcccg
2341 ggggcccccc cggctggcaa agcgcccccc gccgggcggc tccaggcccg ccagcaccgc
2401 ctccgcgtcc gacgcgccca gggctccccc gctgacggcc tggtggacca gggcgccctg
2461 gcggagcccc gaggcgacgc cggaggccgc gtgcttgggg cgcgcgcgga ccgggtggcg
2521 gcgggtgacg tcctgcacgg cccgctggac cagcgcgagg atctcctcgt tctcttgcgt
2581 gatggacacg tcctccgcgg tggccgtgtc gcctcccggg gccgtgagct gctcctccgg
2641 ggagatgggg gggtctgggg tgccgacaac ggccggcccg gccccgcccg agaccgagga
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2881 gtaactgaac aggagcacgc gggcacaggt cgcccacggg ccccacgcca ggcgcagcgc
2941 cgcgaccgtg tacgggtcgt acacgccttg ggcgtcgcac gcgaccggca gggagacgaa
3001 cagcccgccc gcgctgggga cgcgcggcag gaggtccggg tgcgccggga tgacgggggc
3061 taggatcgcc cccaccgcat ccgccggcac gtaggcggca aacgccgaac gccacggggt
3121 gcagtcgccg gtcgcgtggg cccgggtctg ggtttcgacc cggaagttcg cggccgcccc
3181 accgtcgggg cggccgcgca cgagggcgga cagcgggacc cccgccgccg ccaggcactc
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SEQ HSV2 UL29
KEYWORD PROTEIN
SEQ ID No: 79

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1       MDTKPKTTTT VKVPPGPMGY VYGRACPAEG LELLSLLSAR SGDADVAVAP LIVGLTVESG
61      FEANVAAVVG SRTTGLGGTA VSLKLMPSHY SPSVYVFHGG RHLAPSTQAP NLTRLCERAR
121     PHFGFADYAP RPCDLKHETT GDALCERLGL DPDRALLYLV ITEGFREAVC ISNTFLHLGG
181     MDKVTIGDAE VHRIPVYPLQ MFMPDFSRVI ADPFNCNHRS IGENFNYPLP FFNRPLARLL
241     FEAVVGPAAV ALRARNVDAV ARAAAHLAFD ENHEGAALPA DITFTAFEAS QGKPQRGARD
301     AGNKGPAGGF EQRLASVMAG DAALALESIV SMAVFDEPPP DITTWPLLEG QETPAARAGA
361     VGAYLARAAG LVGAMVFSTN SALHLTEVDD AGPADPKDHS KPSFYRFFLV PGTHVAANPQ
421     LDREGHVVPG YEGRPTAPLV GGTQEFAGEH LAMLCGFSPA LLAKMLFYLE RCDGGVIVGR
481     QEMDVFRYVA DSGQTDVPCN LCTFETRHAC AHTTLMRLRA RHPKFASAAR GAIGVFGTMN
541     SAYSDCDVLG NYAAFSALKR ADGSENTRTI MQETYRAATE RVMAELEALQ YVDQAVPTAL
601     GRLETIIGNR EALHTVVNNI KQLVDREVEQ LMRNLIEGRN FKFRDGLAEA NHAMSLSLDP
661     YTCGPCPLLQ LLARRSNLAV YQDLALSQCH GVFAGQSVEG RNFRNQFQPV LRRRVMDLFN
721     NGFLSAKTLT VALSEGAAIC APSLTAGQTA PAESSFEGDV ARVTLGFPKE LRVKSRVLFA
781     GASANASEAA KARVASLQSA YQKPDKRVDI LLGPLGFLLK QFHAVIFPNG KPPGSNQPNP
841     QWFWTALQRN QLPARLLSRE DIETIAFIKR FSLDYGAINF INLAPNNVSE LAMYYMANQI
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901       LRYCDHSTYF INTLTAVIAG SRRPPSVQAA AAWAPQGGAG LEAGARALMD SLDAHPGAWT
961       SMFASCNLLR PVMAARPMVV LGLSISKYYG MAGNDRVFQA GNWASLLGGK NACPLLIFDR
1021      TRKFVLACPR AGFVCAASSL GGGAHEHSLC EQLRGIIAEG GAAVASSVFV ATVKSLGPRT
1081      QQLQIEDWLA LLEDEYLSEE MMEFTTRALE RGHGEWSTDA ALEVAHEAEA LVSQLGAAGE
1141      VFNFGDFGDE DDHAASFGGL AAAAGAAGVA RKRAFHGDDP FGEGPPEKKD LTLDML
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KEYWORD DNA(NC_001798 REGION: 58805..62447)
SEQ ID No: 80

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  61 tatccaacgt caggtccttt ttctccggtg gtccctcccc aaacggatcg tcgccgtgaa
 121 acgcccgctt tcgggcgacg ccggccgccc ccgccgccgc cgccaaaccg ccgaacgacg
 181 ccgcgtggtc atcctcgtcg ccgaaatccc caaagttaaa cacctccccg gcggcgccga
 241 gctggctgac cagggcctcc gcctcgtggg ccacctccag ggccgcgtcg gtcgaccact
 301 cgccatgccc gcgctccagg gcgcgggtgg taaactccat catttcctcg ctcaggtact
 361 cgtcctccag cagcgccagc cagtcctcga tctgcagctg ctgggtgcgg gggcccaggc
 421 tcttgacggt cgccacaaac acgctgctgg cgaccgccgc cccgccctcc gcaatgatgc
 481 cccggagctg ctcgcacagc gaatgctcgt gggccccgcc cccgagactc gacgccgcgc
 541 acacaaaccc ggccctgggg caggccagga caaacttgcg ggtgcggtca aagatcagca
 601 gcgggcacgc gtttttgccg cccagcaggc tggcccagtt cccggcctga aacacgcggt
 661 cgttgccggc catgccgtag tatttgctga tgctgaggcc cagcacgacc atcgggcgcg
 721 cggccatcac gggccgcagc aggttgcagc tcgcgaacat ggacgtccag gcgccggggt
 781 gcgcgtcgag ggagtccatc agcgcgcggg ccccggcctc caggcccgcg ccgccctgcg
 841 gggcccaggc ggccgccgcc tgcacgctgg ggggacggcg ggacccggcg atgacggccg
 901 tgagggtgtt tatgaagtac gtcgagtggt cgcagtacct caagatctgg ttggccatgt
 961 agtacatggc cagttcgctc acgttattgg gggccaggtt gataaagtta atcgcgccgt
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1141 accccggggg cttgccgttg ggaaagatga ccgcgtggaa ctgcttcagc aggaagccca
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1321 tcttgacgcg cagttccttg ggaaacccaa gggtcacgcg ggcaacgtcg ccctcgaagc
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1441 ccgagagcgc gaccgtcagc gtcttcgccg acaggaaccc gttgttgaac aggtccatga
1501 cgcgccgccg cagcaccggt tggaattgat tgcgaaagtt gcgccccctcg accgactgcc
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2041 ccccaatggc cccccgggcg gcgctcgcga acttggggtg gcgggcccgc agccgcatca
2101 gcgtcgtgtg cgcgcaggcg tggcgggtct cgaaggtaca caggttgcag ggcacgtcgg
2161 tctggcccga gtccgcgacg tagcgaaaca cgtccatctc ctggcgcccg acgatgactc
2221 cgccgtcgca gcgctccagg taaaacagca tcttggccag cagggccgga gagaacccgc
2281 acagcatggc caggtgctcg ccggcgaact cctgggttcc gccgacgagg ggcgccgtgg
2341 ggcgcccctc gtacccgggc accacgtggc cctcgcggtc cagctgcggg ttggccgcca
2401 cgtgcgtgcc gggcacgaga aagaagcggt aaaaggaggg cttgctgtgg tccttggggt
2461 ccgccggccc ggcgtcgtcc acctcggtca ggtggagggc cgaattggtg ctgaacacca
2521 tggcgcccac gaggcccgcg gcgcgcgcca ggtacgcccc gacggcgccg gcgcgggccg
2581 cgggcgtttc ctggccctca agcaggggcc acgtggtgat gtcgggggcc ggctcgtcaa
2641 agaccgccat cgacacgatg gactccaggg ccagggcggc gtcgcccgcc atcaccgagg
2701 ccaggcgctg ctcaaacccg cccgccgggc ccttgttccc ggcgtcgcgc gcgccccgct
2761 ggggcttacc ctggctggcc tcgaaggccg tgaacgtaat gtcggcgggg agggccgcgc
2821 cctcgtggtt ttcgtcgaac gccaggtggg cggccgcgcg ggccacggcg tccacgttcc
2881 gggcacgcag ggccacggcg gcgggcccga cgaccgcctc gaacagcagg cgggcgaggg
2941 ggcggttgaa aaacggaagg gggtagttga aattctcccc gatcgatcgg tggttgcagt
3001 taaacggatc ggcgatgacc cggctaaaat ccggcataaa catctgcagc ggatacacgg
3061 ggatgcggtg aacctccgcg tccccgatgg ttaccttgtc catcccgccc agatgcagga
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3121 aggtgttgct gatgcacacg gcctccccgga agccctccgt gatcaccaga tacagcaagg
3181 cccggtccgg gtccagtccg agccgctcgc acagcgcgtc ccccgtcgtc tcgtgcttta
3241 ggtcgcaggg ccggggcgcg tagtccgcga agccaaaatg cgggcgcgcc cgctcgcaga
3301 gccgcgtcag gttgggggcc tgggtgctgg gggccaggtg gcggccgccg tgaaagacgt
3361 aaacggacgg gctgtagtgc gagggcataa gcttgaggga caccgcggtc cccccaaggc
3421 ccgtcgtgcg ggacccgacg accgcggcca cgttggcctc aaacccgctc tccacggtca
3481 ggccgacgat gaggggcgcg acggcgacgt ccgcgtcgcc gctgcgcgcc gacagtagcg
3541 acagcagctc caggccttcg gccggacagg cgcggccata cacgtacccc atcggccccg
3601 gaggaacctt gacggtggtc gtcgttttgg gcttggtgtc cat
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SEQ HSV-2 UL30
KEYWORD PROTEIN
SEQ ID No: 81

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1    MFCAAGGPAS PGGKPAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL AQTGTQPKAL
61   GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL RRAPKVYCGG DERDVLRVGP
121  EGFWPRRLRL WGGADHAPEG FDPTVTVFHV YDILEHVEHA YSMRAAQLHE RFMDAITPAG
181  TVITLLGLTP EGHRVAVHVY GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS
241  FRGISADHFE AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA
301  TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN LAVEGAMCDL
361  PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY DLSTTALEHI LLFSLGSCDL
421  PESHLSDLAS RGLPAPVVLE FDSEFEMLLA FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL
481  TEIYKVPLDG YGRMNGRGVF RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK
541  LNAVAEAVLK DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS
601  AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE APKRPAVPRG
661  EGERPGDGNG DEDKDDDEDG DEDGDEREEV ARETGGRHVG YQGARVLDPT SGFHVDPVVV
721  FDFASLYPSI IQAHNLCFST LSLRPEAVAH LEADRDYLEI EVGGRRLFFV KAHVRESLLS
781  ILLRDWLAMR KQIRSRIPQS TPEEAVLLDK QQAAIKVVCN SVYGFTGVQH GLLPCLHVAA
841  TVTTIGREML LATRAYVHAR WAEFDQLLAD FPEAAGMRAP GPYSMRIIYG DTDSIFVLCR
901  GLTAAGLVAM GDKMASHISR ALFLPPIKLE CEKTFTKLLL IAKKKYIGVI CGGKMLIKGV
961  DLVRKNNCAF INRTSRALVD LLFYDDTVSG AAAALAERPA EEWLARPLPE GLQAFGAVLV
1021 DAHRRITDPE RDIQDFVLTA ELSRHPRAYT NKRLAHLTVY YKLMARRAQV PSIKDRIPYV
1081 IVAQTREVEE TVARLAALRE LDAAAPGDEP APPAALPSPA KRPRETPSHA DPPGGASKPR
1141 KLLVSELAED PGYAIARGVP LNTDYYFSHL LGAACVTFKA LFGNNAKITE SLLKRFIPET
1201 WHPPDDVAAR LRAAGFGPAG AGATAEETRR MLHRAFDTLA
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KEYWORD DNA(NC_001798 REGION: 63265..67026)
SEQ ID No: 82

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121 cgccggcaga acttctacaa cccccacctc gctcagaccg gaacgcagcc aaaggccctc
181 gggccggctc agcgccatac gtactacagc gagtgcgacg aatttcgatt tatcgccccg
241 cgttcgctgg acgaggacgc ccccgcggag cagcgcaccg gggtccacga cggccgcctc
301 cggcgcgccc ctaaggtgta ctgcgggggg gacgagcgcg acgtcctccg cgtgggcccg
361 gagggcttct ggccgcgtcg cttgcgcctg tggggcggtg cggaccatgc ccccgagggg
421 ttcgacccca ccgtcaccgt cttccacgtg tacgacatcc tggagcacgt ggaacacgcg
481 tacagcatgc gcgccgccca gctccacgag cgatttatgg acgccatcac gcccgccggg
541 accgtcatca cgcttctggg tctgacccca gaaggccatc gcgtcgccgt tcacgtctac
601 ggcacgcggc agtactttta catgaacaag gcggaggtgg atcggcacct gcagtgccgt
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781 tattacgaaa cgcgcccgac cctgtactac cgcgtcttcg tgcgaagcgg gcgcgcgctg
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901 accaccccggt ttatcctgga caacccgggg tttgtcacct tcggctggta ccgcctcaag
961 cccggccgcg ggaacgcgcc ggcccaaccg cgccccccga cggcgttcgg aacctcgagc
1021 gacgtcgagt ttaactgcac ggcggacaac ctggccgtcg agggggccat gtgtgacctg
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1201 gacctgtcca ccaccgccct cgagcacatc ctcctgtttt cgctcggatc ctgcgacctc
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1261 cccgagtccc acctcagcga tctcgcctcc aggggcctgc cggccccccgt cgtcctggag
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3601 tggcaccccc cggacgacgt ggccgcgcgg ctcagggccg cggggttcgg gccggcgggg
3661 gccggcgcta cggcggagga aactcgtcga atgttgcata gagcctttga tactctagca
3721 tgagcccccc gtcgaagctg atgtcccgca tcttgcaata aa
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SEQ HSV-2 UL32
KEYWORD PROTEIN
SEQ ID No: 83

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1       MATSAPGVPS SAAVREESPG SSWKEGAFER PYVAFDPDLL ALNEALCAEL LAACHVVGVP
61      PASALDEDVE SDVAPAPPRP RGAAREASGG RGPGSARGPP ADPTAEGLLD TGPFAAASVD
121     TFALDRPCLV CRTIELYKQA YRLSPQWVAD YAFLCAKCLG APHCAASIFV AAFEFVYVMD
181     HHFLRTKKAT LVGSFARFAL TINDIHRHFF LHCCFRTDGG VPGRHAQKQP RPTPSPGAAK
241     VQYSNYSFLA QSATRALIGT LASGGDDGAG AGAGGGSGTQ PSLTTALMNW KDCARLLDCT
301     EGKRGGGDSC CTRAAARNGE FEAAAGALAQ GGEPETWAYA DLILLLLAGT PAVWESGPRL
361     RAAADARRAA VSESWEAHRG ARMRDAAPRF AQFAEPQPQP DLDLGPLMAT VLKHGRGRGR
421     TGGECLLCNL LLVRAYWLAM RRLRASVVRY SENNTSLFDC IVPVVDQLEA DPEAQPGDGG
481     RFVSLLRAAG PEAIFKHMFC DPMCAITEME VDPWVLFGHP RADHRDELQL HKAKLACGNE
541     FEGRVCIALR ALIYTFKTYQ VFVPKPTALA TFVREAGALL RRHSISLLSL EHTLCTYV
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KEYWORD DNA(NC_001798 REGION: 66850..69638)
SEQ ID No: 84

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 481 ggtcctggag gggggtgctg tggcggtcgg ccagcacgac cagggaggcc agaaaggtgc
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 661 agtagcccat gcccgagagg gtcaggcagt tgtcggccac ggtctggtcc aggctgaagg
 721 ggagcgacac gggggtcgtc ttcaccaggg gcacggagag cgagcgcacg atggcgatct
 781 cctcggaggg cgtctgggcg agggcggcga agaagccgcg gtagcgacgg cgctcgtgca
 841 ggcagagctc cagcctgcgc gcgtgcgacg gcaggctctt gcgggaggcc cggcgctcca
 901 cgccggggtt cccggcggcg gaaaagcgcg accgccgccg ggtcttgtcg cggccgggcc
 961 cgggccggga gccggagcga cgggggcga tgtcatacat aggtacagag ggtgtgctcc
1021 agggacagga gagagatcga gtgtcgtctg agcagcgcgc cggcctcgcg gacaaatgtg
1081 gccagcgcgg tgggcttcgg cacaaatacc tggtacgtct tgaaggtgta gatgagggcc
1141 cgcagggcta tacagacccg cccctcgaac tcgttgccgc aggccaactt ggccttgtga
1201 agctgcagct cgtcgcgatg gtcggcgcgg gggtggccaa acaggaccca ggggtcgact
1261 tccatctccg tgatggcgca catcggatcg cagaacatgt gcttgaagat ggcctcgggg
1321 cccgcggccc gaagcaggct cacgaaccgg cccccgtccc cgggctgcgc ctcggggtcc
1381 gcctcgagct ggtccacgac cggcactatg cagtcgaaga ggctggtgtt gttctccgag
1441 tagcggacga cggacgccct caggcgtcgc atggccagcc agtaggcccg caccagcaac
1501 agattgcaca gcaggcattc cccgccggtg cgcccgcgcc cccggccgtg cttcagcacg
1561 gtggccatca gcgggcccag gtccaggtcg ggctggggct ggggctcggc gaactgcgca
1621 aaacgcgggg ccgcgtcgcg catgcgcgcc ccgcggtgcg cttcccagga ctcgctgacc
1681 gcggcgcggc gggcgtccgc ggcggcgcgc agccggggcc ccgactccca gacggcgggg
1741 gtgccggcga gcagcagcag gatcaggtcg gcgtacgccc acgtctccgg ctcacccccc
1801 tgcgccagcg ccccggcggc ggcctcgaac tccccgttgc gggcggcggc gcgcgtgcag
1861 cagctgtctc cgcccccgcg cttgccctcg gtgcagtcga gcaggcgggc gcagtccttc
1921 cagttcatca gggcggtggt gagggagggt tgcgttcccg agcccccgcc cgcccccgcc
1981 cccgccccgt catcgccccc ggaggccagg gtcccgatga gggcccgggt tgcggactgc
2041 gcgaggaagg aatagttgga gtactgcacc ttggcggcgc ccggggaggg cgtcggcctg
2101 ggttgcttct gggcgtggcg cccgggcacc ccgccgtcgg tccggaagca gcagtggaga
2161 aagaaatgcc ggtggatgtc gttgatggtc agggcgaagc gcgcgaagga gccgacaagg
2221 gtcgccttct tggtgcgcag gaagtggtgg tccatgacgt agacgaactc gaaggcggcc
2281 acgaagatgc tcgcggcgca gtggggcgcg cccaggcact tggcgcagag gaacgcgtaa
2341 tcggccaccc actggggcga gaggcggtag gcctgcttgt acagctcgat ggtgcggcag
2401 accagacagg ggcggtccag cgcgaaggtg tcgacggacg ccgcggcgaa gggccccgtg
2461 tccaagagtc cctctgccgt ggggtctgcg ggcgggccgc gggcggaccc cggcccccgc
2521 ccccccgaag cctcgcgcgc ggccccgcgc ggccgcgggg gggcgggcgc gacgtcgctc
2581 tccacgtcct cgtcgagcgc gctcgcgggc ggcacgccta ccacgtgaca ggccgccagg
2641 agctcggcgc acagggcctc gttaagagcc agaaggtcgg gatcgaaggc cacatacgga
2701 cgctcgaacg cgccctcctt ccagctgctg cccggcgact cttcgcgcac ggcggcgctc
2761 gacggcaccc ccggggcgga cgtcgccat
```

SEQ HSV-2 UL33
KEYWORD PROTEIN
SEQ ID No: 85

```
1   MAGRAGRTRP RTLRDAIPDC ALRSQTLESL DARYVSRDGA GDAAVWFEDM TPAELEVIFP
61  TTDAKLNYLS RTQRLASLLT YAGPIKAPDG PAAPHTQDTA CVHGELLARK RERFAAVINR
121 FLDLHQILRG
```

KEYWORD DNA(NC_001798 REGION: 69637..71469)
SEQ ID No: 86

```
   1 atggccggtc gagcggggcg cacgcgtccg cgaacgttac gggacgcgat ccccgactgc
```

```
  61 gcgctgcggt cccagaccct ggaaagtcta gacgcgcgct acgtctcgcg agacggcgcg
 121 ggggacgcgg ccgtctggtt cgaggacatg acccccgccg aactagaggt tatattcccg
 181 accacggacg ccaagctgaa ctacctctcg cggacgcagc ggctggcctc cctcctgacg
 241 tacgccgggc ctataaaagc gcccgacggc cccgccgccc cacatacgca ggacaccgcg
 301 tgcgtgcacg gcgagctgct cgcccgaaag cgcgaacggt tcgcggcggt cattaaccgg
 361 ttcctggacc tgcaccagat cctgcggggc tgacgcgcgc ttcggcgggg caccggcacc
 421 gggaccgact tgttttacat aacagtaggg ggtgggggaa cgcgcaccct tgcccggtcg
 481 cgatggcggg gatggggaag ccctacggcg gccgcccggg ggacgcgttc gagggtctcg
 541 ttcagcgcat caggctcatt gttcccgcca cgctgcgcgg cgggggtggg gagtcgggcc
 601 cctactcgcc atccaacccg ccctcgagat gtgccttcca gttccacggc caggatgggt
 661 ccgacgaggc cttcccgatc gagtacgtcc tgcggctcat gaacgactgg gccgatgtgc
 721 cctgcaaccc ctacctgcgc gtgcagaaca ccggcgtttc ggtgctgttt caggggtttt
 781 ttaaccggcc ccacggcgcc ccgggggggcg cgatcacggc ggagcagacc aacgtgattc
 841 tgcactccac cgagacgacg ggactgtccc tcggagacct ggacgacgtc aaggggcgcc
 901 tcggcctggá cgcccggccg atgatggcca gcatgtggat cagctgcttt gtgcgcatgc
 961 cccgggtgca gctcgcgttt cggttcatgg gccccgagga cgccgttcgc acgcggcgga
1021 tcctgtgtcg cgccgccgag caggccctcg cccgtcgccg ccggtccagg cggtcccagg
1081 atgactacgg ggcggtggtg gtggcggcgg cgcaccactc ttccggagcg cccgggccgg
1141 gggtcgccgc ctcgggcccg ccagcgccgc ccggacgggg accggcccgt ccgtggcatc
1201 aggccgtgca gttgttccgg gccccgcgtc cgggcccccc ggcgcttctg ttgctggcgg
1261 cggggctgtt tctgggggcc gctatctggt gggcggttgg cgcgcgccta tgaaaggggg
1321 cgagccaccg tcccgcccgc cagtgcatcc cagacgcccg cgagccgcac atcccctccg
1381 ctcccgcctc cggcccgatt cttacggcgc gacccaaggt cccgatggcc gccccgcagt
1441 ttcaccgccc cagcaccatt accgccgaca acgtccgggc gctcggcatg cgcgggctcg
1501 tgttggccac caacaacgct cagttcatca tggataacag ctacccgcat ccgcacggaa
1561 cgcagggtgc ggtgcgagag tttcttcgcg ggcaggccgc ggcgctgacg gacctcgggg
1621 tgacccacgc caacaacacg ttcgccccgc agcctatgtt cgcgggcgac gccgcggccg
1681 aatggctgcg gccctcgttc ggtcttaagc gcacgtattc ccccctttgtc gttcgcgacc
1741 ccaagacccc cagcaccccg tgagtcctcg gcgggtccct ccgcggccgt ctctcgttgc
1801 ccccctttcc cccttcccgg gtggttcaat aaa
```

SEQ HSV-2 UL34
KEYWORD PROTEIN
SEQ ID No: 87

```
1   MAGMGKPYGG RPGDAFEGLV QRIRLIVPAT LRGGGGESGP YSPSNPPSRC AFQFHGQDGS
61  DEAFPIEYVL RLMNDWADVP CNPYLRVQNT GVSVLFQGFF NRPHGAPGGA ITAEQTNVIL
121 HSTETTGLSL GDLDDVKGRL GLDARPMMAS MWISCFVRMP RVQLAFRFMG PEDAVRTRRI
181 LCRAAEQALA RRRRSRRSQD DYGAVVVAAA HHSSGAPGPG VAASGPPAPP GRGPARPWHQ
241 AVQLFRAPRP GPPALLLLAA GLFLGAAIWW AVGARL
```

KEYWORD DNA(NC_001798 REGION: 70119..71469)
SEQ ID No: 88

```
  1 atggcgggga tggggaagcc ctacggcggc cgcccggggg acgcgttcga gggtctcgtt
 61 cagcgcatca ggctcattgt tcccgccacg ctgcgcggcg ggggtgggga gtcgggcccc
121 tactcgccat ccaacccgcc ctcgagatgt gccttccagt tccacggcca ggatgggtcc
181 gacgaggcct tcccgatcga gtacgtcctg cggctcatga acgactgggc cgatgtgccc
241 tgcaaccccc acctgcgcgt gcagaacacc ggcgtttcgg tgctgtttca ggggtttttt
301 aaccggcccc acggcgcccc gggggggcgcg atcacggcgg agcagaccaa cgtgattctg
361 cactccaccg agacgacggg actgtccctc ggagacctgg acgacgtcaa ggggcgcctc
421 ggcctggacg cccggccgat gatggccagc atgtggatca gctgctttgt gcgcatgccc
481 cgggtgcagc tcgcgtttcg gttcatgggc cccgaggacg ccgttcgcac gcggcggatc
541 ctgtgtcgcg ccgccgagca ggccctcgcc cgtcgccgcc ggtccaggcg gtcccaggat
601 gactacgggg cggtggtggt ggcggcggcg caccactctt ccggagcgcc cgggccgggg
661 gtcgccgcct cgggcccgcc agcgccgccc ggacggggac cggcccgtcc gtggcatcag
721 gccgtgcagt tgttccgggc cccgcgtccg ggccccccgg cgcttctgtt gctggcggcg
781 gggctgtttc tgggggccgc tatctggtgg gcggttggcg cgcgcctatg aaaggggggcg
841 agccaccgtc ccgcccgcca gtgcatccca gacgcccgcg agccgcacat cccctccgct
901 cccgcctccg gcccgattct tacggcgcga cccaaggtcc cgatggccgc cccgcagttt
```

```
 961 caccgcccca gcaccattac cgccgacaac gtccgggcgc tcggcatgcg cgggctcgtg
1021 ttggccacca acaacgctca gttcatcatg gataacagct acccgcatcc gcacggaacg
1081 cagggtgcgg tgcgagagtt tcttcgcggg caggccgcgg cgctgacgga cctcggggtg
1141 acccacgcca acaacacgtt cgccccgcag cctatgttcg cgggcgacgc cgcggccgaa
1201 tggctgcggc cctcgttcgg tcttaagcgc acgtattccc cctttgtcgt tcgcgacccc
1261 aagaccccca gcaccccgtg agtcctcggc gggtccctcc gcggccgtct ctcgttgccc
1321 ccctttcccc cttcccgggt ggttcaataa a
```

SEQ HSV-2 UL42
KEYWORD PROTEIN
SEQ ID No: 89

```
1   MAHLPGGAAA APLSEDAIPS PRERTEDWPP CQIVLQGAEL NGILQAFAPL RTSLLDSLLV
61  VGDRGILVHN AIFGEQVFLP LDHSQFSRYR WGGPTAAFLS LVDQKRSLLS VFRANQYPDL
121 RRVELTVTGQ APFRTLVQRI WTTASDGEAV ELASETLMKR ELTSFAVLLP QGDPDVQLRL
181 TKPQLTKVVN AVGDETAKPT TFELGPNGKF SVFNARTCVT FAAREEGASS STSAQVQILT
241 SALKKAGQAA ANAKTVYGEN THRTFSVVVD DCSMRAVLRR LQVGGGTLKF FLTADVPSVC
301 VTATGPNAVS AVFLLKPQRV CLNWLGRSPG SSTGSLASQD SRAGPTDSQD SSSEPDAGDR
361 GAPEEEGLEG QARVPPAFPE PPGTKRRHPG AEVVPADDAT KRPKTGVPAA PTRAESPPLS
421 ARYGPEAAEG GGDGGRYACY FRDLQTGDAS PSPLSAFRGP QRPPYGFGLP
```

KEYWORD DNA(NC_001798 REGION: 93769..95255)
SEQ ID No: 90

```
   1 atggctcatc ttcccggcgg tgcggccgcc gccccccttt cggaggacgc gatcccgtcg
  61 ccgcgcgagc ggacggaaga ctggccgccc tgccagatag tgctgcaggg cgccgagctg
 121 aacgggatcc tgcaggcctt tgcgccgctt cgcacgagcc ttttggactc gctcctggtc
 181 gtgggcgacc gaggcatcct tgtacataac gcgattttcg gcgagcaggt gtttctgccc
 241 ctcgaccatt cgcagttcag tcgctatcga tggggcggac ccaccgcggc gttcctgtct
 301 ctcgtggacc agaagcgatc cctgctgagc gtgtttcgcg ccaaccagta ccctgacctg
 361 cggcgggtgg agctgacggt cacgggccag gccccgtttc gcacgctggt gcagcgcata
 421 tggacgaccg cgtccgacgg agaggccgtg gagcttgcca gcgagacgct catgaaacgc
 481 gagttgacga gcttcgcggt actactcccc cagggcgacc ccgacgtcca gctgcgcctc
 541 acgaagcccc agctcacgaa ggtggtgaac gccgtcgggg acgagaccgc caaacccacc
 601 acgttcgagc tcggccccaa cggcaagttt tccgtgttta acgcgcgcac ctgcgtcacc
 661 tttgccgccc gcgaggaggg cgcgtcgtcc agcaccagcg cccaggtcca gattctgacc
 721 agcgcgctga agaaggcggg ccaagcggcc gccaacgcca agacggtcta cggggaaaac
 781 acacaccgca cattctcggt ggtcgtcgac gactgcagca tgcgggcggt cctccggcgg
 841 ctccaggtcg gcgggggggac cctcaagttc ttcctcacgg ccgacgtccc cagcgtgtgt
 901 gtcaccgcca ccggccccaa cgcggtgtcg gcggtgtttc ttttaaaacc ccagcgggtc
 961 tgcctgaact ggctcggccg gagcccgggt tcctcgaccg ggagcttggc gtcccaggac
1021 tctcgggccg gcccgaccga cagccaggac tcctcctccg agccggacgc gggcgaccgc
1081 ggcgccccag aagaagaagg cctcgagggc caggcccggg taccgcccgc gttcccggaa
1141 ccgccgggaa ccaagcggag gcacccccggg gccgaagttg tccccgcgga cgacgccacc
1201 aagcgcccga agacgggcgt gcccgccgcc cccacgcgag ccgagtcgcc ccccctctcc
1261 gcgagatacg gacccgaggc ggcggagggt ggtggggacg gcggccgcta cgcgtgctac
1321 tttcgcgacc tccagaccgg cgacgcgagc cccagccccc tctccgcctt ccggggtccc
1381 caaagacccc catacggctt tgggttgccc tgacggcaac gggtggtggc cgaacgcctc
1441 accgcgcccg ggcacgcggg gtgcgttgtg ttaaaaaaat aaataaa
```

SEQ HSV2 UL52
KEYWORD PROTEIN
SEQ ID No: 91

```
1   MGTEDCDHEG RSVAAPVEVT ALYATDGCVI TSSLALLTNC LLGAEPLYIF SYDAYRSDAP
61  NGPTGAPTEQ ERFEGSRALY RDAGGLNGDS FRVTFCLLGT EVGVTHHPKG RTRPMFVCRF
121 ERADDVAVLQ DALGRGTPLL PAHVTATLDL EATFALHANI IMALTVAIVH NAPARIGSGS
181 TAPLYEPGES MRSVVGRMSL GQRGLTTLFV HHEARVLGAY RRAYYGSAQS PFWFLSKFGP
241 DEKSLVLAAR YYLLQAPRLG GAGATYDLQA VKDICATYAI PHDPRPDTLS AASLTSFAAI
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301       TRFCCTSQYS RGAAAAGFPL YVERRIAADV RETGALEKFI AHDRSCLRVS DREFITYIYL
361       AHFECFSPPR LATHLRAVTT HDPSPAASTE QPSPLGREAV EQFFRHVRAQ LNIREYVKQN
421       VTPRETALAG DAAAAYLRAR TYAPAALTPA PAYCGVADSS TKMMGRLAEA ERLLVPHGWP
481       AFAPTTPGDD AGGGTAAPQT CGIVKRLLKL AATEQQGTTP PAIAALMQDA SVQTPLPVYR
541       ITMSPTGQAF AAAARDDWAR VTRDARPPEA TVVADAAAAP EPGALGRRLT RRICARGPAL
601       PPGGLAVGGQ MYVNRNEIFN AALAVTNIIL DLDIALKEPV PFPRLHEALG HFRRGALAAV
661       QLLFPAARVD PDAYPCYFFK SACRPRAPPV CAGDGPSAGG DDGDGDWFPD AGGPGDEEWE
721       EDTDPMDTTH GPLPDDEAAY LDLLHEQIPA ATPSEPDSVV CSCADKIGLR VCLPVPAPYV
781       VHGSLTMRGV ARVIQQAVLL DRDFVEAVGS HVKNFLLIDT GVYAHGHSLR LPYFAKIGPD
841       GSACGRLLPV FVIPPACEDV PAFVAAHADP RRFHFHAPPM FSAAPREIRV LHSLGGDYVS
901       FFEKKASRNA LEHFGRRETL TEVLGRYDVR PDAGETVEGF ASELLGRIVA CIEAHFPEHA
961       REYQAVSVRR AVIKDDWVLL QLIPGRGALN QSLSCLRFKH GRASRATART FLALSVGTNN
1021      RLCASLCQQC FATKCDNNRL HTLFTVDAGT PCSRSAPSST SRPSSS
```

KEYWORD DNA(NC_001798 REGION: 109875..114314)
SEQ ID No: 92

```
   1 atggggacgg aagactgcga tcacgaaggg cggtcggttg cggctcccgt ggaggttacg
  61 gcgctgtatg cgaccgacgg gtgcgttatc acctcctcgc tcgccctcct cacaaactgc
 121 ctgctggggg ccgagccgtt gtatatattc agctacgacg cgtaccggtc cgatgcgccc
 181 aatggcccca cgggcgcgcc caccgaacag gagaggttcg aggggagccg ggcgctctac
 241 cgggatgcgg gggggctaaa tggcgattca tttcgggtga ccttttgttt attggggacg
 301 gaagtgggcg tgacccacca cccgaaaggg cgcacccggc ccatgtttgt gtgccgcttc
 361 gagcgagcgg acgacgtcgc cgtgctccaa gacgccctgg gccgcgggac cccattgctc
 421 ccggcccacg tcacagcaac tctggacttg gaggcgacgt ttgcgctcca cgctaacatc
 481 atcatggctc tcaccgtggc catcgtccac aacgcccccg cccgcatcgg cagcggcagc
 541 accgcccccc tgtatgagcc cggcgaatcg atgcgctcgg tcgtcgggcg catgtccctg
 601 gggcagcgcg gcctcaccac gctgttcgtg caccacgagg cgcgcgtgct gggggcgtac
 661 cgccgggcgt attatgggag cgcccaaagc ccctttggt ttctgagcaa attcggcccg
 721 gacgaaaaga gcctggtgct ggccgctagg tactacctac tccaggctcc gcgcttgggg
 781 ggcgccggag ccacgtacga tctgcaggcc gtgaaagaca tctgcgcgac ctacgcaatc
 841 ccccacgacc cacgccccga caccctcagt gccgcgtcct tgacctcgtt cgccgccatc
 901 actcggttct gttgcacgag ccagtactcc cgcggggccg cggccgctgg gtttccgctg
 961 tatgtggagc gccgcatcgc cgccgacgta cgcgagaccg gcgcgctgga gaagttcatc
1021 gcccacgatc gcagctgcct gcgcgtgtcc gaccgggaat tcattacgta catctacctg
1081 gcccactttg agtgcttcag ccccccgcgc ctggccacgc atctccgggc cgtgaccacc
1141 cacgacccca gccccgcggc cagcacggag cagccctcgc ccctgggtcg ggaggcggtg
1201 gaacagttct tccggcacgt gcgcgcccag ctgaacatcc gcgagtacgt aaagcaaaac
1261 gtcaccccca gggaaaccgc cctggcggga gacgcggccg ccgcctacct gcgcgcgcgc
1321 acgtatgccc cggcggccct cacgcccgcc cccgcgtact gcggggtcgc agactcgtcc
1381 accaaaatga tgggacgtct ggcggaagca gaaaggctcc tagtccccca cggctggccc
1441 gcgttcgcac caacaacccc cggggacgac gcgggggggcg gcactgccgc cccccagacc
1501 tgcggaatcg tcaagcgcct cctcaagctg gccgccacgg agcagcaggg cacgacgccc
1561 ccggcgatcg cggctctcat gcaggacgcg tcggtccaaa ccccctgcc cgtgtacagg
1621 attaccatgt ccccgaccgg ccaggcgttt gccgcggcgg cgcgggacga ctgggcccgc
1681 gtgacgcggg acgcgcgccc gccggaagcg accgtggtcg cggacgcggc ggcggcgccc
1741 gagcccggcg cgctcggccg gcggctcacg cgccgcattt gcgcccgggg ccccgcgctc
1801 cccccgggcg gcctggccgt cgggggccag atgtacgtga accgcaacga gatcttcaac
1861 gccgcgctgg ccgttacgaa catcatcctg gatctggaca tcgccctgaa ggagcccgtc
1921 ccctttcccc ggctccacga ggccctgggt cactttaggc gcggggcgct ggcggcggtt
1981 cagctgttgt ttcccgcggc ccgcgtagac cccgacgcct atccctgtta ttttttcaaa
2041 agcgcctgtc ggccccgcgc gccgcccgtc tgtgcgggcg acgggccctc ggccggtggc
2101 gacgacggcg acggggactg gttccccgac gccggtggtc ccggcgacga ggagtgggag
2161 gaggacacgg accccatgga cacgacccac ggcccccctcc cggacgacga ggccgcgtac
2221 ctcgacctgc tacacgaaca gataccagcg gcgacgccca gcgaaccgga ctccgtcgtg
2281 tgttcctgcg ccgacaagat cgggctgcgc gtgtgcctac cggtccccgc cccgtacgtt
2341 gtgcacggct ccctgacgat gcgtggggtg gcgagggtga tccagcaggc ggtgctgttg
2401 gaccgcgact tcgtggaggc cgtagggagc cacgtaaaga acttttgct gatcgatacg
2461 ggcgtgtacg cccacggcca cagcctgcgc ttgccgtatt tcgccaagat cggccccgac
2521 ggctccgcgt gcggccggtt attgcccgtc ttcgtgatcc cccccgcgtg cgaggacgtt
2581 ccggcgttcg tcgccgcgca cgccgacccg cggcgcttcc actttcacgc cccgcccatg
```

```
2641 ttttccgcgg ccccgcggga gatccgcgtc ctccacagcc tgggcgggga ctatgtcagc
2701 tttttcgaga agaaggcgtc gcgcaacgcc ctggagcact ttgggcgacg cgagaccctg
2761 acggaggttc tgggccgcta cgatgtgcgg cccgacgccg gggagaccgt ggaggggttc
2821 gcgtcagaac tgctggggcg aatagtcgcg tgcatcgagg ctcactttcc cgagcacgcg
2881 cgggaatatc aggccgtgtc cgttcgccgg gccgtcatta aggacgactg ggtcctgctg
2941 cagctgatcc ccggccgcgg cgccctgaac caaagcctct cgtgtctgcg cttcaagcac
3001 ggcagggcaa gtcgcgcgac ggcccggacc tttctcgcgc tgagcgtcgg gaccaacaac
3061 cgcctatgcg cgtccctgtg tcagcagtgc tttgccacta aatgcgataa caaccgcctg
3121 cacacgctgt ttaccgtcga tgcgggcacg ccatgctcgc ggtccgctcc ctccagcacc
3181 tcacgaccgt catcttcata acggcctacg gcctcgtgct cgcgtggtac atcgtctttg
3241 gtgccagtcc gctccaccga tgtatttacg cggtgcgccc cgccggggcg cacaacgata
3301 ccgccctcgt gtggatgaag ataaaccaga cgctgttgtt tctgggcccg ccgaccgccc
3361 cccccggcgg ggcatggacc ccccacgccc gcgtctgcta cgccaatatc atcgaaggtc
3421 gggccgtgtc cctcccggcc atccccggcg ccatgagccg ccgggtcatg aacgtgcacg
3481 aggccgtaaa ctgcttggag gccctctggg acacccagat gcgcctggtg gtcgtcggtt
3541 ggtttctgta tctagcgttc gtcgcccttc accaacgacg atgcatgttc ggcgtcgtga
3601 gtcccgcgca cagcatggtg gccccggcga cctatctttt gaactacgcc ggccgcatag
3661 tgtcgagcgt gttcttgcaa tacccctaca cgaaaatcac ccgcctcctc tgcgagctat
3721 ccgttcaacg ccagaccctg gtgcagctgt tcgaggcgga tccggtcacc ttcttgtacc
3781 accgcccggc cattggcgtc atcgtgggct gcgagctgct gctccgcttc gtggccctcg
3841 gtctcatcgt cggcaccgct ctcatctccc ggggcgcctg cgcgatcaca cacccctgt
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