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(54) **Title**: SCREEN FOR INHIBITORS OF FILOVIRUS AND USES THEREFOR

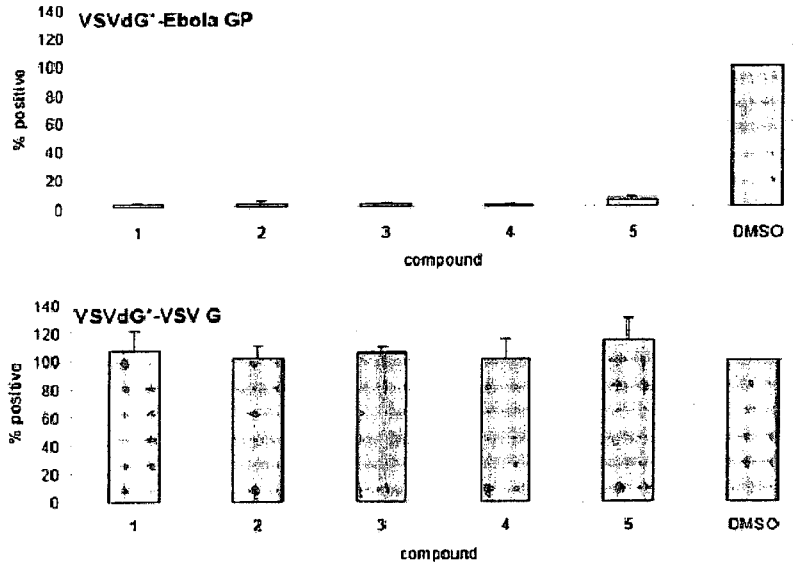


Fig. 14

(57) **Abstract**: The invention provides methods to identify agents useful to prevent, inhibit or treat viral infections, e.g., filovirus infections, as well as compositions having one or more agents to prevent, inhibit or treat viral infection.

WO 2010/053573 A2

SCREEN FOR INHIBITORS OF FILOVIRUS AND USES THEREFOR

Cross-Reference to Related Applications

This application claims the benefit of the filing date of U.S. application Serial No. 61/112,524, filed on November 7, 2008 and U.S. application Serial No. 61/150,486, filed on February 6, 2009, the disclosures of which are incorporated by reference herein.

Statement of Government Rights

The invention was made with a grant from the Government of the United States of America (Grant AI057153 from the National Institutes of Health). The Government has certain rights in the invention.

Background

Ebolaviruses (family *Filoviridae*) cause severe hemorrhagic fevers in humans and nonhuman primates, with mortality rates as high as 90% (Sanchez et al., 2007). *Ebolaviruses* and the closely related *Marburgviruses* belong to the *Filoviridae* family (Feldman et al., 2004). Currently, there are no approved vaccines or antivirals for use against filoviruses. Antivirals are not only desirable for local populations in epidemic areas and for health care workers during an outbreak, but also for researchers studying these viruses. Short interfering RNA molecules (Geisbert et al., 2006), and S-adenosylhomocysteine hydrolase inhibitors (Bray et al., 2000; Huggins et al., 1999) have been shown to inhibit Ebola viral growth *in vitro* and/or *in vivo*. However, the most effective approach to *filovirus* control will likely come from a combination of pharmacologic agents with different mechanisms of action (Bray & Paragas, 2002).

High throughput molecular screening (HTS) is an automated, simultaneous testing of thousands of distinct chemical compounds in models of biological mechanisms or disease. Since authentic *Ebolaviruses* are biosafety level 4 (BSL-4) agents, HTS with the viruses is not feasible. The lack of sufficient BSL-4 space, trained personnel, and the rigors of working in BSL-4 laboratories have severely hampered basic research with *Ebolaviruses* as well as the development of vaccines. These limitations have prompted examination of various steps in the *Ebolavirus* viral life cycle in the absence of infectious virus: (*i*) replication and transcription were studied by use of reporter gene assays that are based on the expression of necessary viral components from plasmids (Boehmann et al., 2005; Groseth et al., 2005; Muhlberger et al., 1999; Modrof et al., 2003; Modrof et al., 2002); (*ii*) entry and fusion processes were assessed with pseudotyping assays that rely on the use of recombinant vesicular stomatitis or retroviruses (Yonezawa et al., 2005; Wool-Lewis et al., 1998; Takada et al., 1997; Marzi et al., 2006); and (*iii*) budding was examined using virus-like particles that are generated from viral proteins provided by protein expression plasmids (Jasenosky et al., 2001; Licata et al., 2004; Noda et al., 2002; McCarthy et al., 2006; Johnson et al., 2006). However, several recent findings suggest that data obtained with these artificial systems may not always be reproducible with live, authentic *Ebolavirus* (Neumann et al., 2005).

Summary of the Invention

The invention provides a method to identify modulators, e.g., inhibitors, of filovirus infection. The method includes contacting a host cell, e.g., a mammalian cell including a human cell or non-human primate cell, with one or more agents and, in one embodiment, a replication incompetent rhabdovirus having filovirus glycoprotein and a mutant rhabdovirus genome with sequences for a reporter gene

product. It is then determined whether the one or more agents inhibit the expression or levels of the reporter gene product, e.g., a reporter protein. In one embodiment, at least one agent inhibits reporter expression or levels by at least 50%, 60%, 70% or more, e.g., 80%, 85%, 90% or more, for instance, by at least 95%, that of reporter expression or levels in a corresponding host cell not contacted with the agent(s). In one embodiment, the host cell is contacted with one agent. In one embodiment, the host cell is contacted with a library of agents. For instance, the host cell may be contacted with a chemically synthesized library, cDNA library or siRNA library. The replication incompetent pseudotyped rhabdovirus may be prepared by contacting a host cell with a vector to express mutant rhabdovirus vRNA with a deletion of rhabdovirus glycoprotein sequences and an insertion of reporter gene sequences. Vectors for protein expression include vectors expressing a filovirus glycoprotein and optionally one or more vectors for protein expression of at least one of P, M, N or L rhabdovirus proteins.

In one embodiment, the invention provides a method to identify one or more agents that inhibit viral infection or replication, e.g., *Ebolavirus* infection or replication. The method includes contacting a host cell, e.g., a mammalian cell including a human cell or non-human primate cell, with at least one agent and a recombinant negative-sense, single stranded RNA virus, the genome of which contains a deletion of viral sequences, i.e., it is a mutant genome. In one embodiment, the host cell is infected with the virus before being contacted with the one or more agents and in one embodiment, a lysate is prepared, e.g., after contact with the one or more agents. In one embodiment, the deleted viral sequences correspond to those for a viral glycoprotein. In one embodiment, the deleted viral sequences correspond to those for a nonstructural or nonglycosylated viral protein that is essential *in trans* for viral replication. In one embodiment, the deletion is effective to inhibit or prevent viral replication upon infection of a cell with the recombinant negative-sense, single stranded RNA virus. For example, the deletion may be effective to prevent expression of a functional nonstructural or nonglycosylated protein, or functional glycoprotein, upon infection of a cell with the recombinant negative-sense, single stranded RNA virus. In one embodiment, the deletion may be in filovirus sequences for a viral protein corresponding to Ebola virus VP30. Such a deletion may include a deletion of 1 or more nucleotides, e.g., a deletion of at least 0.1%, 1%, 5%, 10%, 50%, 60%, 70%, 80%, 90%, or any integer in between, and up to 100% of the viral sequences corresponding to those for a nonstructural or nonglycosylated viral protein that is essential *in trans* for viral replication, e.g., sequences that do not overlap with those for another viral protein encoded by the viral genome. The deletion is one that is stable over multiple passages and is readily detectable, e.g., by RT-PCR. In one embodiment, the deletion may be in rhabdovirus sequences for a rhabdovirus glycoprotein.

As described herein, a biologically contained *Ebolavirus* (EbolaΔVP30) was employed to identify anti-*Ebolavirus* candidates using a high throughput screening assay. To determine the steps in the viral life cycle inhibited by an anti-viral compound, an *Ebolavirus* binding/entry assay and a minigenome replication assay were employed. Anti-viral specificity was defined by using viral growth inhibition tests with EbolaΔVP30, veccinia virus, adenovirus, influenza virus, and vesicular stomatitis virus. Gedunin and gedunin derivatives were identified as anti-*Ebolavirus* candidates in the high throughput screening assay. These compounds inhibited the growth of EbolaΔVP30 but not that of vaccinia virus, adenovirus, influenza virus, or vesicular stomatitis virus. Further, these compounds inhibited *Ebolavirus* binding/entry and some also inhibited viral genome replication and protein expression. Thus, gedunin and gedunin derivatives are potent inhibitors of *Ebolavirus in vitro*. Their inhibitory mechanisms rely mainly upon virus binding/entry.

In one embodiment, an isolated recombinant, biologically contained Ebola virus includes a genome which contains a deletion in sequences corresponding to Ebola virus VP30 sequences. The deletion is effective to inhibit or prevent viral replication, e.g., by preventing expression of a functional protein corresponding to Ebola virus VP30 protein, upon infection of a cell that lacks sequences that encode the functional protein (e.g., the cell that does not express functional VP30 *in trans*) with the recombinant, biologically contained Ebola virus. In one embodiment, at least 90% of sequences corresponding to VP30 sequences in the viral genome of the virus are deleted. In one embodiment, the genome of the recombinant, biologically contained filovirus further comprises heterologous sequences, for instance, positioned within the deletion. The heterologous sequences may be selected as ones that are not toxic to one or more host cells, e.g., reporter, selectable marker or viral sequences (for instance, neo^R, a fluorescent protein such as green fluorescent protein (GFP), luciferase or influenza virus sequences for mammalian cells).

To prepare such virus, a reverse genetics systems for negative-sense RNA viruses was exploited to generate *Ebolaviruses* that lack the VP30 gene (which encodes an essential transcription factor), termed EbolaΔVP30 virus. These viruses were maintained, genetically stable, and biologically confined to a cell line expressing VP30. Hence, the EbolaΔVP30 virus fulfills several criteria of a vaccine virus: it can be grown to reasonably high titers in helper cells, is genetically stable (as determined by sequence analysis after seven serial passages in VP30-expressing Vero cells), and is safe. Moreover, as described herein, the resultant viruses resemble wild-type virus in their life cycle, their morphology, and their growth properties, but could be handled in a non-BSL-4 laboratory, opening new opportunities for study of the *Ebolavirus* life cycle and for the identification of effective antiviral compounds.

Other negative-sense, single stranded RNA viruses may likewise be manipulated, e.g., the genome of Nipah virus, Hendravirus, Henipavirus, and the like, may be manipulated to mutate or delete sequences corresponding to those for a nonstructural or nonglycoslyated viral protein that is required for viral replication. Thus, genomes of viruses in the following families may be manipulated to provide for an infectious, biologically contained virus that resembles wild-type virus in its life cycle, morphology, and growth properties, can be grown to reasonably high titers in helper cells, is genetically stable, and is safe: Bornaviridae, Rhabdoviridae, Filoviridae (genera Marburgvirus and Ebolavirus), Paramyxoviridae, Avulavirus, Henipavirus, Morbillivirus, Respirovirus, or Rubulavirus.

The invention further provides screening methods for antivirals that employ the recombinant infectious, biologically contained virus. In one embodiment, the methods include those that identify one or more agents that inhibit virus infection or replication. The methods include contacting the recombinant infectious, biologically contained virus of the invention, a host cell, e.g., a helper cell, such as a mammalian cell including a human cell or non-human primate cell, and one or more agents. Then it is determined whether the one or more agents inhibit viral replication or infection. In one embodiment, the one or more identified agents do not substantially decrease host cell viability, e.g., host cell viability is at least 65%, 70%, 75%, 80% or more in the presence of the one or more agents. Further provided is a method to identify one or more agents that inhibit virus infection or replication, which includes contacting a host cell infected with a recombinant infectious, biologically contained filovirus, or a lysate thereof, and one or more agents. Then it is determined whether the one or more agents inhibit viral replication or infection. In one embodiment, the one or more identified agents do not substantially decrease host cell viability, e.g., host cell viability is at least 65%, 70%, 75%, 80% or more. In one embodiment, the anti-viral

agent has an IC_{50} of less than about 10.0 μM, e.g., less than 5 μM, 1 μM, or 0.1 μM, e.g., an IC_{50} from 0.001 μM to 10 μM. In one embodiment, the anti-viral agent has a CC_{50} of more than than about 0.1 μM, e.g., more than 1 μM, 5 μM, 10 μM or 50 μM, e.g., a CC_{50} from 0.1 μM to 100 μM. In one embodiment, the agent has an IC_{50} of less than about 10.0 μM, e.g., less than 5 μM, 1 μM, or 0.1 μM and a CC_{50} of more than about 0.1 μM, e.g.,more than than 1 μM, 5 μM, 10 μM or 50 μM.

In one embodiment, the screening method identifies inhibitors of filovirus glycoprotein receptor binding or fusion. The method includes contacting a host cell, e.g., a mammalian cell including a human cell or non-human primate cell, with one or more agents and a recombinant replication incompetent pseudotyped rhabdovirus comprising filovirus glycoprotein and a mutant negative sense rhabdovirus genome which lacks sequences for a rhabdovirus glycoprotein but comprises a sequence for a reporter protein, e.g., a fluorescent protein or a bioluminescent protein. At least one agent is identified that inhibits reporter protein levels or expression in the host cell.

Also provided is a method which includes contacting a host cell with a plurality of agents, for example, a composition having the plurality of agents, and recombinant virus, e.g., sequentially or simultaneously.

Further provided are agents identified by the methods and the use of anti-virals in methods to prevent, inhibit or treat viral infection in a mammal, e.g., a human. Agents identified by the method or useful to prevent, inhibit or treat viral, e.g., filovirus, infection, include but are not limited to, an inhibitor of Hsp90, gedunin and gedunin derivatives, a triphenylethylene, an inhibitor of calcium-independent phospholipase A_2 and/or of magnesium-dependent phosphatidate phosphohydrolase, an inhibitor of PGE_2 synthase, a steroid, dopamine antagonist, or anticholinergic, including a compound of formula (I)-(XIII). Such agents are useful treatments in *Ebolavirus* infection management and biosafety defense, as well as platforms for developing new chemical entities for use in *Ebolavirus* treatment.

In addition, the invention provides a method to prevent, inhibit or treat viral infection in a mammal, e.g., a human, by administering a composition having an effective amount of a triphenylethylene, tamoxifen or a derivative thereof such as raloxifene and clomiphene, a calcium channel blocker, a tetranortriterpenoid, an antipsychotic, a sigma receptor agonist, an anticholinergic, a steroid, an inhibitor of calcium-independent phospholipase A_2, an inhibitor of magnesium-dependent phosphatidate phosphohydrolase, an inhibitor of the inducible microsomal PGE_2 synthase, a Hsp90 inhibitor, a dopamine antagonist, or a compound of formula (I)-(XIII), including compositions having those agents or compounds and pharmaceutically acceptable carriers and/or excipients. In one embodiment a composition for administration in prophylactic or therapeutic methods includes but is not limited to bepridil hydrochloride, clomiphene citrate, benzotropin mesylate, 7-deacetoxy-3-deacetyl-7-oxokhivorin, 1,2alpha-epoxy-7-deacetoxy-7-oxodihxdrogedunin, epoxygedunin, 1,3-dideacetyl-7-deacetoxy-7-oxokhivorin, gedunin, gedunol, dihydrogedunin, 3beta-acetoxydeoxodihydrogedunin, 3alpha-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 3beta-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 1,2alpha-epoxydeacetoxydihydrogedunin, 3beta-hydroxydeoxydesacetoxy-7-oxogedunin, tridesacetoxykhivorin, 1,3-dideacetylkhivorin, heudelottin C, tamoxifen citrate, fluspirilene, raloxifene hydrochloride, bromoenol lactone, cortexolone maleate, (R,R)-cis,diethyl tetrahydro-2,8-chrysenediol, MK-866, L-687, 384 hydrochloride, cycloheximide, HTS00384, NRB03063, CD03565, KM0483, SPB06885, CD04265, CD02075, PD00647, HTS07940, HTS13483, JFD02423, and/or HTS04029.

Thus, the invention provides compounds for use in medical therapy, such as agents that prevent, inhibit or treat filovirus infection in a mammal, optionally in conjunction with other compounds. Also provided is the use of the compounds for the manufacture of a medicament to prevent, inhibit or treat filovirus infection.

Brief Description of the Figures

Figure 1. Schematic diagram of EbolaΔVP30 constructs. (Top row) Schematic diagram of the *Ebolavirus* genome flanked by the leader sequence (l) and the trailer sequence (t) in positive-sense orientation. Two unique restriction sites for *Sal*I and *Sac*I (positions 6180 and 10942 of the viral antigenome, respectively) allowed the subcloning of a fragment that spans the VP30 gene. The subgenomic fragment was then used to replace the VP30 gene with genes encoding neomycin (neo) or enhanced green fluorescence protein (eGFP), respectively. Using the unique restriction sites, the altered subgenomic fragments were cloned back into the full-length *Ebolavirus* cDNA construct.

Figure 2. Characterization of EbolaΔVP30-neo virus. (A) Expression of *Ebolavirus* antigens by infected VeroVP30 cells. Confluent VeroVP30 cells (left panel) or wild-type Vero cells (right panel) were infected with EbolaΔVP30-neo for 60 minutes, washed, and overlaid with propagation medium with 1.5% methyl cellulose. Seven days later, cells were fixed with 10% buffered formaldehyde and an immunostaining assay with an antibody to *Ebolavirus* VP40 protein was performed. The formation of plaques in the VeroVP30 cell monolayer (left panel), but not in monolayers of wild-type Vero cells (right panel), illustrates thatEbolaΔVP30-neo virus is biologically contained. (B) Detection of EbolaΔVP30-neo viral proteins. Supernatants derived from infected VeroVP30 (labeled '+') or wild-type Vero (labeled '-') cells were collected 5 days after infection and partially purified over 20% sucrose. Protein pellets were suspended in PBS and separated on polyacrylamide gels, transferred to membranes and probed with specific antibodies to *Ebolavirus* proteins.

Figure 3. Replication kinetics of wild-type *Ebolavirus* and EbolaΔVP30-neo virus. VeroVP30 cells (top panels) and wild-type Vero cells (bottom panels) were infected with *Ebolavirus* or EbolaΔVP30-neo at a high m.o.i. of 1.0 (left panels) or a low m.o.i. of 0.01 (right panels). Supernatants were harvested every 24 hours postinfection for 6 days. Viral titers of the respective viruses were determined by infecting confluent VeroVP30 cells or wild-type Vero cells with tenfold dilutions of the supernatants and subsequent immunostaining. Virus titers for EbolaΔVP30-neo virus (solid squares) and wild-type *Ebolavirus* (open circles) were comparable in VeroVP30 cells (top panels). In wild-type Vero cells (bottom panels), no replication was detected for EbolaΔVP30-neo virus (solid squares).

Figure 4. Morphology of *Ebolaviruses* budding from infected cells. Vero cells infected with wild-type *Ebolavirus* (left panels) and VeroVP30 cells infected with EbolaΔVP30-neo virus (right panels) were processed for TEM 3 days postinfection. The pictures show virus budding from infected cells. No significant differences in morphology or budding efficiencies were observed for wild-type *Ebolavirus* and EbolaΔVP30-neo virus. Top panel, 6,000x magnification; bottom panel, 20,000x magnification of boxed area from top panel.

Figure 5. Ebola ΔVP30 virus generates an antibody response against the Ebola virus glycoprotein, GP. (A) Flow chart of vaccination of 4-week-old Balb/c mice with EbolaΔVP30 virus to determine the antibody titer to Ebola GP. Mice (n=4) were vaccinated three times with 10^7 FFU of Ebola ΔVP30 at three-week intervals; control mice (n=4) were simultaneously mock-vaccinated. Serum samples

were collected two weeks after each vaccination. (B) The amounts of IgG against purified Ebola virus GP in the samples was determined by ELISA. Results are expressed as the mean absorbance at 405 nm (+/- standard deviations) of samples diluted to 1:100.

Figure 6. Cellular immune response in Ebola ΔVP30-vaccinated mice. Mice (n=4) were vaccinated with EbolaΔVP30; control mice (n=2) were simultaneously mock-vaccinated. Splenocytes were collected 8 days after the second vaccination and stimulated with an NP peptide. Cells were stained for the cell surface antigen $CD8^+$ and for intracellular IFNγ. The number of cytokine-producing $CD8^+$ T cells was determined by using a FACSCalibur flow cytometer (BD Biosciences).

Figure 7. Flow chart of the vaccination schedule to determine the protective efficacy of the EbolaΔVP30 virus. Four-week-old Balb/c mice were vaccinated with EbolaΔVP30 virus. In group 1, mice (n=14) were vaccinated with nonpurified EbolaΔVP30 virus directly from cell culture supernatant, while control mice (n=8) were mock-vaccinated. In group 2, mice (n=15) were vaccinated with purified EbolaΔVP30 virus, while control mice (n=10) were mock-vaccinated. All mice were challenged with a 1000 MLD_{50} of mouse-adapted Ebola virus.

Figure 8. Body weight changes (A) and Kaplan-Meier survival curve (B) of mice vaccinated with EbolaΔVP30 compared to control mice. Mice from group 1 were vaccinated three times with non-purified EbolaΔVP30 virus while mice from group 2 were vaccinated twice with purified EbolaΔVP30 virus. Mice from the vaccinated groups and control groups were challenged with a 1000 MLD_{50} of mouse-adapted Ebola virus.

Figure 9. Virus titers in the serum of mice following lethal challenge. Vaccinated (n=3) and control (n=3) mice from groups 1 and 2 were euthanized on day 4 post-challenge. Virus titers from the serum were determined by the plaque assay. ND, not detectable.

Figure 10. Representative filovirus sequences (Accession numbers NC006432, NC004161, AY769362, AY142960, AF522874, AF499101, L11365, NC001608, DQ447652, DQ447649, AB050936, NC002549, NC001608, AF086833 and AF272001, the disclosures of which are incorporated by reference herein; SEQ ID NOs:1-30).

Figure 11. Compounds screened in an assay of the invention.

Figure 12. Chemical structures of gedunin (**1**), epoxygedunin (**2**), 1,3-Dideacetly-7-Deacetoxy-7-Oxokivorin (**3**), 7-Deacetoxy-3-deacetyl-7-Oxokhivorin (**4**), and 1,2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin (**5**).

Figure 13. Growth kinetics of viruses. Compounds were added to cell culture media 2 hours prior to virus infections. Cells were inoculated with EbolaΔVP30 virus, vaccinia virus, or adenovirus at an MOI of 10^{-3}, or *influenzavirus* or VSV at an MOI of 10^{-5}. Cell culture media (EbolaΔVP30, *influenzavirus*, and VSV) or cell culture media and cells (vaccinina virus and adenovirus) were collected 24, 48, and 72 hours post-infection for virus titer determinations. Dots and error bars indicate mean titers and standard deviations from three individual experiments, respectively.

Figure 14. Gedunin and gedunin-like compounds inhibit *Ebolavirus* GP-dependent virus entry. Compounds were added to cell culture media at 2 hours prior to VSVΔG*-*Ebolavirus* GP or VSVΔG*-VSV G virus infection. The number of GFP-positive cells was determined after an overnight incubation. % infectivity = 100 x number of GFP-positive cells + compound/number of GFP-positive cells + DMSO. Columns and error bars indicate mean % infectivities and standard deviations from four individual experiments, respectively.

Figure 15. Gedunin and epoxygedunin inhibit protein expression from the *Ebolavirus* minigenome. Compounds were added to cell culture media 6.5 hours post-transfection. Luciferase (luc) activities, expressed from the *Ebolavirus* minigenome, were measured on day 3 post-transfection. % luc activity = 100 x luc activity + compound/ luc activity + DMSO. Columns and error bars indicate mean % luc activities and standard deviations from three individual experiments, respectively.

Figure 16. Hsp90 inhibitors inhibit protein expression from the *Ebolavirus* minigenome. (A) Hsp90 inhibitors (10 μM) inhibit growth of EbolaΔVP30-GFP. Dots and error bars indicate mean titers and standard deviations from three individual experiments, respectively. (B) and (C) Hsp90 inhibitors (10 μM) do not substantially reduce *Ebolavirus* GP-mediated (or VSV-G-mediated) virus binding/entry. (D) Hsp90 inhibitors (10 μM) reduce protein expression from the *Ebolavirus* minigenome. Columns and error bars indicate mean % infectivities and standard deviations from four individual experiments, respectively.

Detailed Description of the Invention

Definitions

The term "isolated" when used in relation to a nucleic acid (e.g., vector or plasmid), peptide, polypeptide or virus refers to a nucleic acid sequence, peptide, polypeptide or virus that is identified and separated from at least one contaminant nucleic acid, polypeptide or other biological component with which it is ordinarily associated in its natural source, e.g., so that it is not associated with *in vivo* substances, or is substantially purified from *in vitro* substances. Isolated nucleic acid, peptide, polypeptide or virus is present in a form or setting that is different from that in which it is found in nature. For example, a given DNA sequence (e.g., a gene) is found on the host cell chromosome in proximity to neighboring genes; RNA sequences, such as a specific mRNA sequence encoding a specific protein, are found in the cell as a mixture with numerous other mRNAs that encode a multitude of proteins. An example of such DNA "isolated" from a source would be a useful DNA sequence that is excised or removed from said source by chemical means, e.g., by the use of restriction endonucleases, so that it can be further manipulated, e.g., amplified, for use in the invention, by the methodology of genetic engineering. The isolated nucleic acid molecule may be present in single-stranded or double-stranded form. When an isolated nucleic acid molecule is to be utilized to express a protein, the molecule will contain at a minimum the sense or coding strand (i.e., the molecule may single-stranded), but may contain both the sense and anti-sense strands (i.e., the molecule may be double-stranded).

A "vector" or "construct" (sometimes referred to as gene delivery or gene transfer "vehicle") refers to a macromolecule or complex of molecules comprising a polynucleotide to be delivered to a host cell, either *in vitro* or *in vivo*. The polynucleotide to be delivered may comprise a coding sequence of interest for gene therapy. Vectors include, for example, viral vectors (such as adenoviruses, adeno-associated viruses (AAV), lentiviruses, herpesvirus and retroviruses), liposomes and other lipid-containing complexes, and other macromolecular complexes capable of mediating delivery of a polynucleotide to a host cell. Vectors can also comprise other components or functionalities that further modulate gene delivery and/or gene expression, or that otherwise provide beneficial properties to the targeted cells. Such other components include, for example, components that influence binding or targeting to cells (including components that mediate cell-type or tissue-specific binding); components that influence uptake of the vector nucleic acid by the cell; components that influence localization of the polynucleotide within the cell after uptake (such as agents mediating nuclear localization); and components that influence expression of

the polynucleotide. Such components also might include markers, such as detectable and/or selectable markers that can be used to detect or select for cells that have taken up and are expressing the nucleic acid delivered by the vector. Such components can be provided as a natural feature of the vector (such as the use of certain viral vectors which have components or functionalities mediating binding and uptake), or vectors can be modified to provide such functionalities. A large variety of such vectors are known in the art and are generally available. When a vector is maintained in a host cell, the vector can either be stably replicated by the cells during mitosis as an autonomous structure, incorporated within the genome of the host cell, or maintained in the host cell's nucleus or cytoplasm.

A "recombinant viral vector" refers to a viral vector comprising one or more heterologous genes or sequences. Since many viral vectors exhibit size constraints associated with packaging, the heterologous genes or sequences are typically introduced by replacing one or more portions of the viral genome. Such viruses may become replication-defective (biologically contained), requiring the deleted function(s) to be provided in *trans* during viral replication and encapsidation (by using, e.g., a helper virus or a packaging cell line carrying genes necessary for replication and/or encapsidation). Modified viral vectors in which a polynucleotide to be delivered is carried on the outside of the viral particle have also been described.

"Gene delivery," "gene transfer," and the like as used herein, are terms referring to the introduction of an exogenous polynucleotide (sometimes referred to as a "transgene") into a host cell, irrespective of the method used for the introduction. Such methods include a variety of well-known techniques such as vector-mediated gene transfer (by, e.g., viral infection/transfection, or various other protein-based or lipid-based gene delivery complexes) as well as techniques facilitating the delivery of "naked" polynucleotides (such as electroporation, "gene gun" delivery and various other techniques used for the introduction of polynucleotides). The introduced polynucleotide may be stably or transiently maintained in the host cell. Stable maintenance typically requires that the introduced polynucleotide either contains an origin of replication compatible with the host cell or integrates into a replicon of the host cell such as an extrachromosomal replicon (e.g., a plasmid) or a nuclear or mitochondrial chromosome. A number of vectors are known to be capable of mediating transfer of genes to mammalian cells, as is known in the art.

By "transgene" is meant any piece of a nucleic acid molecule (for example, DNA) which is inserted by artifice into a cell either transiently or permanently, and becomes part of the organism if integrated into the genome or maintained extrachromosomally. Such a transgene may include at least a portion of an open reading frame of a gene which is partly or entirely heterologous (i.e., foreign) to the transgenic organism, or may represent at least a portion of an open reading frame of a gene homologous to an endogenous gene of the organism, which portion optionally encodes a polypeptide with substantially the same activity as the corresponding full-length polypeptide or at least one activity of the corresponding full-length polypeptide.

By "transgenic cell" is meant a cell containing a transgene. For example, a cell stably or transiently transformed with a vector containing an expression cassette is a transgenic cell that can be used to produce a population of cells having altered phenotypic characteristics. A "recombinant cell" is one which has been genetically modified, e.g., by insertion, deletion or replacement of sequences in a nonrecombinant cell by genetic engineering.

The term "wild-type" or "native" refers to a gene or gene product that has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which

is most frequently observed in a population and is thus arbitrarily designated the "normal" or "wild-type" form of the gene. In contrast, the term "modified" or "mutant" refers to a gene or gene product that displays modifications in sequence and or functional properties (i.e., altered characteristics) when compared to the wild-type gene or gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

The term "transduction" denotes the delivery of a polynucleotide to a recipient cell either *in vivo* or *in vitro*, via a viral vector and in one embodiment via a replication-defective viral vector.

The term "heterologous" as it relates to nucleic acid sequences such as gene sequences encoding a protein and control sequences, denotes sequences that are not normally joined together, and/or are not normally associated with a particular cell, e.g., are from different sources (for instance, sequences from a virus are heterologous to sequences in the genome of an uninfected cell). Thus, a "heterologous" region of a nucleic acid construct or a vector is a segment of nucleic acid within or attached to another nucleic acid molecule that is not found in association with the other molecule in nature. For example, a heterologous region of a nucleic acid construct could include a coding sequence flanked by sequences not found in association with the coding sequence in nature, i.e., a heterologous promoter. Another example of a heterologous coding sequence is a construct where the coding sequence itself is not found in nature (e.g., synthetic sequences having codons different from the native gene). Similarly, a cell transformed with a construct which is not normally present in the cell would be considered heterologous for purposes of this invention.

By "DNA" is meant a polymeric form of deoxyribonucleotides (adenine, guanine, thymine, or cytosine) in double-stranded or single-stranded form found, *inter alia*, in linear DNA molecules (e.g., restriction fragments), viruses, plasmids, and chromosomes. In discussing the structure of particular DNA molecules, sequences may be described herein according to the normal convention of giving only the sequence in the 5' to 3' direction along the nontranscribed strand of DNA (i.e., the strand having the sequence complementary to the mRNA). The term captures molecules that include the four bases adenine, guanine, thymine, or cytosine, as well as molecules that include base analogues which are known in the art.

As used herein, the terms "complementary" or "complementarity" are used in reference to polynucleotides (i.e., a sequence of nucleotides) related by the base-pairing rules. For example, the sequence "A-G-T," is complementary to the sequence "T-C-A." Complementarity may be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be "complete" or "total" complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. This is of particular importance in amplification reactions, as well as detection methods that depend upon binding between nucleic acids.

DNA molecules are said to have "5' ends" and "3' ends" because mononucleotides are reacted to make oligonucleotides or polynucleotides in a manner such that the 5' phosphate of one mononucleotide pentose ring is attached to the 3' oxygen of its neighbor in one direction via a phosphodiester linkage. Therefore, an end of an oligonucleotide or polynucleotide is referred to as the "5' end" if its 5' phosphate is not linked to the 3' oxygen of a mononucleotide pentose ring and as the "3' end" if its 3' oxygen is not linked to a 5' phosphate of a subsequent mononucleotide pentose ring. As used herein, a nucleic acid

sequence, even if internal to a larger oligonucleotide or polynucleotide, also may be said to have 5' and 3' ends. In either a linear or circular DNA molecule, discrete elements are referred to as being "upstream" or 5' of the "downstream" or 3' elements. This terminology reflects the fact that transcription proceeds in a 5' to 3' fashion along the DNA strand. The promoter and enhancer elements that direct transcription of a linked gene are generally located 5' or upstream of the coding region. However, enhancer elements can exert their effect even when located 3' of the promoter element and the coding region. Transcription termination and polyadenylation signals are located 3' or downstream of the coding region.

A "gene," "polynucleotide," "coding region," "sequence," "segment, " "fragment" or "transgene" which "encodes" a particular protein, is a nucleic acid molecule which is transcribed and optionally also translated into a gene product, e.g., a polypeptide, *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The coding region may be present in either a cDNA, genomic DNA, or RNA form. When present in a DNA form, the nucleic acid molecule may be single-stranded (i.e., the sense strand) or double-stranded. The boundaries of a coding region are determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus. A gene can include, but is not limited to, cDNA from prokaryotic or eukaryotic mRNA, genomic DNA sequences from prokaryotic or eukaryotic DNA, and synthetic DNA sequences. A transcription termination sequence will usually be located 3' to the gene sequence.

The term "control elements" refers collectively to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites ("IRES"), enhancers, splice junctions, and the like, which collectively provide for the replication, transcription, post-transcriptional processing and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present so long as the selected coding sequence is capable of being replicated, transcribed and translated in an appropriate host cell.

The term "promoter" is used herein in its ordinary sense to refer to a nucleotide region comprising a DNA regulatory sequence, wherein the regulatory sequence is derived from a gene which is capable of binding RNA polymerase and initiating transcription of a downstream (3' direction) coding sequence.

By "enhancer" is meant a nucleic acid sequence that, when positioned proximate to a promoter, confers increased transcription activity relative to the transcription activity resulting from the promoter in the absence of the enhancer domain.

By "operably linked" with reference to nucleic acid molecules is meant that two or more nucleic acid molecules (e.g., a nucleic acid molecule to be transcribed, a promoter, and an enhancer element) are connected in such a way as to permit transcription of the nucleic acid molecule. "Operably linked" with reference to peptide and/or polypeptide molecules is meant that two or more peptide and/or polypeptide molecules are connected in such a way as to yield a single polypeptide chain, i.e., a fusion polypeptide, having at least one property of each peptide and/or polypeptide component of the fusion. The fusion polypeptide is, in one embodiment, chimeric, i.e., composed of heterologous molecules.

"Homology" refers to the percent of identity between two polynucleotides or two polypeptides. The correspondence between one sequence and to another can be determined by techniques known in the art. For example, homology can be determined by a direct comparison of the sequence information between two polypeptide molecules by aligning the sequence information and using readily available computer programs. Alternatively, homology can be determined by hybridization of polynucleotides under conditions which form stable duplexes between homologous regions, followed by digestion with single

strand-specific nuclease(s), and size determination of the digested fragments. Two DNA, or two polypeptide, sequences are "substantially homologous" to each other when at least about 80%, e.g., at least about 90%, or at least about 95% of the nucleotides, or amino acids, respectively match over a defined length of the molecules, as determined using the methods above.

By "mammal" is meant any member of the class *Mammalia* including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats, rabbits and guinea pigs, and the like.

By "derived from" is meant that a nucleic acid molecule was either made or designed from a parent nucleic acid molecule, the derivative retaining substantially the same functional features of the parent nucleic acid molecule, e.g., encoding a gene product with substantially the same activity as the gene product encoded by the parent nucleic acid molecule from which it was made or designed.

By "expression construct" or "expression cassette" is meant a nucleic acid molecule that is capable of directing transcription. An expression construct includes, at the least, a promoter. Additional elements, such as an enhancer, and/or a transcription termination signal, may also be included.

The term "exogenous," when used in relation to a protein, gene, nucleic acid, or polynucleotide in a cell or organism refers to a protein, gene, nucleic acid, or polynucleotide which has been introduced into the cell or organism by artificial or natural means. An exogenous nucleic acid may be from a different organism or cell, or it may be one or more additional copies of a nucleic acid which occurs naturally within the organism or cell. By way of a non-limiting example, an exogenous nucleic acid is in a chromosomal location different from that of natural cells, or is otherwise flanked by a different nucleic acid sequence than that found in nature.

As used herein, the term "recombinant nucleic acid" or "recombinant DNA sequence, molecule or segment" refers to a nucleic acid, e.g., to DNA, that has been derived or isolated from a source, that may be subsequently chemically altered *in vitro*, and includes, but is not limited to, a sequence that is naturally occurring, is not naturally occurring, or corresponds to naturally occurring sequences that are not positioned as they would be positioned in the native genome. An example of DNA "derived" from a source, would be a DNA sequence that is identified as a useful fragment, and which is then chemically synthesized in essentially pure form. An example of such DNA "isolated" from a source would be a useful DNA sequence that is excised or removed from said source by chemical means, e.g., by the use of restriction endonucleases, so that it can be further manipulated, e.g., amplified, for use in the invention, by the methodology of genetic engineering.

The term "recombinant protein" or "recombinant polypeptide" as used herein refers to a protein molecule that is expressed from a recombinant DNA molecule.

The term "peptide", "polypeptide" and protein" are used interchangeably herein unless otherwise distinguished.

The term "sequence homology" means the proportion of base matches between two nucleic acid sequences or the proportion amino acid matches between two amino acid sequences. When sequence homology is expressed as a percentage, e.g., 50%, the percentage denotes the proportion of matches over the length of a selected sequence that is compared to some other sequence. Gaps (in either of the two sequences) are permitted to maximize matching; gap lengths of 15 bases or less are usually used, 6 bases or less are preferred with 2 bases or less more preferred. When using oligonucleotides as probes

or treatments, the sequence homology between the target nucleic acid and the oligonucleotide sequence is generally not less than 17 target base matches out of 20 possible oligonucleotide base pair matches (85%); such as not less than 9 matches out of 10 possible base pair matches (90%), and, for example, not less than 19 matches out of 20 possible base pair matches (95%).

The term "selectively hybridize" means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments of the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and fragments of the invention and a nucleic acid sequence of interest is at least 65%, and more typically with increasing homologies of at least about 70%, about 90%, about 95%, about 98%, and 100%.

Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. The two sequences or parts thereof are more likely homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program.

The term "corresponds to" is used herein to mean that a polynucleotide sequence is homologous (e.g., is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence that encodes a polypeptide or its complement, or that a polypeptide sequence is identical in sequence or function to a reference polypeptide sequence. For illustration, the nucleotide sequence "TATAC" corresponds to a reference sequence "TATAC" and is complementary to a reference sequence "GTATA".

The following terms are used to describe the sequence relationships between two or more polynucleotides: "reference sequence", "comparison window", "sequence identity", "percentage of sequence identity", and "substantial identity". A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA or gene sequence given in a sequence listing, or may comprise a complete cDNA or gene sequence. Generally, a reference sequence is at least 20 nucleotides in length, frequently at least 25 nucleotides in length, and often at least 50 nucleotides in length. Since two polynucleotides may each (1) comprise a sequence (i.e., a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) may further comprise a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity.

A "comparison window", as used herein, refers to a conceptual segment of at least 20 contiguous nucleotides and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence

(which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by using local homology algorithms or by a search for similarity method, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA Genetics Software Package or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected.

The term "sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" means that two polynucleotide sequences are identical (i.e., on a nucleotide-by-nucleotide basis) over the window of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, U, or I) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The terms "substantial identity" as used herein denote a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 85 percent sequence identity, e.g., at least 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison window of at least 20 nucleotide positions, frequently over a window of at least 20-50 nucleotides, wherein the percentage of sequence identity is calculated by comparing the reference sequence to the polynucleotide sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the window of comparison.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least about 80% sequence identity, e.g., at least about 90% sequence identity, including at least about 95% percent sequence identity, or at least about 99% sequence identity.

A "protective immune response" and "prophylactic immune response" are used interchangeably to refer to an immune response which targets an immunogen to which the individual has not yet been exposed or targets a protein associated with a disease in an individual who does not have the disease, such as a tumor associated protein in a patient who does not have a tumor.

A "therapeutic immune response" refers to an immune response which targets an immunogen to which the individual has been exposed or a protein associated with a disease in an individual who has the disease.

The term "prophylactically effective amount" is meant to refer to the amount necessary to, in the case of infectious agents, prevent an individual from developing an infection, and in the case of diseases, prevent an individual from developing a disease.

The term "therapeutically effective amount" is meant to refer to the amount necessary to, in the case of infectious agents, reduce the level of infection in an infected individual in order to reduce symptoms or eliminate the infection, and in the case of diseases, to reduce symptoms or cure the individual.

"Inducing an immune response against an immunogen" is meant to refer to induction of an immune response in a naïve individual and induction of an immune response in an individual previously exposed to an immunogen wherein the immune response against the immunogen is enhanced.

As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition), and may be a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present. Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, for example, more than about 85%, about 90%, about 95%, and about 99%. Min one embodiment, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

"Transfected," "transformed" or "transgenic" is used herein to include any host cell or cell line, which has been altered or augmented by the presence of at least one recombinant DNA sequence. The host cells of the present invention are typically produced by transfection with a DNA sequence in a plasmid expression vector, as an isolated linear DNA sequence, or infection with a recombinant viral vector.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the compounds useful in the present invention can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985), the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

One diastereomer of a compound disclosed herein may display superior activity compared with the other. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Thomas J .Tucker, et al., J. Med. Chem. 1994 37, 2437-2444. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g. Mark A. Huffman, et al., J. Org. Chem. 1995, 60, 1590-1594.

As used herein, "treating" or "treat" includes (i) preventing a pathologic condition from occurring (e.g. prophylaxis); (ii) inhibiting the pathologic condition or arresting its development; (iii) relieving the pathologic condition; and/or diminishing symptoms associated with the pathologic condition.

As used herein, the term "patient" refers to organisms to be treated by the methods of the present invention. Such organisms include, but are not limited to, mammals such as humans. In the context of the invention, the term "subject" generally refers to an individual who will receive or who has received treatment (e.g., administration of a compound of the invention).

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated by the present invention.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. When a substituent is keto (i.e., =O) or thioxo (i.e., =S) group, then 2 hydrogens on the atom are replaced.

"Interrupted" is intended to indicate that in between two or more adjacent carbon atoms, and the hydrogen atoms to which they are attached (e.g., methyl (CH_3), methylene (CH_2) or methine (CH)), indicated in the expression using "interrupted" is inserted with a selection from the indicated group(s), provided that the each of the indicated atoms' normal valency is not exceeded, and that the interruption results in a stable compound. Such suitable indicated groups include, e.g., non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), imine (C=NH), sulfonyl (SO) or sulfoxide (SO_2).

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

"Alkyl" refers to a C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-

$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$.

The alkyl can optionally be substituted with one or more alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. The alkyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2). Additionally, the alkyl can optionally be at least partially unsaturated, thereby providing an alkenyl.

"Alkenyl" refers to a C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl (-$CH=CH_2$), allyl (-$CH_2CH=CH_2$), cyclopentenyl (-C_5H_7), and 5-hexenyl (-CH_2 $CH_2CH_2CH_2CH=CH_2$).

The alkenyl can optionally be substituted with one or more alkyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. Additionally, the alkenyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2).

"Alkylidenyl" refers to a C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methylidenyl (=CH_2), ethylidenyl (=$CHCH_3$), 1-propylidenyl (=$CHCH_2CH_3$), 2-propylidenyl (=$C(CH_3)_2$), 1-butylidenyl (=$CHCH_2CH_2CH_3$), 2-methyl-1-propylidenyl (=$CHCH(CH_3)_2$), 2-butylidenyl (=$C(CH_3)CH_2CH_3$), 1-pentyl (=$CHCH_2CH_2CH_2CH_3$), 2-pentylidenyl (=$C(CH_3)CH_2CH_2CH_3$), 3-pentylidenyl (=$C(CH_2CH_3)_2$), 3-methyl-2-butylidenyl (=$C(CH_3)CH(CH_3)_2$), 3-methyl-1-butylidenyl (=$CHCH_2CH(CH_3)_2$), 2-methyl-1-butylidenyl (=$CHCH(CH_3)CH_2CH_3$), 1-hexylidenyl (=$CHCH_2CH_2CH_2CH_2CH_3$), 2-hexylidenyl (=$C(CH_3)CH_2CH_2CH_2CH_3$), 3-hexylidenyl (=$C(CH_2CH_3)(CH_2CH_2CH_3)$), 3-methyl-2-pentylidenyl (=$C(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentylidenyl (=$C(CH_3)CH_2CH(CH_3)_2$), 2-methyl-3-pentylidenyl (=$C(CH_2CH_3)CH(CH_3)_2$), and 3,3-dimethyl-2-butylidenyl (=$C(CH_3)C(CH_3)_3$.

The alkylidenyl can optionally be substituted with one or more alkyl, alkenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. Additionally, the alkylidenyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2).

"Alkenylidenyl" refers to a C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: allylidenyl (=CHCH=CH_2), and 5-hexenylidenyl (=$CHCH_2CH_2CH_2CH$=CH_2).

The alkenylidenyl can optionally be substituted with one or more alkyl, alkenyl, alkylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. Additionally, the alkenylidenyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2).

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH_2-) 1,2-ethyl (-CH_2CH_2-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

The alkylene can optionally be substituted with one or more alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. Additionally, the alkylene can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2). Moreover, the alkylene can optionally be at least partially unsaturated, thereby providing an alkenylene.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

The alkenylene can optionally be substituted with one or more alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. Additionally, The alkenylene can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), sulfonyl (SO) or sulfoxide (SO_2).

The term "alkoxy" refers to the groups alkyl-O-, where alkyl is defined herein. Preferred alkoxy groups include, e.g., methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The alkoxy can optionally be substituted with one or more alkyl, alkylidenyl, alkenylidenyl, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and $COOR^x$, wherein each R^x and R^y are independently H, alkyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Preferred aryls include phenyl, naphthyl and the like.

The aryl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and $COOR^x$, wherein each R^x and R^y are independently H, alkyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The cycloalkyl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and $COOR^x$, wherein each R^x and R^y are independently H, alkyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl. .

The cycloalkyl can optionally be at least partially unsaturated, thereby providing a cycloalkenyl.

The term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

"Haloalkyl" refers to alkyl as defined herein substituted by 1-4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12,12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, and the like.

The term "heteroaryl" is defined herein as a monocyclic, bicyclic, or tricyclic ring system containing one, two, or three aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include, but are not limited to, 2*H*-pyrrolyl, 3*H*-indolyl, 4*H*-quinolizinyl, 4n*H*-carbazolyl, acridinyl, benzo[*b*]thienyl, benzothiazolyl, β-carbolinyl, carbazolyl, chromenyl, cinnaolinyl, dibenzo[b,d]furanyl, furazanyl, furyl, imidazolyl, imidizolyl, indazolyl, indolisinyl, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, naptho[2,3-*b*], oxazolyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, triazolyl, and xanthenyl. In one embodiment the term "heteroaryl" denotes a monocyclic aromatic ring containing five or six ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from the group non-peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, alkyl, phenyl or benzyl. In another embodiment heteroaryl denotes an ortho-fused bicyclic heterocycle of about eight to ten ring atoms

derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, or tetramethylene diradical thereto.

The heteroaryl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and $COOR^x$, wherein each R^x and R^y are independently H, alkyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl.

The term "heterocycle" refers to a saturated or partially unsaturated ring system, containing at least one heteroatom selected from the group oxygen, nitrogen, and sulfur, and optionally substituted with alkyl or $C(=O)OR^b$, wherein R^b is hydrogen or alkyl. Typically heterocycle is a monocyclic, bicyclic, or tricyclic group containing one or more heteroatoms selected from the group oxygen, nitrogen, and sulfur. A heterocycle group also can contain an oxo group (=O) attached to the ring. Non-limiting examples of heterocycle groups include 1,3-dihydrobenzofuran, 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2*H*-pyran, 2-pyrazoline, 4*H*-pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuclidine, and thiomorpholine.

The heterocycle can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, NR^xR^y and $COOR^x$, wherein each R^x and R^y are independently H, alkyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxyl.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles. In one specific embodiment of the invention, the nitrogen heterocycle can be 3-methyl-5,6-dihydro-4H-pyrazino[3,2,1-jk]carbazol-3-ium iodide.

Another class of heterocyclics is known as "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating units of the formula $[-(CH_2-)_aA-]$ where a is equal to or greater than 2, and A at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, $[-(CH_2)_3-NH-]_3$, $[-((CH_2)_2-O)_4-((CH_2)_2-NH)_2]$ and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "alkanoyl" refers to C(=O)R, wherein R is an alkyl group as previously defined.

The term "acyloxy" refers to –O-C(=O)R, wherein R is an alkyl group as previously defined. Examples of acyloxy groups include, but are not limited to, acetoxy, propanoyloxy, butanoyloxy, and pentanoyloxy. Any alkyl group as defined above can be used to form an acyloxy group.

The term "alkoxycarbonyl" refers to C(=O)OR, wherein R is an alkyl group as previously defined.

The term "amino" refers to $-NH_2$, and the term "alkylamino" refers to $-NR_2$, wherein at least one R is alkyl and the second R is alkyl or hydrogen. The term "acylamino" refers to RC(=O)N, wherein R is alkyl or aryl.

The term "imino" refers to –C=NH.

The term "nitro" refers to $-NO_2$.

The term "trifluoromethyl" refers to $-CF_3$.

The term "trifluoromethoxy" refers to $-OCF_3$.

The term "cyano" refers to -CN.

The term "hydroxy" or "hydroxyl" refers to –OH.

The term "oxy" refers to –O-.

The term "thio" refers to –S-.

The term "thioxo" refers to (=S).

The term "keto" refers to (=O).

As to any of the above groups, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

The compounds described herein can be administered as the parent compound, a pro-drug of the parent compound, or an active metabolite of the parent compound.

"Pro-drugs" are intended to include any covalently bonded substances which release the active parent drug or other formulas or compounds of the present invention in vivo when such pro-drug is administered to a mammalian subject. Pro-drugs of a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation in vivo, to the parent compound. Pro-drugs include compounds of the present invention wherein a carbonyl, carboxylic acid, hydroxy or amino group is bonded to any group that, when the pro-drug is administered to a mammalian subject, cleaves to form a free carbonyl, carboxylic acid, hydroxy or amino group. Examples of pro-drugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention, and the like.

"Metabolite" refers to any substance resulting from biochemical processes by which living cells interact with the active parent drug or other formulas or compounds of the present invention in vivo, when such active parent drug or other formulas or compounds of the present are administered to a mammalian subject. Metabolites include products or intermediates from any metabolic pathway.

"Metabolic pathway" refers to a sequence of enzyme-mediated reactions that transform one compound to another and provide intermediates and energy for cellular functions. The metabolic pathway can be linear or cyclic.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

Methods of the Invention

The present invention provides a method for screening for compounds that prevent or inhibit viral infection, e.g., prevent or inhibit viral binding to a host cell surface molecule, e.g., receptor, or prevent or inhibit viral membrane fusion with host cell membrane(s). In one embodiment, the screening method includes contacting cells permissive for viral infection with one or more test agents and a recombinant virus, e.g., a pseudotyed virus or a replication defective, e.g., biologically contained, virus to identify agents that prevent or inhibit viral infection. In one embodiment, cells are first contacted with one or more test agents and then with a recombinant virus to identify agents that prevent or inhibit viral infection. In one embodiment, cells are contacted with a recombinant virus and then with one or more test agents. The methods thus identify compounds that may be used alone or in conjunction with other anti-virals, or other prophylactic or therapeutic compounds.

Agents identified as having anti-viral properties, e.g., agents identified in the screening methods of the invention as having anti-viral properties, are useful in methods to prevent, inhibit or treat viral infection in a mammal. For example, a dopamine antagonist identified as useful to inhibit viral infection or replication *in vitro* may be employed to prevent, inhibit or treat viral infection *in vivo*.

Exemplary Viruses Useful in Methods of the Invention

The invention provides isolated vectors, e.g., plasmids, which encode proteins of negative-sense, single stranded RNA viruses and/or express vRNA from recombinant nucleic acid corresponding to sequences for mutant negative-sense, single stranded RNA viruses. In one embodiment, when introduced into a cell, a combination of these vectors is capable of yielding recombinant infectious, biologically contained virus. Thus, the invention includes host cells that produce recombinant infectious, biologically contained virus. In one embodiment, the invention provides isolated vectors, e.g., plasmids, which encode filovirus proteins and/or express mutant filovirus vRNA which, when introduced into a cell, are capable of yielding recombinant infectious, biologically contained filovirus. In one embodiment, the invention provides isolated vectors, e.g., plasmids, which express mutant negative sense vRNA having reporter sequences and lacking viral glycoprotein sequence and vectors that encode filovirus glycoprotein and optionally non-filovirus proteins which, when introduced into a cell, are capable of yielding a pseudotyped recombinant virus. The invention includes host cells that transiently or stably produce the recombinant virus, including helper cells, and isolated recombinant virus prepared by the methods disclosed herein.

Thus, vectors of the invention include those for mRNA production and vRNA production. In one embodiment, the vectors include filovirus DNA, for example, vectors for mRNA production with sequences corresponding to one or more open reading frames encoding filovirus proteins, or vectors for vRNA production that include a deletion of the full-length genomic sequence, which deletion includes internal filovirus sequences corresponding to at least a portion of one open reading frame. The RNA produced from the vRNA vector is capable of being packaged into virions in the presence of filovirus proteins but as

part of the resulting virion, is not capable of being replicated and so does not result in virus production when that virion is introduced to a cell that otherwise supports filovirus replication and which cell does not express at least one filovirus protein *in trans*, e.g., a cell that is not a filovirus helper cell.

For example, *Ebolaviruses* possess a negative-sense, nonsegmented RNA genome, approximately 19 kilobases in length that encodes seven structural proteins and at least one non-structural protein (Sanchez et al., 2007). NP, viral protein (VP)35, VP30, and L, the RNA-dependent RNA polymerase, are components of the nucleocapsid involved in viral replication and transcription (Muhlberger et al., 1999). VP40 is the matrix protein and is involved in viral budding (Harty et al., 2000; Panchal et al., 2003). VP24 is involved in the formation of nucleocapsids composed of NP, VP35 and viral RNA (Huang et al., 2002). The only viral surface glycoprotein, GP, plays a role in viral attachment and entry (Chan et al., 2001; Manicassamy et al., 2005; Shimojima et al., 2006; Chandran et al., 2005). Candidate sequences for deletion/mutation and optional replacement with heterologous sequences include but are not limited to Ebola virus VP30 sequences or corresponding sequences in other negative-sense, single stranded RNA viruses, e.g., sequences for nonstructural, nonpolymerase and/or nonglycosylated viral proteins. Although deletions in other Ebola virus sequences, i.e., in GP and VP40, were prepared, only deletions in VP30 sequences resulted in virus that could be recovered. However, deletions in sequences that do not correspond to VP30 sequences in other negative-sense, single stranded RNA viruses may yield infectious, biologically contained virus that is useful in vaccines or in drug screening.

The vectors may include gene(s) or portions thereof other than those of a negative-sense, single stranded RNA virus such as a filovirus (heterologous sequences), which genes or portions thereof are intended to be expressed in a host cell, either as a protein or incorporated into vRNA. Thus, a vector of the invention may include in addition to viral sequences, for instance, filovirus sequences, a gene or open reading frame of interest, e.g., a heterologous gene for an immunogenic peptide or protein useful as a vaccine or a therapeutic protein.

To express vRNA, e.g., mutant vRNA, the promoter which is operably linked to viral and reporter gene sequences, which may be in antisense (antigenomic orientation for negative-sense viruses), may be, for example, a RNA polymerase I promoter, a RNA polymerase II promoter, a RNA polymerase III promoter, a T7 promoter, or a T3 promoter. The transcription termination sequence may be a RNA polymerase I transcription termination sequence, a RNA polymerase II transcription termination sequence, a RNA polymerase III transcription termination sequence, or a ribozyme.

Any promoter may be employed to express a viral protein. A promoter for the vectors includes but is not limited to a RNA polymerase I promoter, a RNA polymerase II promoter, a RNA polymerase III promoter, a T7 promoter, and a T3 promoter. Each vector comprising an open reading frame may include a transcription termination sequence such as a RNA polymerase I transcription termination sequence, a RNA polymerase II transcription termination sequence, a RNA polymerase III transcription termination sequence, or a ribozyme. Preferred promoters for the vectors for vRNA include, but are not limited to, a RNA polymerase I promoter, a RNA polymerase II promoter, a RNA polymerase III promoter, a T7 promoter, and a T3 promoter. In one embodiment, the vector or plasmid which expresses vRNA comprises a promoter, e.g., a RNA polymerase I, suitable for expression in a particular host cell, e.g., avian or mammalian host cells such as canine, feline, equine, bovine, ovine, or primate cells including human cells. In one embodiment, the RNA polymerase I promoter is a human RNA polymerase I

promoter. The vectors or plasmids comprising DNA useful to prepare influenza vRNA may comprise RNA polymerase I transcription termination sequences. Preferred transcription termination sequences for the vectors for vRNA include, but are not limited to, a RNA polymerase I transcription termination sequence, a RNA polymerase II transcription termination sequence, or a RNA polymerase III transcription termination sequence, or a ribozyme.

If more than one vector is employed, the vectors may be physically linked or each vector may be present on an individual plasmid or other, e.g., linear, nucleic acid delivery vehicle. The vectors or plasmids may be introduced to any host cell, e.g., a eukaryotic cell such as a mammalian cell, that supports viral replication. Host cells useful to prepare virus of the invention include but are not limited to insect, avian or mammalian host cells such as canine, feline, equine, bovine, ovine, or primate cells including simian or human cells. In one embodiment, the host cell is one that is approved for vaccine production.

The viruses produced by methods described herein are useful in viral mutagenesis studies, drug screening and in the production of vaccines (e.g., for AIDS, influenza, hepatitis B, hepatitis C, rhinovirus, filoviruses, malaria, herpes, and foot and mouth disease) and gene therapy vectors (e.g., for cancer, AIDS, adenosine deaminase, muscular dystrophy, ornithine transcarbamylase deficiency and central nervous system tumors). In particular, infectious, biologically contained filovirus of the invention which induces strong humoral and cellular immunity may be employed as a vaccine vector, as they are unlikely to give rise to infectious recombinant virus.

Thus, a virus for use in medical therapy (e.g., for a vaccine or gene therapy) is provided. For example, the invention provides a method to immunize an animal against a pathogen, e.g., a bacteria, virus such as Ebola virus, or parasite, or a malignant tumor. The method comprises administering to the animal an effective amount of at least one isolated virus of the invention which encodes and expresses, or comprises nucleic acid for an immunogenic peptide or protein of a pathogen or tumor, optionally in combination with an adjuvant, effective to immunize the animal.

To prepare expression cassettes for transformation herein, the recombinant DNA sequence or segment may be circular or linear, double-stranded or single-stranded. A DNA sequence which encodes an RNA sequence that is substantially complementary to a mRNA sequence encoding a gene product of interest is typically a "sense" DNA sequence cloned into a cassette in the opposite orientation (i.e., 3□ to 5□ rather than 5□ to 3□). Generally, the DNA sequence or segment is in the form of chimeric DNA, such as plasmid DNA, that can also contain coding regions flanked by control sequences which promote the expression of the DNA in a cell. As used herein, "chimeric" means that a vector comprises DNA from at least two different species, or comprises DNA from the same species, which is linked or associated in a manner which does not occur in the "native" or wild-type of the species.

Aside from DNA sequences that serve as transcription units, or portions thereof, a portion of the DNA may be untranscribed, serving a regulatory or a structural function. For example, the DNA may itself comprise a promoter that is active in eukaryotic cells, e.g., mammalian cells, or in certain cell types, or may utilize a promoter already present in the genome that is the transformation target of the lymphotropic virus. Such promoters include the CMV promoter, as well as the SV40 late promoter and retroviral LTRs (long terminal repeat elements), e.g., the MMTV, RSV, MLV or HIV LTR, although many other promoter elements well known to the art may be employed in the practice of the invention.

Other elements functional in the host cells, such as introns, enhancers, polyadenylation sequences and the like, may also be a part of the recombinant DNA. Such elements may or may not be necessary for the function of the DNA, but may provide improved expression of the DNA by affecting transcription, stability of the mRNA, or the like. Such elements may be included in the DNA as desired to obtain the optimal performance of the transforming DNA in the cell.

The recombinant DNA to be introduced into the cells may contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of transformed cells from the population of cells sought to be transformed. Alternatively, the selectable marker may be carried on a separate piece of DNA and used in a co-transformation procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers are well known in the art and include, for example, antibiotic and herbicide-resistance genes, such as *neo, hpt, dhfr, bar, aroA, puro, hyg, dapA* and the like. See also, the genes listed on Table 1 of Lundquist et al. (U.S. Patent No. 5,848,956).

Reporter genes are used for identifying potentially transformed cells and for evaluating the functionality of regulatory sequences. Reporter genes which encode for easily assayable proteins are well known in the art. In general, a reporter gene is a gene which is not present in or expressed by the recipient organism or tissue and which encodes a protein whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Exemplary reporter genes include the chloramphenicol acetyl transferase gene (cat) from Tn9 of *E. coli*, the beta-glucuronidase gene (gus) of the *uidA* locus of *E. coli*, the green, red, or blue fluorescent protein gene, and the luciferase gene. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells.

The general methods for constructing recombinant DNA which can transform target cells are well known to those skilled in the art, and the same compositions and methods of construction may be utilized to produce the DNA useful herein. For example, Sambrook et al., Molecular Cloning: A Laboratory Manual (2002) provides suitable methods of construction.

The recombinant DNA can be readily introduced into the host cells, e.g., mammalian, yeast or insect cells, by transfection with an expression vector comprising the recombinant DNA by any procedure useful for the introduction into a particular cell, e.g., physical or biological methods, to yield a transformed (transgenic) cell having the recombinant DNA so that the DNA sequence of interest is expressed by the host cell. In one embodiment, at least one of the recombinant DNA which is introduced to a cell is maintained extrachromosomally. In one embodiment, at least one recombinant DNA is stably integrated into the host cell genome.

Physical methods to introduce a recombinant DNA into a host cell include calcium-mediated methods, lipofection, particle bombardment, microinjection, electroporation, and the like. Biological methods to introduce the DNA of interest into a host cell include the use of DNA and RNA viral vectors. Viral vectors, e.g., retroviral or lentiviral vectors, have become a widely used method for inserting genes into eukaryotic, such as mammalian, e.g., human, cells. Other viral vectors useful to introduce genes into cells can be derived from poxviruses, e.g., vaccinia viruses, herpes viruses, adenoviruses, adeno-associated viruses, baculoviruses, and the like.

To confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such assays include, for example, molecular biological assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; biochemical assays, such as

detecting the presence or absence of a particular gene product, e.g., by immunological means (ELISAs and Western blots) or by other molecular assays.

To detect and quantitate RNA produced from introduced recombinant DNA segments, RT-PCR may be employed. In this application of PCR, it is first necessary to reverse transcribe RNA into DNA, using enzymes such as reverse transcriptase, and then through the use of conventional PCR techniques amplify the DNA. In most instances PCR techniques, while useful, will not demonstrate integrity of the RNA product. Further information about the nature of the RNA product may be obtained by Northern blotting. This technique demonstrates the presence of an RNA species and gives information about the integrity of that RNA. The presence or absence of an RNA species can also be determined using dot or slot blot Northern hybridizations. These techniques are modifications of Northern blotting and only demonstrate the presence or absence of an RNA species.

While Southern blotting and PCR may be used to detect the recombinant DNA segment in question, they do not provide information as to whether the recombinant DNA segment is being expressed. Expression may be evaluated by specifically identifying the peptide products of the introduced DNA sequences or evaluating the phenotypic changes brought about by the expression of the introduced DNA segment in the host cell.

The recombinant viruses described herein have modifications in genomic sequences relative to a corresponding wild-type viral genome, i.e., the genome of the recombinant virus has a modification which includes a deletion, and optionally an insertion, in a region corresponding to sequences for a viral protein that is associated with transcription, is nonstructural or nonglycosylated, or is a glycoprotein. The mutation in the viral genome is effective to inhibit or prevent production of at least one functional viral protein from that genome when those sequences are present in a nontransgenic cell which supports viral replication. In one embodiment, the deletion includes from 1 up to thousands of nucleotides, e.g., 1%, 10%, 50%, 90% or more of sequences corresponding to the coding region for the viral protein. In one embodiment, the deleted sequences correspond to sequences with a substantial identity, e.g., at least 80% or more, e.g., 85%, 90% or 95% and up to 100% or any integer in between, nucleic acid sequence identity, to VP30 sequences.

In one embodiment, the viral genome in an infectious, replication-incompetent negative-sense, single-stranded RNA virus of the invention includes a deletion in sequences corresponding to those in a wild-type viral genome for a protein that is associated with transcription or is nonstructural or nonglycoslyated, or is a glycoprotein, and includes heterologous sequences that are nontoxic to host cells including cells in an organism to be immunized. In one embodiment, the heterologous sequence is a marker sequence, a selectable sequence or other sequence which is detectable or capable of detection, e.g., GFP or luciferase, or a selectable gene such as an antibiotic resistance gene, e.g., a hygromycin B resistance gene or neomycin phosphotransferase gene, which marker gene or selectable gene is not present in the host cell prior to introduction of the vector.

Pharmaceutical Compositions

Pharmaceutical anti-viral compositions of the present invention, suitable for administration, e.g., nasal, parenteral or oral administration, such as by intravenous, intramuscular, topical or subcutaneous routes, optionally further comprising sterile aqueous or non-aqueous solutions, suspensions, and emulsions. The compositions can further comprise auxiliary agents or excipients, as known in the art. The composition of the invention is generally presented in the form of individual doses (unit doses).

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and/or emulsions, which may contain auxiliary agents or excipients known in the art. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, or sweetening, flavoring, or perfuming agents.

When a composition of the present invention is used for administration to an individual, it can further comprise salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. For vaccines, adjuvants, substances which can augment a specific immune response, can be used. Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same site of the organism being immunized.

In one embodiment, the pharmaceutical composition is part of a controlled release system, e.g., one having a pump, or formed of polymeric materials (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger & Peppas, J. Macromol. Sci. Rev. Macromol. Chem., 23:61 (1983); see also Levy et al., Science, 228:190 (1985); During et al., Ann. Neurol., 25:351 (1989); Howard et al., J. Neurosurg., 71:105 (1989)). Other controlled release systems are discussed in the review by Langer (Science, 249:1527 (1990)).

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of one or more anti-viral compounds, for instance, those identified by the screening methods of the invention, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeiae for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the pharmaceutical composition is administered. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. These compositions can be formulated as a suppository. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the virus, such as one in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

The compositions may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent. For oral administration, the compound(s) may be combined with one or more excipients and used in the form of ingestible capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such useful compositions is such that an effective dosage level will be obtained.

The compositions may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. Various other materials may be present. For instance, a syrup or elixir may contain the virus, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form, including sustained-release preparations or devices, should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. The composition also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the compound(s)can be prepared in water or a suitable buffer, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of undesirable microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of undesirable microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it may be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride.

Sterile injectable solutions are prepared by incorporating the compound(s)in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization.

Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compound(s) can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads,

used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Useful dosages of the compositions of the invention can be determined by comparing their *in vitro* activity and *in vivo* activity in animal models.

Pharmaceutical Purposes

The administration of the composition may be for either a "prophylactic" or "therapeutic" purpose. When provided prophylactically, the compositions of the invention are provided before any symptom or clinical sign of a pathogen infection becomes manifest. The prophylactic administration of the composition serves to prevent or attenuate any subsequent infection.

When provided therapeutically, the compositions of the invention are provided upon the detection of a symptom or clinical sign of actual infection. The therapeutic administration of the compound(s) serves to attenuate any actual infection.

Thus, a composition of the present invention may be provided either before the onset of infection (so as to prevent or attenuate an anticipated infection) or after the initiation of an actual infection.

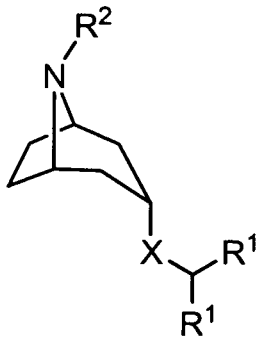
A composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient mammal. Such an agent is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. A composition of the present invention is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient, e.g., enhances at least one primary or secondary humoral or cellular immune response against at least one strain of a virus.

The "protection" provided need not be absolute, i.e., the infection need not be totally prevented or eradicated, if there is a statistically significant improvement compared with a control population or set of mammals. Protection may be limited to mitigating the severity or rapidity of onset of symptoms or clinical signs of the virus infection.

Exemplary Compounds and Formulations

Compounds useful in methods of the invention include, but are not limited to, triphenylethylenes, tamoxifen and derivatives thereof such as raloxifene and clomiphene, calcium channel blockers, tetranortriterpenoids, antipsychotics, sigma receptor agonists, anticholinergics, steroids, inhibitor of calcium-independent phospholipase A_2, inhibitors of magnesium-dependent phosphatidate phosphohydrolase, inhibitors of the inducible microsomal PGE_2 synthase, inhibitors of Hsp90, and dopamine antagonists.

In one embodiment, the compound may be a compound of formula (I):



(I)

wherein

X is O or NH;

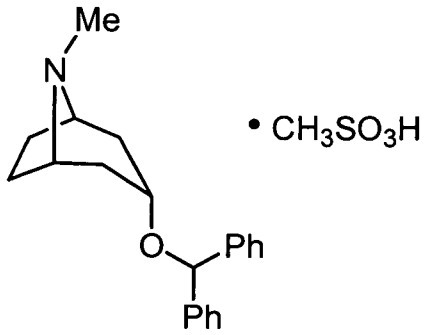
each R^1 is independently aryl, heteroaryl, $(C_1\text{-}C_{10})$alkyl, or $(C_1\text{-}C_{10})$alkaryl;

R^2 is $(C_1\text{-}C_{10})$alkyl; and

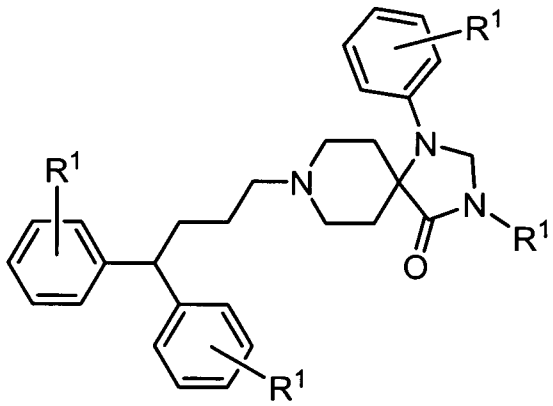
any aryl, heteroaryl, alkyl of R^1 and R^2 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

The various salts of formula I, and of formulas II-VII below, can be formed from, for example, pharmaceutically acceptable acids such as methane sulfonic acid, benzene sulfonic acid, or toluene sulfonic acid. In one specific embodiment, the compound of formula (I) is benztropine mesylate:



In another embodiment, the compound may be a compound of formula (II):



(II)

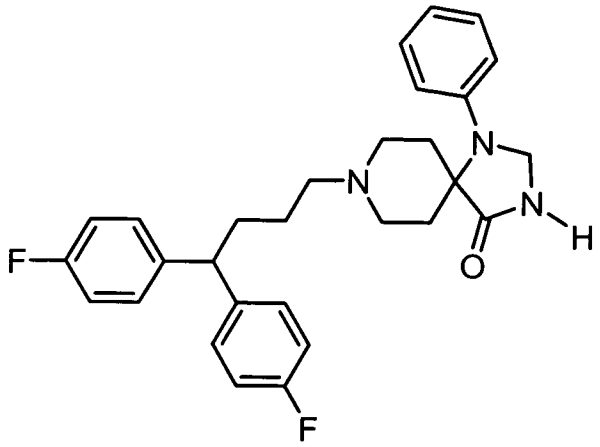
wherein

each R^1 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, $(C_1\text{-}C_{10})$alkyl, or $(C_1\text{-}C_{10})$alkaryl; and

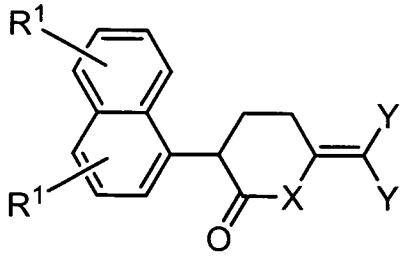
any aryl, heteroaryl, or alkyl of R^1 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (II) may be Fluspirilene (8-[4,4-bis(4-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one):



In another embodiment, the compound may be a compound of formula (III):



(III)

wherein

X is O or NH;

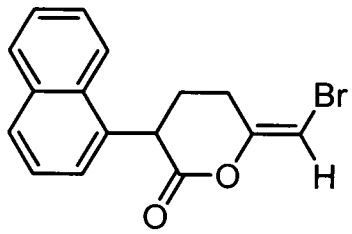
each Y is independently hydrogen or halo;

each R^1 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, $(C_1\text{-}C_{10})$alkyl, or $(C_1\text{-}C_{10})$alkaryl; and

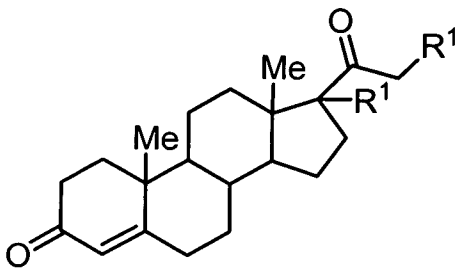
any aryl, heteroaryl, or alkyl of R^1 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (III) may be B1552 bromoenol lactone:



In another embodiment, the compound may be a compound of formula (IV):



(IV)

wherein

each R^1 is independently -X-R^2;

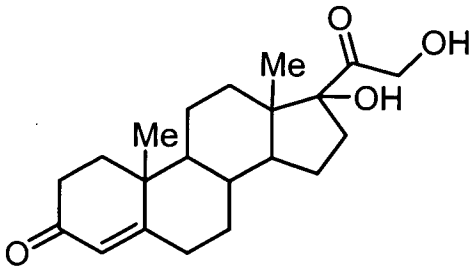
each X is independently O, NH, or a direct bond;

each R^2 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, $(C_1\text{-}C_{10})$alkyl, or $(C_1\text{-}C_{10})$alkaryl; and

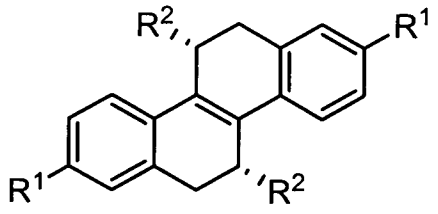
any aryl, heteroaryl, or alkyl of R^2 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (IV) may be cortexolone:



In another embodiment, the compound may be a compound of formula (V):



(V)

wherein

each R^1 is independently -X-R^2;

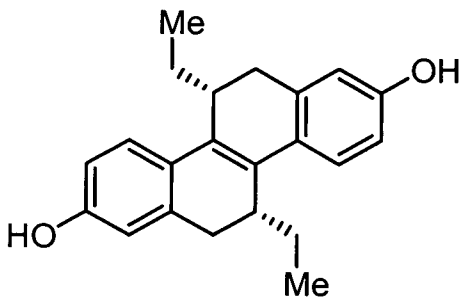
each X is independently O, NH, or a direct bond;

each R^2 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, $(C_1\text{-}C_{10})$alkyl, or $(C_1\text{-}C_{10})$alkaryl; and

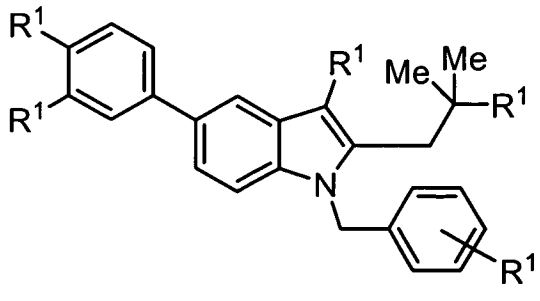
any aryl, heteroaryl, or alkyl of R^2 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (V) may be (*R*,*R*)-*cis*-diethyltetrahydro-2,8-chrysenediol:



In another embodiment, the compound may be a compound of formula (VI):



(VI)

wherein

each R^1 is independently -X-R^2;

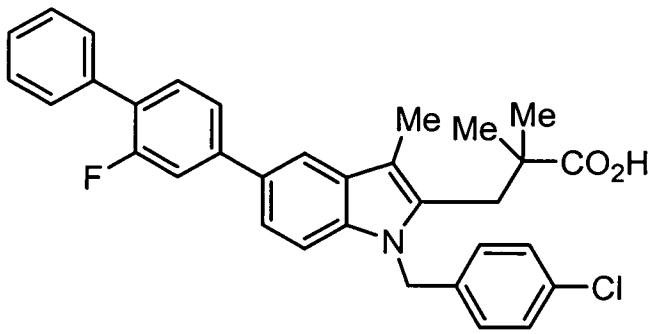
each X is independently O, NH, or a direct bond;

each R^2 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, carboxy, aryl, heteroaryl, (C_1-C_{10})alkyl, or (C_1-C_{10})alkaryl; and

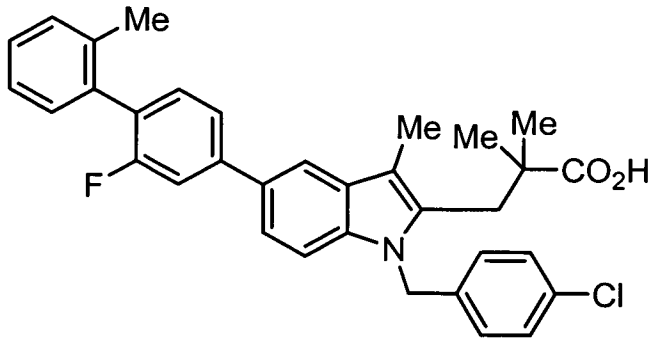
any aryl, heteroaryl, or alkyl of R^2 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In two specific embodiments, the compound of formula (VI) may be:

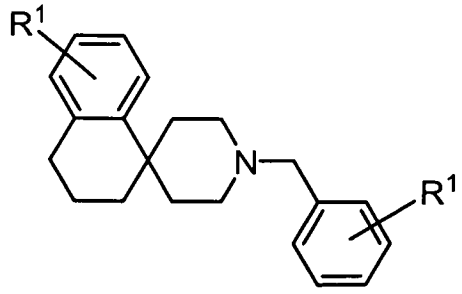


or



.

In another embodiment, the compound may be a compound of formula (VII):



(VII)

wherein

each R^1 is independently -X-R^2;

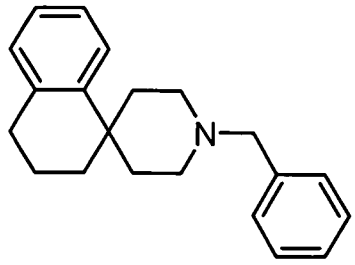
each X is independently O, NH, or a direct bond;

each R^2 is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, carboxy, aryl, heteroaryl, (C_1-C_{10})alkyl, or (C_1-C_{10})alkaryl; and

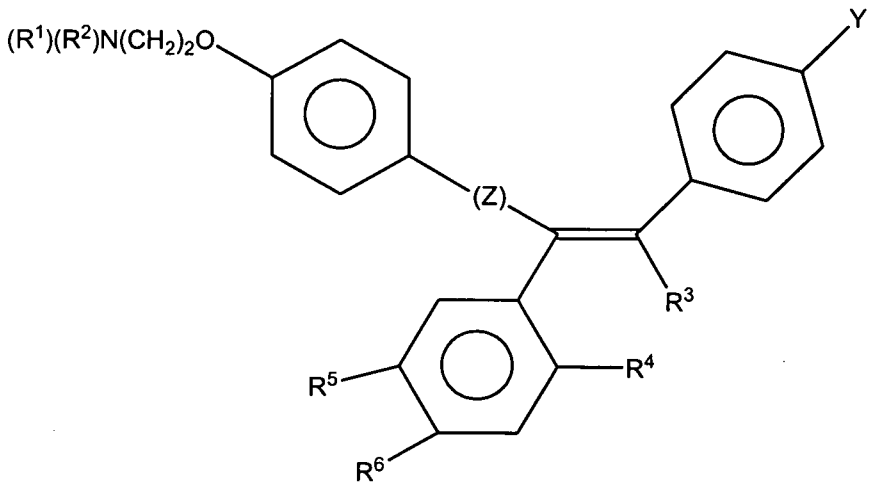
any aryl, heteroaryl, or alkyl of R^2 can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (VII) may be L-687,384 (1-benzyl-spiro(1,2,3,4-tetrahydronaphthalene-1,4-piperidine):



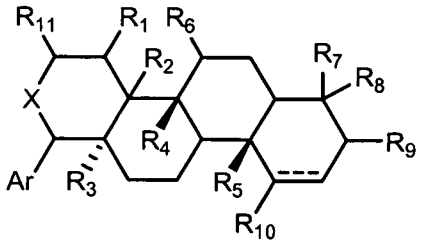
In another embodiment, the compound may be a compound of formula (VIII)



(VIII)

wherein Z is C=O or a covalent bond; Y is H or O(C_1-C_4)alkyl, R^1 and R^2 are individually (C_1-C_4)alkyl or together with N are a saturated heterocyclic group, R^3 is ethyl or chloroethyl, R^4 is H, R^5 is I, O(C_1-C_4)alkyl or H and R^6 is I, O(C_1-C_4)alkyl or H with the proviso that when R^4, R^5, and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt, including mixtures thereof.

In another embodiment, the compound can be a compound of formula (IX):



(IX)

wherein

Ar is a substituted or unsubstituted aryl or heteroaryl moiety;

X is -O-, -NH-, -NRx-, $-CH_2-$, -CHRx-, or $-C(Rx)_2-$, wherein Rx is a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; heteroaryloxy; or heteroarylthio moiety;

a dashed line represents either the presence or absence of a bond;

R_1 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_A$; $-C(=O)R_A$; -CHO; $-CO_2H$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_A$; $-N(R_A)_2$; $-NHC(=O)R_A$; $-NR_AC(=O)R_A$; $-NR_AC(=O)N(R_A)_2$; $-OC(=O)OR_A$; $-OC(=O)R_A$; $-OC(=O)N(R_A)_2$; $-NR_AC(=O)OR_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_2 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; -ORB; $-C(=O)R_B$; -CHO; $-CO_2H$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; -SORB; $-SO_2R_B$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_B$; $-N(R_B)_2$; $-NHC(=O)R_B$; $-NR_BC(=O)R_B$; $-NR_BC(=O)N(R_B)_2$; $-OC(=O)N(R_B)_2$; $-NR_BC(=O)OR_B$; or $-C(R_B)_3$; wherein each occurrence of RB is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; or

R_1 and R_2 taken together form an epoxide ring, aziridine ring, cyclopropyl ring, or a bond of a carbon-carbon double bond;

R_3 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_C$; $-C(=O)R_C$; -CHO; $-CO_2H$; $-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_C$; $-N(R_C)_2$; $-NHC(=O)R_C$; $-NR_CC(=O)R_C$; $-NR_CC(=O)N(R_C)_2$; $-OC(=O)OR_C$; $-OC(=O)R_C$; $-OC(=O)N(R_C)_2$; $-NR_CC(=O)OR_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_4 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_D$; $-C(=O)R_D$; -CHO; $-CO_2H$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_D$; $-N(R_D)_2$; $-NHC(=O)R_D$; $-NR_DC(=O)R_D$; $NR_DC(=O)N(R_D)_2$; $-OC(=O)OR_D$; $-OC(=O)R_D$; $-OC(=O)N(R_D)_2$; $-OC(=O)OR_D$; $-OC(=O)R_D$; $-OC(=O)N(R_D)_2$; $-NR_DC(=O)OR_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a hetero aliphatic moiety, an acyl moiety;

an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_5 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_E$; $-C(=O)R_E$; -CHO; $-CO_2H$; $-CO_2R_E$; -CN; -SCN; $-SR_E$; $-SOR_E$; $-SO_2R_E$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_E$; $-N(R_E)_2$; $-NHC(=O)R_E$; $-NR_EC(=0)R_E$; $-NR_EC(=O)N(R_E)_2$; $-OC(=O)OR_E$; $-OC(=O)R_E$; $-OC(=O)N(R_E)_2$; $-NR_EC(=O)OR_E$; or $-C(R_E)_3$; wherein each occurrence of R_E is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_6 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_F$; $-C(=O)R_F$; -CHO; $-CO_2H$; $-CO_2R_F$; -CN; -SCN; $-SR_F$; $-SOR_F$; $-SO_2R_F$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_F$; $-N(R_F)_2$; $-NHC(=O)R_F$; $-NR_FC(=0)R_F$; $-NR_FC(=O)N(R_F)_2$; $-OC(=O)OR_F$; $-OC(=O)R_F$; $-OC(=O)R_F$; $-OC(=O)N((R_F)_2$; $-NR_FC(=O)OR_F$; or $-C(R_F)_3$; wherein each occurrence of RF is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_G$; $-C(=0)R_G$; -CHO; $-CO_2H$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_G$; $-N(R_G)_2$; $-NHC(=O)R_G$; $-NR_GC(=O)R_G$; $-NR_GC(=O)N(R_G)_2$; $-OC(=O)OR_G$; $-OC(=O)R_G$; $-OC(=O)N(R_G)_2$; $-NR_GC(=O)OR_G$; or $-C(R_G)_3$; wherein each occurrence of $R_G$is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or [mu]nsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; $-OR_H$; $-C(=O)R_H$; - CHO; $-CO_2H$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N_3$; $-NH_2$; $-NHR_H$; $-N(R_H)_2$; $-NHC(=O)R_H$; $-NR_HC(=O)R_H$; $-NR_H(C=O)N(2R_H)_2$; $-OC(=O)OR_H$; $-O(C=O)R_H$; $-NR_HC(=O)OR_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_9 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic;

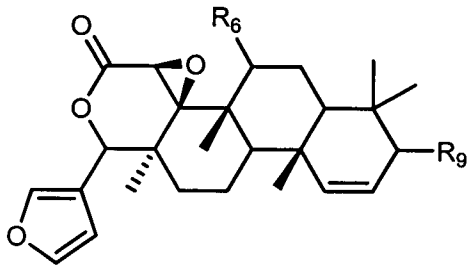
substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; -OR_I; =O; -$C(=O)R_I$; -CHO; -CO_2H; -CO_2R_I; -CN; -SCN; -SR_I; -SOR_I; -SO_2R_I; -NO_2; -N_3; -NH_2; -NHR_I; -$N(R_I)_2$; -$NHC(=O)R_I$; -$NR_IC(=O)R_I$; -$NR_IC(=O)N(RI)_2$; -$OC(=O)OR_I$; -$OC(=O)R_I$; -$OC(=O)N(R_I)_2$; -$NR_IC(=O)OR_I$; or -$C(R_I)_3$; wherein each occurrence of R_I is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_{10} is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; -OH; -OR_J; =O;-$C(=O)R_J$; -CHO; -CO_2H; -CO_2R_J; -CN; -SCN; -SR_J; -SOR_J; -SO_2R_J; -NO_2; -N_3; -NH_2; -NHR_I; -$N(R_J)_2$; -$NHC(=O)R_J$; -$NR_JC(=O)R_J$;-$NR_JC(=O)N(R_J)_2$; -$OC(=O)OR_J$; -$OC(=O)R_J$; -$OC(=O)N(R_J)_2$; -$NR_IC(=O)OR_J$; or -$C(R_J)_3$; wherein each occurrence of R_J is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; hydroxy, alkoxy; aryloxy; thioxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or hetero arylthio moiety;

R_{11} is hydrogen, halo, hydroxy, or a carbonyl;

or a pharmaceutically acceptable salt, stereoisomer, tautomer, or pro-drug thereof.

In yet another embodiment, the compound (e.g., the compound of formula IX) can be a compound of formula (X):



(X)

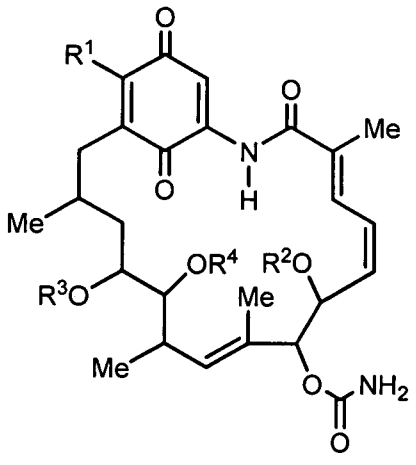
wherein

R_6 is hydrogen; hydroxy; oxo (=O); or acetyl-protected hydroxyl; and

R_9 is hydrogen; hydroxy; oxo (=O); or acetyl-protected hydroxyl.

In various embodiments, compounds of formulas (IX) and (X) can include gedunin, gedunol, epoxygedunin, 1,2α-epoxy-7-deacetoxy-7-oxodihydrogedunin, dihydrogedunin, 3β-acetoxydeoxodihydrogedunin, 3α-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 3β-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 1,2α-epoxydeacetoxydihydrogedunin, 3β-hydroxydeoxydesacetoxy-7-oxogedunin, 7-deacetoxy-3-deacetyl-7-oxokhivorin, 1,3-dideacetyl-7-deacetoxy-7-oxokhivorin, tridesacetoxykhivorin, 1,3-dideacetylkhivorin, and/or Heudelottin C.

In another embodiment, the compound can be a compound of formula (XI):



(XI)

wherein

R^1 is -X-R^X;

X is O, NH, or a direct bond;

R^X is hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl, or (C_1-C_{10})alkylaryl;

R^2 is hydrogen, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl, (C_1-C_{10})alkylaryl, or an oxygen protecting group;

R^3 is hydrogen, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl, (C_1-C_{10})alkylaryl, or an oxygen protecting group;

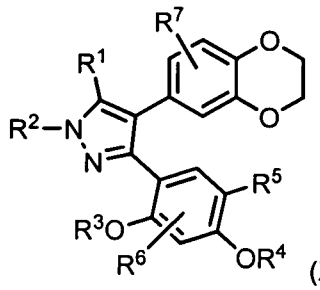
R^4 is hydrogen, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl, (C_1-C_{10})alkylaryl, or an oxygen protecting group; and

any aryl, heteroaryl, or alkyl (e.g., of R^X, R^2, R^3, or R^4) can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, (C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, (C_1-C_{10})alkyl, (C_1-C_{10})alkenyl, (C_1-C_{10})alkoxy, phenyl, benzyl, or trifluoromethyl groups;

or a salt thereof.

In some embodiments, the compound of formula (XI) may be geldanamycin, 17-AAG, or 17-DMAG.

In another embodiment, the compound can be a compound of formula (XII):



(XII)

wherein

R^1 is H, (C_1-C_{10})alkyl or (C_1-C_{10})alkylaryl;

R^2 is H, (C_1-C_{10})alkyl or (C_1-C_{10})alkylaryl;

R^3 is hydrogen, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkylaryl, or an oxygen protecting group;

R^4 is hydrogen, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, (C_1-C_{10})alkylaryl, or an oxygen protecting group;

R^5 is H, (C_1-C_{10})alkyl or (C_1-C_{10})alkylaryl;

R^6 is H or -X-R^X; X is O, NH, or a direct bond;

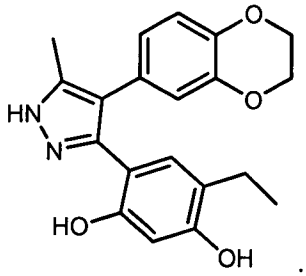
R^7 is -X-R^X; X is O, NH, or a direct bond;

each R^X is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, or (C_1-C_{10})alkaryl; and

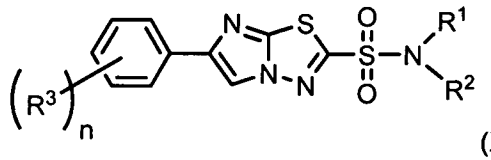
any aryl, heteroaryl, or alkyl can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups;

or a salt thereof.

In one specific embodiment, the compound of formula (XII) may be CCT-018159 (4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methyl-1*H*-pyrazol-3-yl]-6-ethyl-1,3-benzenediol):



In another embodiment, the compound can be a compound of formula (XIII):



(XIII)

wherein

R^1 is H, (C_1-C_{10})alkyl, aryl, or (C_1-C_{10})alkylaryl;

R^2 is H, (C_1-C_{10})alkyl aryl, or (C_1-C_{10})alkylaryl;

each R^3 is independently H or -X-R^X;

X is O, NH, or a direct bond;

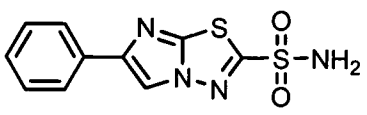
each R^X is independently hydrogen, hydroxy, halo, carboxy, nitro, amino, trifluoromethyl, aryl, heteroaryl, (C_1-C_{10})alkyl, or (C_1-C_{10})alkylaryl;

any aryl, heteroaryl, or alkyl can optionally be substituted with one or more (e.g., one, two, three, four, five, etc.) hydroxy, halo, carboxy, nitro, amino, phenyl, or trifluoromethyl groups; and

n is 1, 2, 3, 4, or 5;

or a salt thereof.

In one specific embodiment, the compound of formula (XIII) may be AEG 3482 (6-phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide):



The compounds of the invention, such as those having formulas (I)-(XIII), can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

The present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it may be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Useful dosages of the compounds of the invention can be determined by comparing their *in vitro* activity and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compounds of the invention in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, e.g., from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, e.g., about 0.5-2.5 wt-%.

The amount of the compound, or an active salt or derivative thereof, required for use alone or with other compounds will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose may be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, such as in the range of 6 to 90 mg/kg/day, or in the range of 15 to 60 mg/kg/day.

The compound may be conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

The active ingredient may be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, e.g., about 1 to 50 μM, such as about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The invention will be further described in the following nonlimiting examples.

Example 1

Methods and Materials

Cells and cell lines. Vero cells (green monkey kidney cells) were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal calf serum (FCS), L-glutamine, vitamins, nonessential amino acid solution and antibiotics. The VeroVP30 cell line was established by cotransfecting Vero cells with pCAG-VP30 (for the expression of VP30) and pPur, a protein expression plasmid for the puromycin resistance gene (Clontech, Mountain View, CA), using the transfection reagent TransIT LT-1 (Mirus, Madison, WI). Two days after transfection, puromycin-resistant cells were selected with 5 μg/mL puromycin (Sigma, St. Louis, MO). Individual cell clones were screened for VP30 expression by flow cytometry with a polyclonal peptide antibody to VP30.

Human embryonic kidney 293T cells were grown in high-glucose Dulbecco's modified Eagle medium containing 10% FCS, L-glutamine, and antibiotics. All cells were maintained at 37°C and 5% CO_2.

Flow cytometry. Cells were detached in phosphate-buffered saline (PBS) containing 0.02% EDTA and then washed once with cold PBS supplemented with 2% FCS and 0.1% sodium azide (wash buffer). Cells were incubated with a VP30 antibody on ice for 20 minutes. After washing in buffer, the cells were further incubated with a secondary antibody labeled with fluorescent isothiocyanate (Zymed Laboratories, Carlsbad, CA). They were then washed with buffer and analyzed by FACSCalibur with Cell Quest software (Becton Dickinson, Franklin Lakes, NJ).

Generation of EbolaΔVP30 viruses. The plasmid pTM-T7G-Ebo-Rib, containing the full-length *Ebolavirus* cDNA flanked by T7 RNA polymerase promoter and ribozyme sequences, is described in Newmann et al. (2002). First, a fragment encompassing nucleotides 6180 to 10942 (numbers refers to the positive-sense antigenome) was subcloned into a kanamycin-resistant cloning vector. Next, the VP30 ORF was replaced with those encoding neo or eGFP, respectively, by a series of overlapping PCR amplification steps using *Pfu* Turbo (Stratagene, La Jolla, CA). The altered subgenomic fragments were transferred back into the full-length *Ebolavirus* cDNA plasmid using two unique restriction sites, *SalI* and *SacI* (Figure 1). The resultant plasmids, designated pTM-EbolaΔVP30-neo or -eGFP, were sequenced to verify the replacement of the VP30 ORF and the lack of any unwanted mutations.

To artificially generate *Ebolavirus*, 5 x 10^5 293T cells were transfected with 1.0 μg pTM-EbolaΔVP30, 2.0 μg pCAG-L, 1.0 μg pCAG-NP, 0.5 μg pCAG-VP35, 0.5 μg pCAG-VP30, and 1.0 μg pCAG-T7 pol, using TransIT LT1 (Mirus, Madison, WI) in BSL-4 containment (Neumann et al., 2002). Five days after transfection, the supernatant was harvested, cellular debris removed by low speed centrifugation, and the virus amplified in VeroVP30 cells at 37°C and 5% CO_2 with propagation medium containing 2% FCS in MEM supplemented with L-glutamine, vitamins, nonessential amino acid solution and antibiotics without puromycin.

Plaque assay and immunostaining assay. To determine the titers of wild-type *Ebolavirus* or EbolaΔVP30 viruses, tenfold dilutions of the viruses were absorbed to confluent VeroVP30 or wild-type Vero cells for 1 hour at 37°C, after which any unbound virus was removed by washing cells with propagation medium. The cells were then overlaid with propagation medium containing 1.5% methyl cellulose (Sigma). Seven days after infection, cells were fixed with 10% buffered formaldehyde, taken out of BSL-4, permeabilized with 0.25% Triton X-100 in PBS for 10 minutes, and blocked with 4% goat serum and 1% bovine serum albumin (BSA) in PBS for 60 minutes. Cells were then incubated for 60 minutes with a 1:1000 dilution of a mouse anti-VP40 monoclonal antibody, washed with PBS, and incubated for 60 minutes with a 1:1000 dilution of an antimouse IgG-peroxidase-conjugated secondary antibody (Kirkegaard & Perry Laboratories Inc., Gaithersburg, MD). After washing with PBS, cells were incubated with 3,3'-diaminobenzidine tetrahydrochloride (DAB, Sigma) in PBS. The reaction was stopped by rinsing cells with water.

Western blotting. Partially purified virus resuspended in lysis buffer (50 mM Tris-HCl [pH 7.5], 150 mM NaCl, 0.5 % Triton X-100, and 0.1% SDS) containing protease inhibitors (complete protease inhibitor cocktails [Roche]) was incubated at 100°C for 5 minutes, taken out of BSL-4, and separated on 4-20% polyacrylamide gels. Resolved proteins were transferred to Western polyvinylidine difluoride membranes (Schleicher & Schuell, Sanford, ME) and blocked overnight at 4°C with 5% skim milk in PBST (0.05% Tween 20 [Sigma] in PBS). Blots were incubated with primary antibodies (a mouse anti-NP antibody, a rabbit anti-VP35 antibody, a rabbit anti-VP40 antibody, a mouse anti-GP antibody, a rabbit anti-VP30 antibody, or a mouse anti-VP24 antibody) for 60 minutes at room temperature, washed three times with PBST, incubated with the appropriate secondary antibody conjugated to horseradish peroxidase (Zymed) for 60 minutes, and finally washed three times with PBST. Blots were then incubated in Lumi-Light Western blotting substrate (Roche, Indianapolis, IN) and exposed to X-ray film (Kodak, Rochester, NY).

RNA isolation and RT-PCR. Cell culture supernatant from virus-infected VeroVP30 cells was inactivated with guanidinium isothiocyanate buffer and taken out of BSL-4. Viral RNA was isolated with the RNeasy Mini kit (Qiagen, Valencia, CA). RT-PCR was carried out with the RobusT One-Step RT-PCR kit (Finnzyme, Espoo, Finland), using 1 μg of isolated RNA and *Ebolavirus*-specific primers. The resultant PCR products were cloned into pT7Blue (Novagen, San Diego, CA) and sequenced.

Transmission electron microscopy. Ultrathin-section electronmicroscopy was performed as described in Noda et al. (2002). Briefly, at 36 hours postinfection, VeroVP30 cells infected with EbolaΔVP30-neo virus were fixed and inactivated with 2.5% glutaraldehyde in 0.1 M cacodylate buffer, taken out of BSL-4 and postfixed with 2% osmium tetroxide in the same buffer. Cells were then dehydrated with a series of ethanol gradients followed by propylene oxide, before being embedded in Epon 812 Resin mixture (TAAB Laboratories Equipment Ltd., Berkshire, UK). Thin sections were stained with 2% uranyl acetate and Raynold's lead, and examined under a HITACHI H-7500 electron microscope at 80 kV.

Selection of escape mutants. EbolaΔVP30-eGFP was diluted tenfold (10^{-1} to 10^{-6}) and incubated with the indicated mAbs at a concentration of 250 to 500 μg of mAb/mL at 37°C for 60 minutes. The virus/mAb mixtures were inoculated onto VeroVP30 cells for 60 minutes. Viruses were amplified for 5 days in the presence of antibodies. Then, viruses that grew in the presence of mAbs (as determined by GFP expression) were harvested at the highest virus-positive dilution and passaged for a total of 3-6

times in the presence of antibodies. Viral RNA was isolated, RT-PCR amplified, and the GP sequence determined by sequence analysis.

Results

Generation and passage of EbolaΔVP30-neo virus. Previously a full-length cDNA clone of the Zaire *ebolavirus*–Mayinga was generated (Newmann et al., 2002). Using a subgenomic fragment that encompasses nucleotides 6180 to 10942 of the viral genome (numbers refers to the positive-sense antigenome), the ORF for VP30 was replaced with that of neomycin (neo), using a series of overlapping PCR amplification steps. After confirmation of the authenticity of the PCR fragments by sequence analysis, the altered subgenomic fragment was inserted into the full-length *Ebolavirus* cDNA construct via unique *SalI* and *SacI* restriction sites (Figure 1), resulting in an *Ebolavirus* cDNA genome deficient in the VP30 ORF. The artificial generation of *Ebolavirus* from plasmids is afforded by flanking this viral cDNA with T7 RNA polymerase promoter and hepatitis delta virus ribozyme sequences (Neumann et al., 2002).

To amplify VP30-deficient *Ebolaviruses*, a stable Vero E6 cell line (designated VeroVP30) was established by cotransfecting Vero cells with two protein expression plasmids encoding VP30 (pCAG-VP30) and puromycin (pPur, Clontech), and selecting cell clones resistant to 5.0 μg/mL of puromycin. VP30 expression in individual clones was determined by flow cytometry with antibodies to VP30. The clone with the highest percentage of VP30-expressing cells (> 90% as measured by flow cytometry, data not shown) was used in further studies to amplify EbolaΔVP30 viruses.

EbolaΔVP30-neo virus was rescued under BSL-4 conditions as described for wild-type *Ebolavirus* (Neumann et al., 2002). All work involving infectious EboΔVP30 viruses and all steps prior to inactivation of biological material were performed under BSL-4 conditions at the National Microbiology Laboratory of the Public Health Agency of Canada.

Briefly, human embryonic kidney (293T) cells were transfected with a plasmid for the transcription of the VP30-deficient *Ebolavirus* RNA, with plasmids for the expression of the *Ebolavirus* NP, VP30, VP35, and L proteins, and with a plasmid for the expression of T7 RNA polymerase. Five days after transfection, VeroVP30 cells were incubated with undiluted supernatant derived from plasmid-transfected cells. Seven days later, the supernatant was harvested, diluted tenfold, and used to infect fresh VeroVP30 cells for the next passage. A total of seven passages were carried out, using the highest dilution of the inoculum that still produced replicating viruses for each passage. The presence of replicating virus was assessed by cytopathic effects (CPE) and immunostaining of infected VeroVP30 cells with an antibody to VP40 (Figure 2A, left panel). As a control, we also incubated the supernatants from each passage with wild-type Vero cells. As expected, CPE and viral antigens were undetectable in wild-type Vero cells (Figure 2A, right panel), demonstrating that replicating EbolaΔVP30-neo virus was confined to VeroVP30 cells.

Although the manifestation of a CPE in infected VeroVP30 cells suggested the formation of infectious (but biologically contained) *Ebolaviruses*, further evidence was sought for the presence of virions in cell culture supernatant derived from infected VeroVP30 cells. Briefly, 5 days after VeroVP30 cells were infected with EbolaΔVP30-neo virus, supernatant was collected and partially purified over 20% sucrose. The pellet was suspended in PBS and separated on a 4-20% polyacrylamide gel. Western blot analyses were carried out with antibodies specific to the respective *Ebolavirus* protein. All viral proteins (with the exception of L, for which no antibody was available) were detected (Figure 2B, '+' lanes). Note that VP30 protein in virions originates from VeroVP30 cells while the remaining proteins are encoded by

EbolaΔVP30-neo virus. By contrast, no viral proteins were detected in a control sample derived from wild-type Vero cells infected with EbolaΔVP30-neo virus (Figure 2B, '-' lanes).

Genetic stability of EbolaΔVP30-neo virus. A major concern with the use of VP30-deficient *Ebolaviruses* is the potential recombination with VP30 sequences integrated into the genome of the VeroVP30 helper cell line. Thus, to assess the genomic stability of EbolaΔVP30-neo virus, three independent passage experiments were performed (seven passages each). While EbolaΔVP30-neo virus replicated in VeroVP30 cells, viral replication was not observed in wild-type Vero cells. Total viral RNA was isolated from the cell culture supernatant of infected VeroVP30 cells after the seventh passage. A viral genomic fragment spanning the *neo* gene was amplified by RT-PCR, cloned and sequenced. A total of 20 clones were sequenced, and the sequences were identical to that of the EbolaΔVP30 cDNA construct used for virus generation. Hence, there was no evidence of recombination in any of three independent passage experiments, attesting to the genomic stability of the EbolaΔVP30-neo viral genome.

To further demonstrate the biosafety of EbolaΔVP30-neo virus, EbolaΔVP30-neo virus was collected after seven consecutive passages in VeroVP30 cells and this virus used for three consecutive "blind" passages in wild-type Vero cells. Briefly, Vero cells were infected at a multiplicity of infection (m.o.i.) of 5 with EbolaΔVP30-neo virus (passage 7). Six days later, supernatant was used for the next "blind" passage as well as for Western blot analysis. No viral NP protein was detected after any of the "blind" passages (data not shown). After three consecutive "blind" passages, plaque assays and immunostaining were carried out in wild-type Vero cells to confirm the absence of replicating *Ebolavirus*. As expected, replicating virus was not detected (data not shown). Collectively, these data further attest to the biosafety of the EbolaΔVP30 system.

Growth kinetics of EbolaΔVP30-neo virus. One of the major concerns raised by providing viral proteins *in trans* is that their amounts, expression kinetics or both may not match those found in cells infected with wild-type virus, leading to reduced virus titers and/or aberrant virion morphology. To address this potential pitfall, the growth kinetics of EbolaΔVP30-neo virus (Figure 3, solid squares) were compared with that of wild-type *Ebolavirus* (Figure 3, open circles). VeroVP30 cells (Figure 3, top panels) or wild-type Vero cells (Figure 3, bottom panels) were infected at a high m.o.i. of 1.0 or a low m.o.i. of 0.01 and supernatant was harvested every 24 hours. Virus titers of EbolaΔVP30-neo were determined in VeroVP30 cells, while virus titers of wild-type *Ebolavirus* were determined in wild-type Vero cells. To determine virus titers, cells were overlaid with 1.5% methylcellulose and 7 days later, assayed for VP40 expression using an immunostaining assay. EbolaΔVP30-neo virus replicated efficiently in VeroVP30 cells at both conditions tested, reaching 10^7 focal-forming units (FFU)/ml on day 6 postinfection (Figure 3, top panels, solid squares). No replication of EbolaΔVP30-neo was detected in wild-type Vero cells (Figure 3, bottom panels, solid squares); the low titers that were detected for up to three days postinfection likely reflect input virus. Together, these findings attest to the biological confinement of the EbolaΔVP30 system. The replication kinetics of EbolaΔVP30-neo in VeroVP30 cells are similar to those of wild-type *Ebolavirus* in either VeroVP30 (Figure 3, top panels, open circles) or wild-type Vero cells (Figure 3, bottom panels, open circles), establishing the described approach as a highly efficient method for generating biologically contained *Ebolaviruses*.

Morphology of EbolaΔVP30-neo virus. Next, the morphology of EbolaΔVP30-neo virus was assessed by transmission electron microscopy (TEM). VeroVP30 cells were infected with EbolaΔVP30-

neo virus and fixed 36 hours later. Samples were processed for TEM as described in Noda et al. (2002). As shown in Figure 4 (right panels), the particles budding from VeroVP30 cells infected with EbolaΔVP30-neo virus were indistinguishable in their size and shape from wild-type *Ebolaviruses* (Figure 4, left panels). Thus, providing VP30 protein *in trans* does not have a discernable effect on virion morphology, suggesting that the described system would be suitable for studies of virion formation and budding, for example.

Taken together, the above results demonstrate that the EbolaΔVP30-neo virus is biologically contained, replicates to high titers in a helper cell line, is genetically stable, and is morphologically indistinguishable from wild-type virions. Having provided proof-of-concept for the generation of biologically contained *Ebolaviruses*, the utility of this strategy in basic research and drug screening applications was assessed.

Generation of an EbolaΔVP30-eGFP virus and its usefulness for basic research applications. An EbolaΔVP30 virus encoding enhanced green fluorescence protein (eGFP) instead of VP30 was generated (Figure 1; designated EbolaΔVP30-eGFP), using the same procedures described above for EbolaΔVP30-neo virus. Analogous to EbolaΔVP30-neo virus, the eGFP variant replicated efficiently with virus titers reaching 8.0×10^7 FFU/mL. Expression of eGFP was observed as early as 10 hours postinfection (data not shown).

Takada et al. (2003) used replication-competent vesicular stomatitis virus (VSV) pseudotyped with *Ebolavirus* GP and two neutralizing monoclonal antibodies (mAb), 133/3.16 and 226/8.1, to map *Ebolavirus* GP epitopes and to generate escape mutants. To confirm with authentic *Ebolavirus* virions the findings of Takada et al. (2003) based on a VSV-pseudotyping system, escape mutants were generated by amplifying EbolaΔVP30-eGFP virus in the presence of mAb 133/3.16 or 226/8.1. Each of eight escape mutants to mAb 133/3.16 possessed a histidine-to-arginine substitution at position 549 (H549R) in GP, reported by Takada et al. (2003). Using mAb 226/8.1, 12 escape mutants were isolated that all contained an arginine-to-tryptophan substitution at position 134 (R134W), a mutation identical to one identified by Takada et al. (2003). However, the remaining two escape mutations described by Takada et al. (2003) were not detected. Whether this discrepancy in escape mutants reflects differences between the biological systems used or random mutations is presently unclear. Nonetheless, these experiments illustrated one of the ways that biologically contained *Ebolaviruses* could be used in basic research applications.

In conclusion, biologically contained *Ebolaviruses* lacking the VP30 gene afford a safe, alternative way to study authentic *Ebolavirus,* to develop *Ebolavirus* vaccines, and to screen chemical libraries for compounds that interfere with the *Ebolavirus* life cycle. Indeed, each of the three different biologically contained viruses generated (encoding neomycin or eGFP instead of VP30) was biologically contained, as demonstrated by their ability to replicate in VeroVP30 (a Vero cell line that stably expresses VP30 *in trans*), but not in wild-type Vero cells. Moreover, virus titers were in the range of 10^7 FFU/mL and hence comparable to those obtained for wild-type *Ebolavirus* (Figure 3; Volchov et al., 2001; Neumann et al., 2002; Ebihara et al., 2006) while morphological, biochemical, and virological analyses indicated that the tested properties of EbolaΔVP30 viruses were indistinguishable from those of wild-type *Ebolavirus*.

These physical properties, together with the results of studies to illustrate the potential of biologically contained *Ebolaviruses* in basic research and drug screening applications, will greatly accelerate current filovirus research efforts.

Example 2

Ebola viruses (family *Filoviridae*), cause severe hemorrhagic fever in humans and nonhuman primates with mortality rates up to 90% (Johnson et al., 1977). Currently, there are no licensed vaccines or antivirals available against Ebola virus. A vaccine against Ebola virus is not only desirable for local populations in the epidemic areas of Africa, but also for health care workers during an outbreak and for post-exposure treatment of laboratory workers after accidental exposure to the virus. A few vaccine candidates have been shown to protect mice, guinea pigs, or nonhuman primates against a lethal challenge of Ebola virus; however, each of these candidates has disadvantages, such as lack of protection in nonhuman primates, preexisting immunity against the vector in humans, or potential central nervous system involvement (Reed et al., 2007). Moreover, the current vaccine candidates are based on virus-like particles (VLPs) or virus-vectored vaccines, none of which express the full components of the viral antigens. On the other hand, the use of live attenuated vaccines may not be feasible for Ebola virus from a biosafety perspective. To overcome these potential limitations, biologically contained viruses offer an attractive option since they are biologically safe but provide all the viral antigens.

Materials and Methods

Cells. VeroVP30 cells were established as described in Example 1 and grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal calf serum (FCS), L-glutamine, vitamins, non-essential amino acid solution, and 5μg/mL puromycin (Sigma, St. Louis, MO).

Viruses. The EbolaΔVP30 virus was generated as described in Example 1. Briefly, using the plasmid containing the full-length Ebola cDNA genome of the Zaire Mayinga strain of Ebola virus (Neumann et al., 2002), the open reading frame (ORF) of VP30 was replaced with the ORF of the drug-resistant gene neomycin. Using Ebola virus reverse genetics (Neumann et al., 2002), the EbolaΔVP30 virus was generated and passaged in a Vero cell line stably expressing VP30. EbolaΔVP30 was propagated in VeroVP30 cells in MEM medium as described above, but supplemented with 2% FCS. The virus was harvested six days after infection of the cells at a multiplicity of infection (MOI) of 1 and directly stored at -80°C. Harvested virus was also partially purified by ultracentrifugation at 27,000 rpm for 2 hours over 20% sucrose. The viral pellet was resuspended in sterile PBS and stored at -80°C. Viral titers were determined by plaque assay in confluent VeroVP30 cells overlaid with 2% FCS-MEM containing 1.5% methyl cellulose (Sigma).

Since wild-type Ebola virus does not kill mice, challenge studies were carried out with a mouse-adapted Ebola virus (Bray et al., 1998). This virus was generated as described in Ebihara et al., 2006 and used under BSL-4 conditions at the Canadian Centre for Human and Animal Health in Winnipeg, Canada.

Antibody titers. The levels of Ebola glycoprotein (GP)-specific immunoglobulin G (IgG) antibodies in vaccinated mice were examined by using an enzyme-linked immunosorbent assay (ELISA). Briefly, wells of Immulon 2HB plates (Thermon Labsystems, Franklin, MA) were coated with purified Ebola GP (Takada et al., 2001) and blocked with PBS containing 10 mg/mL bovine serum albumin. After incubation of Ebola GP-coated wells with mouse serum from control and vaccinated mice, bound antibodies were detected with goat anti-mouse IgG conjugated to horseradish peroxidase (Kirkegaard & Perry Laboratories Inc., Gaithersburg, MD) by an ELISA plate reader at an absorbance of 405 nm.

Intracellular staining and flow cytometry. The number of cytokine-producing $CD8^+$ T cells was determined by intracellular staining as described Murali-Krishna et al. (1998). Briefly, splenocytes were

stimulated with the Ebola peptide $NP_{279-288}$ (SFKAALSSLA, derived from the nucleoprotein NP; SEQ ID NO: 31) (Olinger et al., 2006; Simmons et al., 2004), $VP40_{171-180}$ (YFTFDLTALK, derived from the matrix protein VP40; SEQ ID NO: 32), or $GP_{161-169}$ (LYDRLASTV, derived from GP; SEQ ID NO: 33) (Olinger et al., 2005; Warfield et al., 2005) for 5 hours in the presence of brefeldin A and IL-2. Following activation, cells were stained for cell surface $CD8^+$ and intracellular IFNγ by using the Cytofix/Cytoperm kit from BD Biosciences (San Jose, CA). The number of cytokine-producing $CD8^+$ T cells was determined by using a FACSCalibur flow cytometer (BD Biosciences).

Vaccination and challenge. Four-week-old female BALB/c mice (The Jackson Laboratory, Bar Harbor, ME) were anesthetized with isoflurane and intraperitoneally (IP) inoculated twice at three-week intervals with 10^6 focus forming units (FFU) of sucrose-purified EbolaΔVP30 virus (Figure 7); control mice were simultaneously inoculated with PBS. A second group of mice received three immunizations (at three-week intervals) with 10^7 FFU of virus harvested from cell culture supernatant (Figure 7), or, as a control, 2% FCS-MEM. Vaccinations were conducted at the University of Wisconsin-Madison. Mice were then transported to the BSL-4 laboratory at the National Microbiology Laboratory of the Public Health Agency of Canada, where they were challenged with 1000 mouse lethal doses 50 (MLD_{50}; i.e., the dose required to kill 50% of infected animals) of mouse-adapted Ebola virus. Four days after challenge, viral titers were determined in the serum of three control and three vaccinated mice from each group. The remaining mice were monitored for survival for 28 days. All animal experiments were performed in accordance with approved animal use protocols and according to the guidelines set forth by the Canadian Council of Animal Care and the University of Wisconsin-Madison.

Results

Antibody response of mice immunized with EbolaΔVP30 virus. To assess the EbolaΔVP30 virus as a potential vaccine, its immunogenicity in mice was determined. Mice vaccinated with the EbolaΔVP30 virus did not show any signs of disease, demonstrating the lack of pathogenicity of the EbolaΔVP30 virus. When serum samples, collected two weeks after each vaccination to determine the levels of antibodies to the Ebola glycoprotein (GP), were tested for IgG antibody by ELISA with purified GP (Figure 5), vaccinated animals showed elevated levels of antibody titers against GP after the first vaccination compared to control mice (Figure 5); these antibody titers further increased after the second and third vaccinations. This finding demonstrates the ability of the biologically contained EbolaΔVP30 virus to elicit antibodies to GP.

$CD8^+$ T-cell responses in vaccinated mice. The cellular response to vaccination in mice was examined. Mice were vaccinated as described above. Eight days after the second immunization, four vaccinated and two control mice were euthanized and their spleens removed. Splenocytes were isolated and stimulated with the Ebola peptide $NP_{279-288}$ (SFKAALSSLA; SEQ ID NO: 31), $VP40_{171-180}$ (YFTFDLTALK; SEQ ID NO: 32) or $GP_{161-169}$ (LYDRLASTV; SEQ ID NO: 33) for 5 hours in the presence of brefeldin A and IL-2. Vaccinated mice had IFNγ-positive $CD8^+$ cells in the range of 0.017% to 0.22% for cells stimulated with Ebola peptide $NP_{279-288}$ (Figure 6). For control mice, the number of IFNγ-positive $CD8^+$ cells was significantly lower, ranging from 0.00513% to 0.00794% (Figure 6). No IFNγ-positive $CD8^+$ cells were detected for cells stimulated with Ebola peptide $VP40_{171-180}$ or $GP_{161-169}$ (data not shown).

Protective efficacy of EbolaΔVP30 virus in mice. To assess the protective efficacy of the EbolaΔVP30 virus, two groups of 4-week-old mice were intraperitoneally immunized, then subjected to lethal challenge with mouse-adapted Ebola virus (Figure 7). 'Group 1' mice were immunized three times

at three-week intervals with 10^7 FFU of non-purified EbolaΔVP30 virus (i.e., virus harvested from cell culture supernatant); eight control mice were inoculated in the same manner with 2% FCS-MEM. Mice from this group were challenged seven weeks after the last immunization with 1000 MLD_{50} of mouse-adapted Ebola virus, which consistently kills mice (Bray et al., 1998; Ebihara et al., 2006). 'Group 2' mice were immunized twice (with a three-week interval) with 10^6 FFU of purified EbolaΔVP30 virus; ten control mice were similarly inoculated with PBS. Mice from 'Group 2' were challenged eight weeks after the last immunization with 1000 MLD_{50} of mouse-adapted Ebola virus. No signs of disease or illness were seen in mice vaccinated with purified or non-purified EbolaΔVP30 virus, whereas control mice from both groups began showing signs of sickness (e.g., ruffled fur) along with weight loss on day 3 post-challenge (Figure 8A). By day 7 post-challenge, all control mice had succumbed to infection (Figure 8B). By contrast, vaccinated mice from both groups showed no signs of disease, as characterized by ruffled fur and weight loss (Figure 8A), and were fully protected against lethal challenge (Figure 8B) up to day 28, when all surviving mice were euthanized. On day 4 post-challenge, mice were sacrificed to determine viral titers in the sera (Figure 9). Vaccinated mice from both groups showed a 3 to 4 log_{10} reduction in viral titers compared to their respective control mice. Taken together, these data demonstrate that the EbolaΔVP30 virus efficiently protects mice against challenge with a lethal dose of mouse-adapted Ebola virus.

Discussion

Here, it was demonstrated that EbolaΔVP30-immunized mice were completely protected from a lethal challenge with mouse-adapted Ebola virus and that the virus titers in sera from these mice were more than 1000-fold lower than those in control mice. These results show the potential of this biologically contained Ebola virus as a vaccine.

The humoral response to Ebola virus infection is important, as demonstrated by protection from a lethal challenge by passive transfer of antibodies to the viral glycoprotein GP (Gupta et al., 2001; Warfield et al., 2003). However, the ability of a vaccine to elicit an antibody response does not in itself correlate with protection from Ebola virus infection. For example, classical vaccine approaches, such as γ-irradiated Ebola and Marburg viruses, along with GP expressed in baculovirus generate a moderate antibody response; however, they fail to protect mice against a lethal challenge (Ignatyeve et al., 1996; Lupton et al., 1980; Mellquist-Riemenschneider et al., 2003). By contrast, Ebola and Marburg VLPs protect mice from a lethal challenge of Ebola or Marburg virus (Warfield et al., 2003; Warfield et al., 2004; Warfield et al., 2005), and not only elicit a humoral response, but also induce a $CD8^+$ T-cell response, highlighting the importance of the latter response for protection against a lethal challenge of Ebola virus (Warfield et al., 2005). Similarly, in non-human primates (NHPs), full protection from a lethal challenge appears to depend on both the humoral response and a $CD8^+$ cellular response (Sullivan et al., 2000). Vaccine candidates that protect NHPs from a lethal Ebola virus challenge, such as recombinant vesicular stomatitis virus (VSV) (Jones et al., 2005) and adenovirus (Sullivan et al., 2000), induce a $CD8^+$ T-cell response in NHPs, albeit to varying degrees (Jones et al., 2005; Sullivan et al., 2000). The EbolaΔVP30 virus induced both humoral and $CD8^+$ T-cell (specific for an Ebola NP epitope) responses, although the extent of the latter responses varied among animals (Figure 6). Whether this $CD8^+$ T-cell response is sufficient to provide protection to NHPs from a lethal Ebola virus infection remains to be tested.

Although vaccine candidates such as recombinant VSV or parainfluenza virus offer protection in various animal models (Bukreyev et al., 2006; Jones et al., 2005), there are safety concerns with the use of these vaccines in humans (Bukreyev et al., 2006; Jones et al., 2005; Reed et al., 2007). Preexisting

immunity to a vaccine based on recombinant adenovirus is also a concern, as is the large amount of virus (10^{10} particles) needed to confer protection in NHPs (Jones et al., 2005; Sullivan et al., 2000). Ebola and Marburg VLPs have been shown to protect mice and guinea pigs from a lethal challenge of these viruses (Warfield et al., 2004; Warfield et al., 2005). While VLPs are safe and, due to the rarity of Ebola virus infection, preexisting immunity to Ebola or Marburg viruses is not a concern for VLP vaccines, it is difficult to produce large quantities of VLPs from cell culture.

The biologically contained EbolaΔVP30 virus is thus an ideal vaccine candidate since it combines the advantages of VLPs and vectored vaccines (i.e., safety and efficacy), yet it can be propagated to high titers in VeroVP30 cells like standard viruses (Example 1). Further studies will include testing the EbolaΔVP30 virus for its protective efficacy in NHPs. In addition, shorter, single vaccination protocols will be evaluated to determine if the EbolaΔVP30 virus vaccine could elicit fast and effective immunity in the event of an outbreak or bioterrorism attack. This includes evaluating the EbolaΔVP30 virus as a vaccine for post-exposure treatment.

Example 3

Generation of Noninfectious Ebola Particles

Materials and Methods

Cells. 293 and 293T human embryonic kidney cells were maintained in DMEM supplemented with 10% fetal calf serum, 2% L-glutamine, and penicillin-streptomycin solution (DMEM-FCS) (Sigma). The cells were grown at 37°C in 5% CO_2.

Construction of Plasmids. To generate cDNA constructs encoding the VP40 protein, primers were used that bind to the start and stop codons (positions 4479 and 5459 of the positive-sense antigenomic RNA) to reverse transcribe and PCR-amplify purified viral RNA (Titan RT-PCR Kit, Roche). The PCR product was cloned in the pT7Blue vector (Novagen) resulting in pT7EboZVP40. The cloned Ebola VP40 gene was sequenced to ensure that unwanted nucleotide replacements were not present.

To generate plasmid pETEBoZVP40His for the expression of 6-histidine-tagged VP40 in *Escherichia coli*, pT7EboZVP40 was used as a template for PCR amplification with the appropriate primers. The PCR product was blunt-end ligated into the *Sma*I-digested site of vector pM (CLONETECH). This construct was digested with *Nde*I and *Eco*RI and the fragment containing VP40 was ligated into the expression vector pET-5a (Promega). To generate plasmids pCEboZVP40, pCEboZVP40AAXY, pCEboZVP40M 14A, pCEboZVP40/1-276, pCEboZVP40/1-226, pCEboZVP40/1-176, pCEboZVP40/50-326, and pCEboZVP40/100-326 (proteins expressed from these plasmids are designated VP40, VP40AAXY, and the like) for expression of VP40 and its mutants in eukaryotic cells, the Ebola Zaire VP40 gene was amplified from pT7EboZVP40 using specific forward primers, each containing an *Eco*RI site 5' to the start of the coding region, and specific reverse primers, each containing a *Bgl*II site 3' to the stop codon for each construct, and blunt-end ligated into the *Eco*RV-digested site of vector pT7Blue. Each construct was digested with *Eco*RI and *Bgl*II, and the fragment containing the VP40 gene or modified VP40 gene was cloned into the *Eco*RI and *Bgl*II-digested eukaryotic expression vector pCAGGS/MCS (expression controlled by the chicken β-actin promoter) (Kobasa et al., 1997; and Niwa et al., 1991).

Antibody. A polyclonal antibody against Ebola Zaire VP40 was produced as follows: BL21 *E. coli* cells were transformed with plasmid pETEboZVP40His. Expression of the 6-His-tagged VP40 protein was

induced with 1 mM IPTG for 3 hours. The *E. coli* cells were lysed and cellular debris was remove by centrifugation. The supernatant was purified over an Ni-NTA agarose column (Qiagen). Expression of VP40 was verified by SDS-PAGE followed by Western blotting using a monoclonal antibody against the histidine tag (Kodak). Rabbits were immunized with approximately 0.5 mg of VP40, and antibody against keratin present in the antiserum was removed with a keratin column (Girault et al., 1989).

Cell Transfection for Expression of VP40 and its Mutants. 293 or 293T cells (60-mm plates) were transfected with expression vectors with the use of the Trans IT LT-1 liposomal reagent (Panvera) according to the manufacturer's instructions. Briefly, DNA and transfection reagent were mixed (6 μL of Trans IT LT-1 with 3 μg of DNA) in 0.2 mL OPTI-MEM (Gibco-BRL), incubated for 30 minutes at room temperature, and added to the cells. Transfected cells were incubated at 37°C until harvest of the supernatant and/or cell monolayer.

Particle Formation Assay. Particles were assayed by the method of Li et al (1993) with some modifications. Forty-eight hours after transfection of 293T cells with pCEboZVP40, pCEboZVP40AAXY, pCEboZVP40M14A, or pCEboZVP40/1-276, the culture medium was removed and placed on ice. The cell monolayer was washed with phosphate-buffered saline (PBS), scraped into lysis buffer (0.25 M Tris-HCl, pH 8.0, 0.5% Triton X-100) and kept at 4°C. The culture medium (2 mL) was centrifuged at 2,000 rpm in a microcentrifuge for 5 minutes to remove cellular debris, layered over 20% sucrose in STE buffer (0.01 M Tris-Cl, pH 7.5, 0.01 M NaCl, 0.001 M EDTA, pH 8.0) (2 ml), and centrifuged at 150,000 x *g* for 2 hours at 4°C. After centrifugation, the supernatant was removed and added to the cell lysate. This mixture was saved for analysis of total protein expression. The pellet was resuspended in 1 mL STE buffer overnight at 4°C. The resuspended pellet was layered over a 10-50% discontinuous sucrose gradient in STE buffer, centrifuged at 150,000 x *g* for 4 hours at 4°C, and fractions (1 mL) were collected from the top of the gradient. Each fraction was mixed with 0.25 ml of 50% trichloroacetic acid (TCA) (10% TCA), the fractions were incubated for 30 minutes on ice, and the precipitated proteins were pelleted by microcentrifugation for 15 minutes. The pellets were washed once with cold acetone, air-dried, and resuspended in 0.05 ml SDS-PAGE sample buffer. Proteins in the mixture of cell lysate and supernatant from centrifugation through 20% sucrose were precipitated with 10% TCA, washed with acetone, and resuspended in 0.5 mL SDS-PAGE sample buffer. Proteins were separated by 12% SDS-PAGE and detected by Western blotting. Fractions are numbered from the top to the bottom of the gradient.

Protease Protection Assay. 293T cells were transfected with pCEboZVP40 and, at 48 hours post-transfection, the culture medium was removed. The medium was microcentrifuged at 2,000 rpm for 5 minutes to remove cellular debris, layered over a 20% sucrose cushion, and centrifuged at 165,000 x *g* for 1 hour at 4°C. The supernatant was removed and the pellet was resuspended overnight at 4°C in 0.4 mL STE buffer. This resuspension was divided into six aliquots and treated following a protocol previously described (Mik et al., 1989): Aliquot 1 received no further treatment; aliquot 2 was treated with soybean trypsin inhibitor (Biofluids) to a final concentration of 3 mg/ml; aliquot 3 with triton X-100 to a final concentration of 1%; aliquot 4 with trypsin (Worthington) to a final concentration of 0.1 mg/mL; aliquot 5 with both Triton X-100 to 1% and trypsin to 0.1 mg/ml final concentration; and aliquot 6 with both trypsin inhibitor (3 mg/ml final) and trypsin (0.1 mg/mL final). The samples were incubated at room temperature for 30 minutes, after which an excess of trypsin inhibitor (5 mg/mL) was added to each aliquot. SDS-PAGE sample buffer (6X) was added to each aliquot. Proteins from each aliquot were separated by 12% SDS-PAGE and detected by Western blotting.

Membrane-Association Assay. The method of Bergmann and Fusco (1988) was used, with some modifications, to determine membrane-association of VP40 and its mutants. Briefly, 48 hours after transfection of 293 cells with pCEboZVP40 or a mutant-VP40 expression plasmid, the culture medium was removed, and the cell monolayer, after a wash with (PBS), was scraped into ice-cold sucrose homogenization buffer (10% wt/wt sucrose, 10 mM Tris-HCl (pH 7.4), 1 mM EDTA, and 10 mM iodoacetamide). Cells were disrupted with 30 strokes of a Dounce homogenizer on ice and microcentrifuged for 3 minutes at 2,000 rpm to remove nuclei. The resulting supernatant was made to 1 M NaCl or left untreated, incubated at room temperature for 20 minutes, made to 80% sucrose (wt/vol), placed at the bottom of a Beckman SW41 centrifuge tube, and overlaid with 5 ml of 65% (wt/vol) sucrose and 2.5 mL of 10% sucrose. The gradient was centrifuged to equilibrium at 150,000 x *g* for 18 hours at 4°C. Fractions (1 mL) were collected from the top of the gradient, diluted 1:1 with TBS-Triton buffer (0.025 M Tris-HCl, pH 7.5, 0.15 M NaCl, 0.5% Triton X-100) or, for experiments involving expression of VP40/100-326, precipitated with TCA (as described for the particle formation assay) owing to the weak signal of this deletion construct in Western analysis, and mixed with SDS-PAGE sample buffer. Proteins from each aliquot were separated by 12% SDS-PAGE and detected by Western blotting.

Triton X-114 Phase Partitioning Analysis. The method used was essentially that of Bordier (1981). Forty-eight hours post-transfection of 293 cells pCEboZY40, pCEboZVP40/1-276, pCEboZVP40/1-226, pCEboZVP40/1-176, pCEboZP40/50-326, pCEboZVP40/100-326, or, as a control, a vector expressing A/WSN/33 (H1N1) influenza virus hemagglutinin (HA), cells were scraped into cold TN buffer (10 mM Tris-HCl, pH 7.4, 150 mM NaCl), disrupted with 30 strokes in a Dounce homogenizer, and subjected to centrifugation at 2,000 rpm for 3 minutes to remove nuclei. Triton X-114 (Sigma) was added to each supernatant to 1%, and the resulting solution was incubated for 15 minutes at 4°C with agitation. Unsolubilized material was pelleted by centrifugation in a picofuge for 5 minutes at 4°C, and the supernatant was heated to 37°C for 5 minutes. The supernatant was layered onto a 37°C sucrose (6%) cushion in TN buffer containing 0.06% Triton X-114 and centrifuged at 2,000 rpm for 3 minutes at room temperature. The detergent (lower) and aqueous (upper) phases were recovered separately, the aqueous phase was extracted a second time, like phases were pooled, and the detergent phase was diluted in TN buffer. Proteins in each phase were precipitated with 50% acetone and resuspended in SDS-PAGE sample buffer. Proteins were separated by 12% SDS-PAGE and analyzed by Western blotting.

Western Blotting. Samples in sample buffer (10 μL) were incubated at 100°C for 5 minutes and separated on 12% polyacrylamide gels. Resolved proteins were transferred to Westran polyvinylidine difluoride membranes (Schleicher & Schuell) and blocked overnight at 4°C with 5% skim milk in PBST (0.05% Tween 20 (Sigma) in PBS). Blots were incubated in primary antibody for 1 hour at room temperature, washed three times with PBST, incubated in biotinylated anti-rabbit secondary antibody (Vector Laboratories) for 30 minutes, washed three times with PBST, incubated in streptavidin-horseradish peroxidase reagent (Vector Laboratories) for 30 minutes and washed three times with PBST. Blots were then incubated in Lumi-Light Western blotting substrate (Boehringer-Mannheim) for 5 minutes and exposed to x-ray film (Kodak).

Results

Expression of VP40 in Mammalian Cells. To ensure that VP40 is expressed at efficient levels in human embryonic kidney 293T cells, the cell lysate was analyzed 24 hours after transfection with pCEboZVP40 by Western blotting. Two bands reacting with anti-VP40 polyclonal antibody were found, a

small distance apart, in the range of 40 kDa. The lysate from cells transfected with the expression vector alone did not react with the antibody.

VP40 contains an internal start codon at nucleotides 40-42 (codon 14) that is in frame with the first AUG. To determine whether protein synthesis from this internal start codon was responsible for the faster-migrating band on the gel, a construct was generated, pCEboZVP40M14A, which expresses a mutant VP40 with this second AUG changed to GCG, which encodes alanine, and expressed it as described above. Analysis of the cell lysate revealed a single, larger-sized band, suggesting that the second AUG is used as a start codon to an appreciable extent in this system.

To determine whether loss of the PPXY motif at amino acids 10-13 of VP40 affects expression of the protein, 293T cells were transfected with pCEboZVP40AAXY, which expresses a mutant VP40 in which the PPEY sequence at amino acids 10-13 was changed to AAEY. Two bands corresponding to those seen with the expression of wild-type VP40 were detected. However, in contrast to the results obtained with wild-type VP40 expression, where the slower-migrating band was the predominate product, pCEboZVP40AAXY expressed the two products at similar levels, indicating that loss of the PPXY motif affects either the translation of VP40 or its stability.

Production of Membrane-Bound Particles. To determine whether VP40-associated vesicles are produced when the protein is expressed in the absence of other viral proteins, 293T cells were transfected with pCEboZVP40 and, after 48 hours, collected the supernatant. After removal of cellular debris, the supernatant was subjected to ultracentrifugation over a 20% sucrose cushion. The pellet was resuspended and centrifuged through a 10-50% discontinuous sucrose gradient, and fractions were analyzed by Western blotting. Fractions 6-8 contained VP40, with the majority of the protein found in fraction 7. The VP40 in fractions 6-8 was most likely associated with membrane lipids in a particle-like structure, as the sucrose densities in these fractions ranged from 1.11 to 1.13 g/mL, which corresponds to findings for matrix protein-generated particles of other viruses (Giddings et al., 1998; Sandefur et al., 1998). Bands detected below full-length protein in the total protein fraction are likely degradation products. These data indicate that VP40 expressed in the absence of other viral proteins can produce membrane-bound particles.

Protease Protection Assay. To confirm the ability of VP40 to produce membrane-bound particles when expressed alone, a trypsin protection assay was employed. Culture supernatant from cells transfected with pCEboZVP40 was centrifuged at 165,000 x *g* through 20% sucrose, and the pellet was resuspended in STE buffer and divided into six equal aliquots. Aliquots 1-3 served as controls (untreated, trypsin inhibitor treated, and triton X-100 treated), aliquot 4 was treated with trypsin, aliquot 5 with trypsin and triton X-100, and aliquot 6 with trypsin inhibitor and trypsin. Trypsin degraded VP40 only in the presence of triton X-100, indicating that the viral protein does induce the production of fully membrane-bound particles; that is, trypsin digestion of VP40 required disruption of the lipid-bilayer surrounding the protein.

VP40 Mutants and Membrane-Bound Particle Formation. Does the PPXY motif at amino acids 10-13 of VP40 contribute to particle production? To address this question, VP40AAXY was expressed in 293T cells and assayed for particles as described for wild-type VP40. VP40AAXY was not detected in fractions corresponding to the sucrose densities to which wild-type VP40 particles migrated. Since VP40AAXY was synthesized at levels similar to wild-type VP40, this finding indicates that mutation of the PPXY motif markedly disrupts VP40-generated vesicle formation.

A substantial amount of VP40M14A was present in fractions 5-8 in the gradient, and the percentage of total VP40M14A expressed in 293T cells that contributed to membrane-bound particle formation was much greater than the percentage of total wild-type VP40 involved in particle formation. This result is consistent with the finding that the PPXY motif present immediately upstream of the second AUG is critical for VP40-associated particle formation.

To determine whether the C-terminus of VP40 is essential for particle formation, a deletion mutant, VP40/1-276, was assayed which lacks the final 50 amino acids of VP40, for particle generation. Since this deletion mutant was not present at the same sucrose densities that characterized the migration of wild-type VP40, it was concluded that the first 276 amino acids of VP40 are not sufficient for particle formation.

VP40 Association with Cell Membranes and Structural Requirements for Activity. Flotation analysis was used to determine if VP40 binds cellular membranes efficiently in mammalian cells. In this method, postnuclear membrane fractions in 80% sucrose are loaded at the bottom of a centrifuge tube and overlaid with 65% and 10% sucrose. During centrifugation, cellular membranes and their associated proteins float to the 10-65% sucrose interface, while soluble proteins remain in the dense sucrose fractions at the bottom of the tube.

A large percentage of wild-type VP40 was found at the 10-65% sucrose interface (fraction 3), while the remaining protein was found in the loading zone (fractions 8-12), indicating that VP40 does indeed bind cellular membranes. To clarify the interactions involved in this association, VP40-associated membranes were treated with 1 M NaCl to determine whether electrostatic interactions were required for this association and subjected them to flotation analysis. Salt treatment had a negligible affect on the ability of VP40 to associate with membranes, suggesting that the protein contains at least one hydrophobic domain able to associate with membranes.

To elucidate the domain(s) of VP40 important for membrane association, deletion mutants were generated. Constructs expressing amino acids 50-326 (pCEboZVP40/50-326), amino acids 100-326 (pCEboZVP40/100-326), amino acids 1-176 (pCEboZVP40/1-176), amino acids 1-226 (pCEboZVP40/1-226), and amino acids 1-276 (pCEboZVP40/1-276) of VP40 were expressed in 293 cells and their membrane association in the presence or absence of 1 M NaCl was examined. The mutants with the largest truncations, VP40/1-176 and VP40/100- 326, showed the highest level of association with the lipid bilayer. Salt treatment did not affect these interactions. Mutants VP40/1-226 and VP40/50-326 associated with membranes to the extent found with wild-type VP40, and these interactions were also relatively unperturbed by treatment with salt. By contrast, only a small portion of VP40/1-276 associated with the lipid bilayer, and this interaction was eliminated upon treatment with salt. These results indicate that loss of the C-terminal 50 amino acids of VP40 markedly alters the membrane-binding capabilities of VP40, primarily by disrupting hydrophobic interactions. This effect was ameliorated when 50 additional C-terminal amino acids were deleted, and membrane-association was promoted when the protein was further truncated to 176 amino acids. Deletion of the N-terminal 49 amino acids of VP40 did not alter the membrane-binding characteristics of the protein, although truncation of 50 additional N-terminal amino acids did enhance protein-membrane association, as seen with VP40/1-176.

Since particle formation was markedly reduced with VP40AAXY, cells expressing this mutant were subjected to flotation analysis in order to determine whether a decreased ability to bind membranes was involved in this deficiency. The loss of the PPXY motif in VP40 did not affect the ability of the protein

to bind membranes, indicating that lack of particle production with this mutant was not due to the loss of membrane association.

Flotation analysis was also used to determine whether the more efficient particle formation induced by VP40M14A, by comparison to wild-type VP40, could be attributed, at least in part, to increased membrane binding by this mutant. The percentage of VP40M14A associated with membranes was only slightly greater than that determined for wild-type VP40, indicating that this mutant relies on another mechanism to increase particle formation.

Triton X-114 Phase Partitioning Analysis. To probe the nature of the VP40-membrane interaction further, Triton X-114 phase partitioning analysis was used as integral membrane proteins and lipid anchored proteins partition in the detergent phase of a protein extraction and peripheral membrane proteins partition in the aqueous phase. HA, an integral membrane protein, was found entirely in the detergent phase of the extraction, as expected. Only a small portion of total VP40 was found in the detergent phase, while VP40/1-276 was found almost entirely in the aqueous phase. VP40/1-226 and VP40/50-326 partitioned in the detergent phase in proportions similar to that found for wild-type VP40. By contrast, when VP40/1-176 and VP40/100-326 were expressed, large proportions of each partitioned in the detergent phase. These results indicate that wild-type VP40 possesses only minor traits of an integral membrane protein, and that deletion of its C-terminal 50 amino acids (VP40/1-276) abrogates these features. Further truncation of the C-terminus (VP40/1-226 and VP40/1-176) enhances the integral membrane character of protein. Deletion of the N-terminal 49 amino acids of VP40 (VP40/50-326) does not alter the general structural features of the protein, while deletion of amino acids 1-99 (VP40/100-326) appears to increase the extent of anchoring to lipids.

Discussion

Thus, VP40 of Ebola virus, when expressed in the absence of other viral proteins, can induce the formation of membrane-encompassed particles, much in the manner of the matrix proteins of VSV, rabies, and simian immunodeficiency virus (Giddings et al., 1998; Harty et al., 1999; Justice et al., 1995; Li et al., 1993). Cellular proteins containing the WW domain are, in all likelihood, crucial for this process, as VP40 containing an altered version of a PPXY motif at amino acids 10-13 induces little or no particle formation. Harty et al. (1999) demonstrated that the matrix proteins of VSV and rabies viruses, which possess this motif at their N-termini, bind the cellular Yes-kinase-associated and Nedd4 proteins via a PPXY motif-WW domain, interaction, and that the loss of this motif results in impaired virus release from infected cells. Jayakar et al. (2000) recently demonstrated that mutation of the PPXY motif in the matrix protein of VSV impedes budding of fully assembled virions at the plasma membrane. The data described herein provides evidence for an important role of the PPXY motif in particle formation induced by VP40, and suggest that cellular proteins are crucial players in this process.

The efficiency of particle production markedly increased when the second ATG codon of VP40 (codon 14) was changed to GCG (alanine), but the reason for this enhancement remains unclear. This ATG codon immediately follows the PPXY motif. Perhaps the faster-migrating version of VP40, which lacks the PPXY motif, interferes with the assembly or budding of full-length VP40 molecules at the cell surface, or with the interaction between VP40 and a cellular protein. Whether translation from this second ATG occurs in actual viral infection or is an artifact of the system employed in this study is unknown.

Ruigrok et al. (2000) reported that VP40 expressed in *E. coli* can bind liposomes *in vitro* and that this interaction is largely electrostatic. In mammalian cells, a substantial amount of VP40 bound to the

cellular membrane, and that this interaction was disrupted negligibly by the presence of 1 M NaCl, indicating that at least one hydrophobic domain is involved in this interaction. A small but appreciable portion of VP40 partitioned with detergent in the manner of an integral membrane or lipid-anchored protein in Triton X-114 phase-partitioning analysis. This result, together with the inability of 1 M NaCl to dissociate VP40 from the lipid bilayer, indicates that the protein has certain properties of an integral membrane protein, as do a number of matrix proteins of negative-stranded RNA viruses (Chong et al., 1993; Zhang et al., 1996), even though Ebola VP40 does not appear to contain a region of significant length and hydrophobicity to span the cell membrane. Short hydrophobic stretches of VP40 may be able to penetrate the lipid bilayer to some extent, lending modest integral-membrane character to the protein.

Ruigrok et al. (2000) also reported that a deletion mutant of VP40 containing amino acids 31-212 failed to bind liposomes efficiently, indicating that the C-terminus of VP40 is absolutely required for membrane binding. To elucidate the domains involved in the association of VP40 with cellular membranes, carboxy and amino-terminal deletion mutants were constructed. VP40 lacking its C-terminal 50 amino acids demonstrated appreciably reduced membrane association. The Kyte-Doolittle hydrophobicity plot (1982) of VP40 indicates that amino acids 277- 326 of the protein are primarily hydrophobic, so that deletion of amino acids 277-326 eliminates a substantial hydrophobic region that is likely important for efficient membrane-binding by the full-length protein. This hypothesis is supported by the fact that 1 M NaCl completely disrupted this association, suggesting that affinity of this deletion construct with the lipid bilayer depends primarily on electrostatic interactions.

When amino acids 227-326 of VP40 were deleted, the resulting truncated protein associated with the lipid bilayer as efficiently as wild-type VP40; moreover, C-terminal deletion of amino acids 177-326 resulted in a protein with much higher affinity for the lipid bilayer than was found for wild-type VP40. Salt treatment did not perturb membrane association of these truncated versions of VP40, indicating the presence of hydrophobic interactions mediated by the N-terminal 176 amino acids of the protein.

The hydrophobicity plot indicates that amino acids 227-276, and particularly amino acids 177-226, are primarily hydrophilic. Deletion of the hydrophilic residues present in this region of VP40 may allow the truncated protein to fold into a structure capable of strong hydrophobic association with the cell membrane, perhaps by effectively exposing the highly hydrophobic central domain of the protein. These results are consistent with data obtained by Triton X-114 extraction analysis. Since VP40 lacking its C-terminal 50 amino acids was unable to produce particles, and these C-terminal residues appear to be required for efficient membrane association of VP40, binding of this highly hydrophobic region to the lipid bilayer may be an essential step in the particle formation process.

The crystal structure of amino acids 31-326 of Ebola virus was recently elucidated by Dessen et al. (2000). It shows VP40 to be distinct from other viral matrix proteins, in that it consists of two similar domains connected by a flexible linker at amino acids 195-200. Ruigrok et al. (2000) showed that amino acids 31-212 of VP40 form hexamers spontaneously in solution. Dessen and associates postulate that, during the life cycle of Ebola virus, VP40 molecules associate with the lipid bilayer through interactions contributed primarily by their C-termini. After membrane binding, the molecules undergo a conformational change that frees their N-termini for hexamerization. These hexamers then form building blocks for a lattice that underlies the plasma membrane, and subsequently may interact with the cytoplasmic tails of viral glycoproteins and/or the ribonucleoprotein complex. This model is based on data demonstrating the hexamerization of VP40 molecules that lack their N-terminal 30 amino acids as well as their C- terminal

114 amino acids. The PPXY motif that appears crucial for membrane-bound particle formation is located at amino acids 10-13 of VP40, and this motif most likely interacts with a cellular protein that exhibits a WW domain during virus particle assembly or budding. It has not yet been demonstrated that VP40 with a truncated C-terminus can form hexamers when the entire N-terminus is present. If hexamerization does occur during virion morphogenesis, the 18 hexamers that form presumably must leave the PPXY motif accessible to cellular proteins that participate in particle formation and/or budding.

Example 4

Particles Comprising Filovirus Matrix Protein and Glycoprotein

Materials and Methods

Cells. 293T human embryonic kidney cells were maintained in Dulbecco's modified Eagle medium supplemented with 10% fetal calf serum, L-glutamine and penicillin-streptomycin-gentamicin solution. The cells were grown in an incubator at 37°C in 5% CO_2.

Plasmids. Full-length cDNAs encoding the Ebola virus (species Zaire) VP40 or GP were cloned separately into a mammalian expression vector, pCAGGS/MCS (Kobasa et al., 1997; Niwa et al., 1991), which contains the chicken β-actin promoter. The resultant constructs were designated pCEboZVP40 and pCEboZGP, respectively.

Cell Transfection for Expression of VP40 and GP. 293T cells (1×10^6) were transfected with plasmids using the Trans IT LT-1 reagent (Panvera, Madison, WI) according to the manufacturer's instructions. Briefly, 1 μg of DNA in 0.1 mL Opti-MEM (Gibco-BRL) and 3 μL of the transfection reagent were mixed, incubated for 10 minutes at room temperature, and added to the cells. Transfected cells were incubated at 37°C for 24 or 48 hours.

Electron Microscopy. Ultrathin section electron microscopy was performed as follows. Twenty-four hours post-transfection of 293T cells with plasmids, the cells were washed with phosphate-buffered saline (PBS) and fixed for 20 minutes with 2.5% glutaraldehyde (GLA) in 0.1 M cacodylate buffer (pH 7.4). They were scraped off the dish, pelleted by low-speed centrifugation and then fixed for 30 minutes with the same fixative. Small pieces of fixed pellet were washed with the same buffer, postfixed with 2% osmium tetroxide in the same buffer for 1 hour at 4°C, dehydrated with a series of ethanol gradients followed by propylene oxide, embedded in Epon 812 Resin mixture (TAAB) and polymerized at 70°C for 2 days. For immune electron microscopy, cells were fixed with 4% paraformaldehyde and 0.1% GLA, dehydrated and embedded in LR White Resin (London Resin Company Ltd.). Thin sections were stained with uranil acetate and lead citrate, and examined with a JEM-1200EX electron microscope at 80 Kv.

For negative staining, culture media of 293T cells were collected at 24 hours post-transfection onto a Formvar-coated copper grid, stained with 2% phosphotungstic acid solution (PTA) and examined with a JEM-1200 electron microscope at 80 Kv.

For immune electron microscopy, the samples were absorbed to Formvar-coated nickel grids and washed with PBS containing 0.5% bovine serum albumin (PBS-BSA). The grids were then treated with mouse anti-GP monoclonal antibody (a mixture of ZGP12, ZGP42, and ZGP133 (31); 1:150 in PBS-BSA) or rabbit anti-VP40 polyclonal antibody (1:300 in PBS-BSA), and rinsed six times with PBS, followed by incubation with a goat antimouse immunoglobulin conjugated to 15-nm gold particles (1:50 dilution; BBInternational) or a goat antirabbit immunoglobulin conjugated to 5-nm gold particles (1:100 dilution; BBInternational). After washing, the samples were fixed for 10 min in 2% glutaraldehyde and negatively stained with 2% PTA.

Results

Pleomorphic Particle Formation by GP. To determine the morphology of vesicles induced by Ebola virus GP expression, GP-expressing cells and their supernatants were analyzed by electron microscopy. The ultrathin sections of these cells showed particle-like structures with surface spikes budding from the plasma membrane; no such structures were observed using cells transfected with the expression vector alone. As previously observed in the recombinant vaccinia virus system (Volchkov et al., 1998), pleomorphic structures similar to virosomes with a range of diameters were apparent in the supernatants of GP-expressing cells. The spikes on the surface of the vesicles reacted with anti-GP monoclonal antibodies, confirming the GP derivation of the structures.

VP40 Induces Filamentous Particle Formation. To determine how VP40 protein expressed in 293T cells is released into culture medium (Harty et al., 2000; Timmins et al., 2001), the VP40-expressing cells were analyzed by transmission electron microscopy. The ultrathin sections of the cells expressing VP40 showed budding of filamentous structures (approximately 65 nm in diameter) on the cell surface. In some cells, the plasma membranes appeared ruffled and to consist of two bilayers. Aggregated ribosomes were occasionally found in the cytoplasm of cells expressing VP40, as were electron-dense filamentous structures (approximately 45 nm in diameter), which were never seen in cells transfected with the expression vector alone. The budding particles and membrane ruffles reacted with rabbit anti-VP40 polyclonal antibody, confirming that VP40 had contributed to the generation of these structures. In studies to further determine the size and morphology of the VP40 particles released from cells, the supernatants of cells expressing this protein were centrifuged through 20% sucrose, and the pelleted material was negatively stained with 2% PTA and analyzed by electron microscopy. Filamentous particles, which had uniform diameters of approximately 65 nm but varied lengths, were observed. These results indicate that VP40 alone can induce the formation of filamentous particles, which bud from the cell surface.

VP40-GP Interaction in Particle Morphogenesis. To determine how GP expression affects VP40-driven particle formation, 293T cells were transfected with both VP40- and GP-expressing plasmids. In ultrathin sections of the transfected cells, filamentous particle-like structures of 80-nm external diameter were observed that were budding from the plasma membrane. The structures possessed spikes of approximately 10 nm on their surface, in contrast to the structures observed in cells expressing VP40 alone. Also, unlike the findings with expression of GP alone, few pleomorphic particles were observed. The particle structures were studied in more detail after negative staining of the particles in culture supernatants of cells expressing both VP40 and GP. Filamentous Ebola virus-like particles with surface spikes of approximately 85-nm in external diameter and lengths that ranged to 10 μm were observed. The spikes projected from the particle surface at 5- to 10-nm intervals and were morphologically indistinguishable from those on the Ebola virion surface (Feldmann et al., 1996; Peters et al., 1995). Labeling of the spikes with a mixture of anti-GP monoclonal antibodies conjugated with gold particles confirmed their identity as GP. Furthermore, when treated with 0.03% Triton X-100 and with both the anti-VP40 antibody conjugated to 5-nm gold particles and a mixture of anti-GP monoclonal antibodies conjugated to 15-nm gold particles, the filamentous particles became labeled with both antibodies, demonstrating that the Ebola vires-like particles contained GP as well as VP40 proteins. These results demonstrate GP incorporation into VP40-generated filamentous structures, without affecting filamentous particle formation.

Discussion

A hallmark of Ebola virus is its filamentous virions as featured in its family name *Filoviridae*. The shape of enveloped viruses are determined by viral proteins in retroviruses (Campbell et al., 1997; Gay et al., 1998; Joshi et al., 2000) or by both viral RNA length and proteins in VSV (Pattnaik et al., 1991). Because specific interactions among viral components are required for the formation of defined virion shapes, understanding of such interactions can lead to the identification of targets for the development of antiviral compounds.

As shown herein by electron microscopy, the expression of VP40 in the absence of any other Ebola virus proteins leads to the formation of filamentous particles, which resemble spikeless virions released into the supernatant of cultured Ebola virus-infected cells (Geisbert et al., 1995). Thus, these results suggest that the Ebola virus VP40 possesses structural information necessary and sufficient to induce the formation of filamentous particles, which then bud from the plasma membrane. Interestingly, some filamentous structures were observed in the cytoplasm of cells expressing VP40 as have been found in the cytoplasm of the cells infected with Ebola virus. Similar structures have also been observed in cells expressing the M1 protein of influenza virus or the GAG protein of retrovirus (Delchambre et al., 1989; Gheyson et al., 1989; Gomez-Puertas et al., 2000). However, the tubular structures observed upon expression of influenza virus M1 alone were not seen during normal viral infection or when M1 was coexpressed with other influenza viral proteins. Thus, VP40 may form intracellular filamentous structures by self-aggregation.

Membrane ruffles containing VP40 protein were observed in some VP40-expressing cells. The M protein of VSV induces similar double-layered membranes at the cell surface when expressed from recombinant Sendai virus (Sakaguchi et al, 1999). IpaC protein secreted by *Shigella flexneri* has also been linked to large-scale membrane extension in macrophages, including lamellipodia and membrane ruffles (Kuwae et al, 2001; Tran Van Nhieu et al., 1999), while *Salmonella typhimurium* triggers the formation of host cell membrane ruffles in nonphagocytic cells (Ginocchio et al., 1994; Zhou et al., 1999). These membrane ruffles are thought to result from interactions between the bacterial proteins, including IpaC, and the actin cytoskeletons of host cells (Tran Van Nhieu et al., 1999; Zhou et al., 1999). In Ebola virus-infected cells, host cell plasma membranes proliferate extensively at the peak stage of viral budding (Geisbert et al, 1995), as observed in cells expressing VP40 alone. Thus, VP40 may interact with actin filaments during the assembly or budding of Ebola virus at the cell surface.

The impact of glycoprotein interaction with the matrix protein on virion morphology differs among viruses. For example, deletion of the cytoplasmic tails of the influenza virus hemagglutinin and neuraminidase alters virus morphology (Jin et al., 1997; Mitnaul et al., 1996), while the characteristic morphology of rabies virus and VSV do not depend on glycoprotein-matrix protein interaction (Mebatsion et al, 1996; Mebatsion et al., 1994; Schnell et al., 1998; Takada et al., 1997). The Ebola virus GP, like VSV-G, was incorporated into filamentous particles without affecting the morphology of the particles. However, such interaction may contribute to the efficiency of budding, as demonstrated by research on VSV (Jayakar et al., 2000; Mebatsion et al., 1999).

In conclusion, VP40 induces VP40 containing-filamentous particle formation and GP spikes are incorporated into VP40 induced-filamentous particles upon coexpression of GP and VP40, resulting in Ebola virus-like particles.

Example 5

A Method to Screen for Modulators of Viral Transcription or Replication

To produce viral vectors for an antiviral screening method, vectors were prepared that expressed a rhabdovirus or filovirus protein and a reporter. In one embodiment, a reporter gene replaces rhabdovirus GP sequences in genomic rhabdovirus DNA. In one embodiment, a reporter gene replaces filovirus GP sequences in genomic filoovirus DNA. In one embodiment, viral protein expression vectors useful with the recombinant genomic DNA may include one expressing filovirus GP and optionally one or more vectors expressing one or more of rhabdovirus N, P, M and L. In another embodiment, a reporter gene replaces sequences in genomic filovirus DNA. The Filovirus protein expression vectors, e.g., Marburg virus or Ebola virus vectors, include one or more of the following sequences: sequences for L, NP, VP30 and/or VP35. If more than one vector is employed, the vectors may be physically linked or each vector may be present on an individual plasmid or other, e.g., linear, nucleic acid delivery vehicle.

To develop an antiviral to *Ebolavirus*, the entry process, including receptor binding and/or fusion, was targeted. To identify compounds that interfere with these steps in the viral life cycle, a replication-incompetent Vesicular Stomatitis Virus (VSV) was employed that lacks the VSV glycoprotein gene and contains the GFP gene instead. This replication-incompetent VSV was pseudotyped with Ebola GP glycoprotein. This pseudotyped virus infects cells once, resulting in GFP gene expression. In the presence of compounds that interfere with Ebola GP-mediated binding or fusion, reporter gene expression is abrogated. This system was used to screen about 6,300 compounds at The National Screening Laboratory for the Regional Centers of Excellence in Biodefense at Harvard University, Boston, MA, and 144 compounds were identified that reduced reporter gene expression by more than 90%.

To verify whether the compounds indeed inhibit *Ebolavirus* infection, a biologically contained *Ebolavirus* expressing GFP protein (EbolaΔVP30-GFP virus) (see Example 2) was employed. 111 of the originally-identified 144 compounds were tested and 24 were identified that reduced the infectivity of the biologically contained *Ebolavirus* by at least 90% (Figure 11). For those compounds, the 50% inhibitory concentration (IC_{50}) and cytotoxic concentration (CC_{50}) were determined. Benztropine mesylate emerged as a lead candidate.

Further studies revealed that benztropine mesylate efficiently reduced the infectivity of VSV pseudotyped with GPs of all known subtypes of *Ebolavirus* (i.e., Zaire, Reston, Sudan, Ivory Coast); the titers of these pseudotyped viruses were reduced by 98-99%. Benztropin mesylate was also effective against VSV pseudotyped with the GP protein of Marburgvirus, although to a lesser extent (reduction of virus titers of about 75%). On the other hand, benztropine mesylate does not affect the growth of viruses such as VSV and influenza virus, indicating the specificity of this compound for *Ebolavirus*.

Binding of *Ebolavirus* to cell surface activates the phosphoinositide-3 (PI3) kinase-Akt pathway. It was determined that benztropine mesylate did not inhibit the phosphoinositide-3 (PI3) kinase-Akt pathway *per se*. However, benztropine mesylate was found to inhibit infection of VSV pseudotyped with Ebola GP that was bound to cell surfaces at 0-4°C, temperatures that may disrupt endocytosis and vesicle trafficking.

Benztropine mesylate is a known and commercially available inhibitor of the dopamine transporter and is used to treat the symptoms of Parkinsons's disease and other neurological disorders. Since benztropine mesylate is known to bind to receptors for neurotransmitters, *Ebolavirus* might utilize these receptors as second receptors for entry. Thus, benztropine mesylate might inhibit binding of *Ebolavirus* to neurotransmitter receptors, resulting in the inhibition of activation of PI3 kinase-Akt pathway for entry.

Alternatively, or in addition to blocking neurotransmitter receptors, benztropine mesylate may inhibit fusion of the virus envelope with the cellular membrane.

Example 6

Materials and Methods

Cells. VeroVP30 cells were established as previously described (Halfmann et al., 2008) and grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal calf serum (FCS). Vero and CV-1 cells were cultured under the same conditions as VeroVP30 cells. 293T cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FCS. Madin-Darby canine kidney (MDCK) cells were kept in MEM containing 5% newborn calf serum (NCS). A549 cells were maintained in Kaighn's Modification of Ham's F-12 (F-12K) medium with 10% FCS. All cells were maintained at 37°C with 5% CO_2.

Viruses. The EbolaΔVP30 expressing GFP (EbolaΔVP30-GFP) and *Influenzavirus* A/WSN/33 (H1N1) were generated, propagated, and titrated as previously described (Halfmann et al., 2008; Neumann et al., 1999). Vesicular stomatitis virus (VSV) strain Indiana, vaccinia virus, and adenovirus Ad-5 were propagated and titrated in Vero cells, CV-1 cells, and A549 cells, respectively.

High throughput screening assay. For compound screening, VeroVP30 cells were seeded in 384-well culture plates. After about 2 hours of incubation at 37°C, 5% CO_2, compounds dissolved in DMSO were added. The cells were then incubated at 37°C for another approximate 2 hours, before being inoculated with EbolaΔVP30-GFP virus. All plates included wells to which DMSO was added without any compound for GFP-positive (virus inoculated) and negative (no virus inoculated) controls for the z'-factor calculation. GFP intensities were measured by use of a Safire II plate reader (Tecan Group Ltd., Mannedorf, Switzerland). Cell viabilities were determined by using a CellTiter-Glo™ Luminescent Cell Viability Assay (Promega, Madison, WI, USA) and compared to GFP-positive controls, which were cells treated with DMSO only and inoculated with virus. The high throughput screen was carried out at the Keck-UWCCC Small Molecule Screening Facility (Madison, WI).

Virus binding and entry assay. Recombinant VSV viruses, VSVΔG*-*Ebolavirus* GP and VSVΔG*-VSV G, were generated as previously described (Ito et al., 1999; Takada et al., 1997). To determine whether the compounds inhibit virus binding/entry, Vero cells in 12-well plates were treated with 500 μL of 2% FCS-MEM containing 10 μM compounds for 2 hours prior to infection with the recombinant viruses. Since the recombinant virus possesses the GFP reporter gene instead of the VSV G gene, cells expressing GFP after virus inoculation indicate that the virus bound, entered, and replicated the protein in the those cells. Therefore, to determine the efficiency of virus binding/entry mediated by *Ebolavirus* GP, GFP-positive cells were counted under a fluorescence microscope 16 to 20 hours after virus inoculation and the numbers compared between the two recombinant VSV viruses.

Virus minigenome replication assay. A plasmid-based minireplicon assay was performed as described by Watanabe et al. (Watanabe et al., 2007). To determine whether the compounds inhibit protein expression from the *Ebolavirus* minigenome, 293T cells were transfected with plasmids for the expression of *Ebolavirus* nucleoprotein (NP), L, VP35, VP30, *Ebolavirus* minigenome encoding firefly luciferase, and T7 polymerase. Compounds were added into the media at a final concentration of 10 μM at 6.5 hours post-transfection. Three days post-transfection, cells were disrupted and mixed with Steady Glo (Promega), and luciferase activities were detected by using Glomax (Promega). A reduction in

luciferase activity indicates either inhibition of *Ebolavirus* RNA-dependent RNA polymerase activity or T7 polymerase activity, which is required for Ebola minigenome expression.

Results

Anti-Ebolavirus high throughput compound screening. To identify anti-*Ebolavirus* compounds, Known Bioactive Library 01, which consists of three commercially available collections totaling 4,160 compounds, was screened with the EbolaΔVP30-VeroVP30 system. The z'-factor, a measure of assay quality, was consistently over 0.5 and averaged 0.66 (range; 0.50-0.76), indicating that the EbolaΔVP30-VeroVP30 system was suitable for the HTS assay. Nineteen compounds were identified as anti-*Ebolavirus* candidates. Six of these were gedunin-like limonoids that shared structural similarities; these six compounds were focused on for further analysis.

Anti-Ebolavirus activities of gedunin and gedunin-derivatives. Known Bioactive Library 01 contains 41 gedunin-like limonoids. To assess whether all of these compounds show anti-*Ebolavirus* activity, 39 accessible compounds were re-screened. For this secondary screening, 1.5×10^4 cells/30 μL/well were seeded in a 384-well plate, compounds were added at a concentration of 10 μM, and 30 μL of the EbolaΔVP30-GFP virus was added at an MOI of 0.1, so that the final concentration of the compounds was 5 μM. Fourteen of the compounds reduced the GFP intensity by more than 75%, while cell viabilities were maintained at more than 70%, relative to the positive control (cells that received DMSO and inoculated the virus) (Table 1). The other 25 gedunin-like limonoids tested reduced the GFP intensity by less than 45% (range; 45% - negative 49%) or cell viabilities by more than 95%.

Table 1

Compound	% GFP inhibition	% cell viability
Epoxygedunin*	103	71
Gedunin*	102	77
1,3-Dideacetyl-7-deacetoxy-7-oxokhivorin*	100	78
Dihydrogedunin	96	79
7-Deacetoxy-3-deacetyl-7-oxokhivorin*	92	80
3beta-Acetoxydeoxodihydrogedunin	90	80
Tridesacetoxykhivorin	89	75
3alpha-Hydroxydeoxodihydrogedunin*	85	94
1,3-Dideacetylkhivorin	82	78
Deacetoxy-7-oxogedunin	80	79
Gedunol	79	82
3beta-Hydroxydeoxodihydrogedunin	75	79
1,2alpha-Epoxydeacetoxydihydrogedunin*	75	77
3beta-Hydroxydeoxydesacetoxy-7-oxogedunin	75	81
Heudelottin C	104	5
Deacetylgedunin	45	86
Deacetoxy-7-oxisogedunin	41	84
1,7-Dideacetoxy-1,7-dioxokhivorin	39	88
Isogedunin	35	86
6-Acetoxyangolensic acid methyl ester	32	88
Tridesacetoxykhivorin	28	94
7-Deacetoxy-7-oxokhivorin	26	90
1-Deacetoxy-1-oxo-3,7-dideacetylkhivorin	19	94
6-Hydroxyangolensic acid methyl ester	15	94
1,7-Dideacetoxy-1,7-dioxo-3-deacetylkhivorin	14	87
7-Deacetylkhivorin	13	91
3-Deacetylkhivorin	6	102
Utilin	4	75

Compound	% GFP inhibition	% cell viability
7-Epikhivorin	4	79
Angolensic acid, methyl ester	4	85
7-Desacetoxy-6,7-dehydrogedunin	2	70
Khivorin	0	82
Entandrophragmin	-12	83
Andirobin	-12	91
Prieurianin	-17	89
2,3-Dihydroisogedunin	-17	91
11alpha-Acetoxykhivorin	-47	93
Heudelottin E	-49	93
7-Deacetyldihydrogedunin	-30	85

* These are the compounds selected for further analyses.

Comparison of compounds with and without anti-*Ebolavirus* activity indicated that those compounds with activity against *Ebolavirus* had a core structure having four benzene rings and a furan ring. In addition, the 1-Keto group of ring A of these compounds may have reduced virus infectivity. For further analysis, five gedunin-like limonoids were selected (Figure 12; gedunin, epoxygedunin, 1,3-Dideacetly-7-Deacetoxy-7-Oxokhivorin, 7-Deacetoxy-3-deacetyl-7-Oxokhivorin, and 1,2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin).

To confirm the anti-*Ebolvirus* activities of these 5 compounds, the growth kinetics of EbolaΔVP30-GFP were assessed in their presence. The compounds (10 μM) were added to Vero VP30 cell culture medium 2 hours prior to infection (MOI = 0.001) and the medium was then harvested 24, 48, and 72 hours post-infection. As shown in Figure 13, all five gedunin-like compounds inhibited the growth of EbolaΔVP30-GFP. Gedunin and epoxygedunin completely inhibited EbolaΔVP30-GFP growth, while the other three compounds reduced virus growth by at least 1 $\log_{10}$ titer (85% reduction) at 72 hours post-infection. These data confirm the anti-*Ebolavirus* activity of these compounds.

To calculate the anti-*Ebolavirus* efficacies of the compounds, their 50% inhibitory concentrations (IC_{50}) were determined by measuring GFP intensity following virus infection at an MOI of 0.1. The compounds showed significant activity with IC_{50} values of 0.56 μM or lower, with the exception of 1,2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin (Table 2), whose IC_{50} was 7.12 μM. The 50% cytotoxic concentrations (CC_{50}) of the compounds were greater than 10 μM, indicating low toxicity to cell culture.

Table 2. IC_{50}s and CC_{50}s of Gedunin and Gedunin derivatives

compound	IC_{50} (μM)	CC_{50} (μM)
Gedunin	0.33	>10
Epoxygedunin	<0.15	>10
1,3-Dideacetly-7-Deacetoxy-7-Oxokhivorin	<0.15	>10
7-Deacetoxy-3-deacetyl-7-Oxokhivorin	0.56	>10
1,2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin	7.12	>10

Virus-specific inhibition of compounds.Gedunin and some gedunin-derivatives have antimalarial (MacKinnon et al., 1997), anti-HIV (http://home.ncifcrf.gov/mtdp/Catalog/compounds/309912.html), anti-insect (Nathan et al., 2005), and anti-cancer (Uddin et al., 2007) activities. Therefore, it was determined whether these five compounds inhibited other viruses, namely vaccinia virus, adenovirus, VSV, and

influenza virus. Experiments were carried out with 10 μM compounds and infections at an MOI of 0.001 (vaccinia virus, adenovirus) or 0.00001 (VSV and influenza virus). As shown in Figure 13, none of the compounds significantly inhibited any of the viruses, although gedunin was slightly inhibitory to adenovirus, indicating that the anti-virus activities of these compounds are not universal.

Inhibition of Ebola GP-dependent virus entry. The first step of *Ebolavirus* infection is virus binding and entry into the host cell via its surface glycoprotein (GP). To examine whether gedunin and gedunin-like compounds inhibit virus entry, we adapted a VSV pseudotype system (Ito et al., 2001; Takada et al., 1997). The pseudotype viruses, VSVΔG*-*Ebolavirus* GP and VSVΔG*-VSV G, possess *Ebolavirus* GP and VSV G on their surfaces, respectively. Initiation of infection relies upon those surface glycoproteins. In addition, these recombinant viruses possess a GFP reporter gene in place of the VSV G gene, such that infected cells can be distinguished by GFP expression.

Compounds were added 2 hours prior to the pseudotype virus infections, and virus infectivy was determined by counting the number of GFP-positive cells after an overnight incubation at 37°C. All five compounds appreciably reduced the infectivity of VSVΔG*-*Ebolavirus* GP but not that of VSVΔG*-VSV G (Figure 14), indicating that these compounds inhibit *Ebolavirus* GP-dependent virus entry. Interestingly, 2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin, which inhibited 75% of GFP expression from EbolaΔVP30-GFP virus (Table 2) and had an IC_50 of 7.12 μM (Table 2), allowed 6.5 ± 1.6% of VSVΔG*-*Ebolavirus* GP infection, whereas the other four compounds, which inhibited more than 90% of GFP expression of EbolaΔVP30-GFP virus infection (Table 2) and had IC_{50}s more than 10 times lower than that of 2alpha-Epoxy-7-Deacetoxy-7-Oxo-Deoxyhydrogedunin, allowed less than 3% of VSVΔG*-*Ebolavirus* GP infection. These data suggest that the level of *Ebolavirus* inhibition of these compounds is associated with their ability to inhibit Ebolavirus GP-dependent virus entry.

Inhibition of protein expression from the Ebolavirus minireplicon. The next steps in *Ebolavirus* replication are virus genome replication and virus protein expression. To examine whether the tested compounds inhibit *Ebolavirus* genome replication and protein expression, an *Ebolavirus* minigenome replication assay was performed. The compounds were added to cell culture media 6.5 hours post-transfection to avoid affecting transfection efficacies. As shown in Figure 15, gedunin and epoxygedunin significantly reduced firefly luciferase reporter protein expression from the *Ebolavirus* minireplicon. The luciferase activities in cells treated with these two compounds were 1.3% ± 0.2% and 1.0% ± 0.1% of those treated with DMSO, respectively. The other three compounds did not reduce the luciferase activities. Since gedunin and epoxygedunin have a 7-acetate group on their ring B, but the other three compounds do not, this residue may contribute to the inhibition of *Ebolavirus* genome replication and/or protein expression.

Hsp90 inhibitors reduce protein expression from the Ebolavirus minireplicon.The inhibitor activities of gedunin and some of its derivatives have been tied to the heat shock protein Hsp90 (Hieronymus et al., 2006), suggesting that their *Ebolavirus* inhibitory mechanisms may involve inhibition of Hsp90 or degradation of its substrate proteins. Therefore, it was deteremined whether Hsp90 inhibitors have anti-*Ebolavirus* activity. Four Hsp90 inhibitors, geldanamycin (GM), 17-AAG (17-Allylamino-17-demethoxygeldanamycin), CCT 018159 (4-[4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5-methyl-1*H*-pyrazol-3-yl]-6-ethyl-1,3-benzenediol), and AEG 3482 (6-Phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide) were assessed for their anti-*Ebolavirus* activities by use of an *Ebolavirus* growth assay, a VSV pseudotype virus assay, and a minireplicon assay.

CCT and 17AAG reduced EbolaΔVP30 virus growth (97% and 92% reduction, respectively, at 72 hours post-infection), but GM and AEG did not (30% and 5% reduction, respectively, 72 hours post-infection) (Figure 16A). Although all five of the gedunin-like compounds significantly reduced virus infection mediated by *Ebolavirus* GP, only CCT 018159 of the Hsp90 inhibitors slightly reduced the *Ebolavirus* GP-mediated virus infection (Figures 16B and 16C). Infectivities of VSVΔG*-*Ebolavirus* GP, which were standardized by the infectivities of VSVΔG*-VSV G, were 137% (GM), 110% (17-AAG), 71% (CCT 018159) and 135% (AEG 3482). All four Hsp90 inhibitors reduced reporter protein expression from the *Ebolavirus* minigenome [luciferase activities were 7.9% ± 1.5% (17-AAG), 8.8% ± 2.6% (CCT 018159), 24.7% ± 7.7% (GM), and 34.0% ± 8.0% (AEG 3482)] (Figure 16D). These data demonstrate that Hsp90 inhibitors are potential anti-*Ebolavirus* agents and that their inhibitory mechanisms likely differ from those of gedunin and its derivatives.

Discussion

A high throughput molecular screen for anti-*Ebolavirus* agents identified gedunin and its derivatives as anti-*Ebolavirus* candidates. Further analysis demonstrated that these compounds inhibit *Ebolavirus* via *Ebolavirus* GP-dependent virus binding/entry and that some of them also reduce *Ebolavirus* genome replication and/or protein expression. Gedunin-like limonoids are found in extracts of plants from the *Meliaceae* (Mahogany) family and have been used in traditional medicine in tropical America and in West and East Africa (Bray et al., 1990), suggesting that there is potential for their use in humans, if *in vivo* experiments confirm their anti-*Ebolavirus* activities.

In this study, the specificity of anti-*Ebolavirus* compounds was assessed by testing their inhibitory activities against *influenzavirus*, VSV, vaccinina virus, and adenovirus because these compounds are reported to have antimalarial (MacKinnon et al., 1997), anti-HIV (http://home.ncifcrf.gov/mtdp/Catalog/compounds/309912.html), anti-insect (Nathan et al., 2005), and anti-cancer (Uddin et al., 2007) activities. However, none of the compounds tested exhibited significant inhibition of these viruses, although gedunin did slightly delay the propagation of vaccinia virus, adenovirus and VSV. The structural features of these compounds may be a determinant of specificity since only 14 of the 41 gedunin-like limonoids that were screened demonstrated inhibitory activity to *Ebolavirus* and since 7-deacetoxy-7-hydroxygedunin and 7-deacetoxy-7-oxogeduin had been identified as anti-HIV compounds but the other gedunin-derivatives had not (http://www.stjuderesearch.org/guy/data/parasite_bioactives_screen/MAL_3D7/Results/87.html). These data suggest that gedunin-like limonoids have potential as general antivirals and further screening of these compounds using other microbial assays may be of value.

The mechanisms by which gedunin and its derivatives inhibit *Ebolavirus* remain unknown; it is not clear whether they interact with host cell components or with *Ebolavirus* proteins and/or genomes. Since it was previously reported that gedunin and its derivatives express anti-cancer activities via degradation of Hsp90 and/or its substrates (Hieronymus et al., 2006) and DNA and RNA virus propagation can be delayed by Hsp90 inhibitors (Basha et al., 2005; Burch & Weller, 2005; Chase et al., 2008; Connor et al., 2007; Li et al., 2004; Ujino et al., 2009), it seemed possible that Hsp90 inhibitory activities may contribute to the anti-*Ebolavirus* activities of gedunin and its derivatives. Therefore, the anti-*Ebolavirus* activities of Hsp90 inhibitors was examined.

Although the four Hsp90 inhibitors tested did not inhibit *Ebolavirus* GP-dependent virus binding/entry to the same extent as the gedunin-like compounds, they reduced protein expression from

the *Ebolavirus* minireplicon and two of the four Hsp90 inhibitors also delayed EbolaΔVP30-GFP replication. Since structurally different compounds have been found with Hsp90 inhibitors to limit reporter protein expression from the *Ebolavirus* minireplicon, it has been suggested that this inhibition may be due not to structural binding to *Ebolavirus* directly, but to Hsp90 inhibitory activities. However, mechanisms other than Hsp90 inhibition should be considered since deacetylegedunin, which shows anti-cancer activity via degradation of Hsp90 substrates (Hieronymus et al., 2006) was one of the 41 gedunin-like limonoids tested, yet it did not show any anti-*Ebolavirus* activity.

CCT 018159 displayed about a 30% reduction in *Ebolavirus* GP-dependent virus infection, unlike GM, 17-AAG, and AEG 3482. It has been reported that CCT 018159 binds to the ATP site located in the N-terminal domain of Hsp90; however, GM and 17-AAG also bind at this location via the same main amino acids (Cheung et al., 2005; Stebbins et al., 1997). Therefore, why only CCT 018159 showed inhibitory activity to *Ebolavirus* binding/entry is unclear. The data suggest that blockage of virus binding/entry mediated by *Ebolavirus* GP may not rely upon Hsp90 and/or its substrate/signaling.

Inhibitors of S-adenosylhomocysteine hydrolase (SAH) have also shown anti-*Ebolavirus* activity *in vitro* and *in vivo* (Huggins et al., 1999). Their IC_{50} values range from 2 to 64 μM, which is higher than gedunin and its derivatives in this study. Although it is not strictly valid to directly compare these values, since they were determined using different assays, IC_{50} values are not assay-dependent or *Ebolavirus* strain-dependent (Huggins et al., 1999). Therefore, the anti-*Ebolavirus* efficacies of gedunin and its derivatives are at least equal to those of SAH inhibitors.

Ebolavirus outbreaks have occurred almost every year in the 21st century in Africa, infecting and killing numerous individuals. Moreover, many people and pigs were infected with *Ebolavirus* Reston in the Philippines in 2008-2009. These reports reflect that *Ebolavirus* infection is an ongoing threat and that therapeutic and prophylactic options are desperately needed. Gedunin-like limonoids are found in traditional medicine in tropical and subtropical regions, where they have been used to treat humans. The compounds identified in the present screen thus show promise as anti-*Ebolavirus* agents, and *in vivo* confirmation of their anti-*Ebolavirus* activities is warranted.

Summary

A library of compounds (Known Bioactive Library (KB01)) at the Keck-UWCCC Small Molecule Screening Facility, University of Wisconsin-Madison, Madison, WI.) was screened to determine whether any of the compounds interfered with *Ebolavirus* replication and infection. The compounds were screened using biologically contained Ebolavirus expressing GFP protein (EbolaΔVP30-GFP virus). In particular, gedunin and gedunin-like compounds were screened. Those compounds are found in extracts of plants from the *Meliaceae* (Mahogany) family and have been used in traditional medicine for the treatment of fevers in tropical American and in West and East Africa. They are known for their antimalarial, anti-HIV, anti-cancer, and anti-insect activities. Gedunin is an inhibitor of Hsp90.

Through the use of EbolaΔVP30-GFP virus and a follow-up screen, 15 gedunin and gedunin-like compounds were identified that reduced GFP expression by at least 75%.

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All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification, this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED IS:

1. A method to identify one or more agents that inhibit Ebola virus infection, comprising:
a) contacting a host cell, one or more agents and recombinant infectious, biologically contained Ebola virus, the genome of which contains a deletion of sequences corresponding to Ebola virus VP30 sequences, which deletion is effective to prevent expression of functional VP30 upon infection of a cell with the recombinant virus; and
b) identifying one or more agents that inhibit viral infection without substantially decreasing host cell viability.

2. The method of claim 1 wherein the host cell is contacted with the virus before or after the one or more agents.

3. The method of claim 1 wherein the host cell is contacted with the virus and the agents simultaneously.

4. The method of any of claims 1 to 3 wherein the identified agent inhibits the infectivity of the virus by at least 90%.

5. The method of any of claims 1 to 4 wherein the detected agent has an IC_{50} of less than about 10.0 μM.

6. The method of any of claims 1 to 5 wherein the detected agent has a CC_{50} of more than about 0.1 μM.

7. A method to identify inhibitors of filovirus glycoprotein receptor binding or fusion, comprising:
a) contacting a host cell with one or more agents and a recombinant replication incompetent pseudotyped rhabdovirus comprising filovirus glycoprotein and a mutant negative sense rhabdovirus genome which lacks sequences for a rhabdovirus glycoprotein but comprises a sequence for a reporter protein; and
b) identifying at least one agent that inhibits reporter protein levels or expression in the host cell.

8. The method of claim 7 wherein the rhabdovirus is VSV.

9. The method of claim 7 or 8 wherein the filovirus glycoprotein is a Marburg virus glycoprotein.

10. The method of claim 7 or 8 wherein the filovirus glycoprotein is an *Ebolavirus* glycoprotein.

11. The method of any of claims 7 to 10 wherein the reporter protein levels or expression in the presence of the one or more agents is compared to reporter protein levels or expression in the absence of the agent(s).

12. The method of any of claims 7 to 11 wherein at least one agent inhibits filovirus glycoprotein binding.

13. The method of any of claims 7 to 11 wherein at least one agent inhibits filovirus glycoprotein fusion.

14. The method of any of claims 1 to 13 wherein the host cell is contacted with a library of agents.

15. The method of any of claims 1 to 14 wherein the host cell is a mammalian cell.

16. The method of any of claims 1 to 15 wherein the at least one agent contacted with the cell is a triphenylethylene.

17. The method of any of claims 1 to 15 wherein the at least one agent contacted with the cell is an inhibitor of calcium-independent phospholipase A_2 and/or of magnesium-dependent phosphatidate phosphohydrolase, an inhibitor of PGE_2 synthase, a steroid, dopamine antagonist, anticholinergic or an Hsp90 inhibitor.

18. The method of any of claims 1 to 17 wherein the at least one agent is a compound of formula (I)-(XIII).

19. An agent identified by the method of any of claims 7 to 13 or 15 to 18 that inhibits reporter protein levels or expression by at least 90%.

20. An agent identified by the method of any of claims 1 to 6 or 14 to 18 that inhibits viral infection by at least 90%.

21. A method to prevent, inhibit or treat filovirus infection in a mammal, comprising administering to the mammal an effective amount of the agent of claim 19 or 20.

22. A method to prevent, inhibit or treat filovirus infection in a mammal, comprising administering to the mammal an effective amount of a compound of formula (I)-(XIII).

23. A method to prevent, inhibit or treat filovirus infection in a mammal, comprising administering to the mammal an effective amount of a pharmaceutical composition comprising an agent, wherein the composition comprises a calcium channel blocker, a tetranortriterpenoid, a sigma receptor agonist, triphenylethylene, an inhibitor of calcium-independent phospholipase A_2, an inhibitor of magnesium-dependent phosphatidate phosphohydrolase, an inhibitor of PGE_2 synthase, a steroid, adopamine antagonist, an inhibitor of Hsp90, or an anticholinergic.

24. The method of any of claims 21 to 23 wherein the mammal is a human.

25. The method of any of claims 21 or 23 to 24 wherein the agent is bepridil hydrochloride, clomiphene citrate, benzotropin mesylate, 7-deacetoxy-3-deacetyl-7-oxokhivorin, 1,2alpha-epoxy-7-deacetoxy-7-oxodihxdrogedunin, epoxygedunin, 1,3-dideacetyl-7-deacetoxy-7-oxokhivorin, gedunin, tamoxifen citrate, fluspirilene, raloxifene hydrochloride, bromoenol lactone, cortexolone maleate, (R,R)-cis,diethyl tetrahydro-2,8-chrysenediol, MK-866, L-687, 384 hydrochloride, cycloheximide, gedunol, dihydrogedunin, 3beta-acetoxydeoxodihydrogedunin, 3alpha-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 3beta-hydroxydeoxodihydrogedunin, deacetoxy-7-oxogedunin, 1,2alpha-epoxydeacetoxydihydrogedunin, 3beta-hydroxydeoxydesacetoxy-7-oxogedunin, tridesacetoxykhivorin, 1,3-dideacetylkhivorin, heudelottin C, geldanamycin, 17-allylamino-17-demethoxygeldanamycin, 4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methyl-1*H*-pyrazol-3-yl]-6-ethyl-1,3-benzenediol, 6-phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide, geldanamycin, 17-Allylamino-17-demethoxygeldanamycin, 4-[4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5-methyl-1*H*-pyrazol-3-yl]-6-ethyl-1,3-benzenediol, 6-Phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide, or any combination thereof.

26. The method of any of claims 21 to 25 wherein the agent is orally administered.

27. The method of any of claims 21 to 25 wherein the agent is intravenously administered.

28. The method of any of claims 21 to 25 wherein the agent is subcutaneously administered.

29. Use of a calcium channel blocker, a tetranortriterpenoid, a sigma receptor agonist, triphenylethylene, an inhibitor of calcium-independent phospholipase A_2, an inhibitor of magnesium-dependent phosphatidate phosphohydrolase, an inhibitor of PGE_2 synthase, a steroid, adopamine antagonist, an inhibitor of Hsp90, or an anticholinergic to prevent, inhibit or treat filovirus infection.

30. Use of a compound of formula (I)-(XIII) in the manufacture of a medicament to prevent, inhibit or treat filovirus infection.

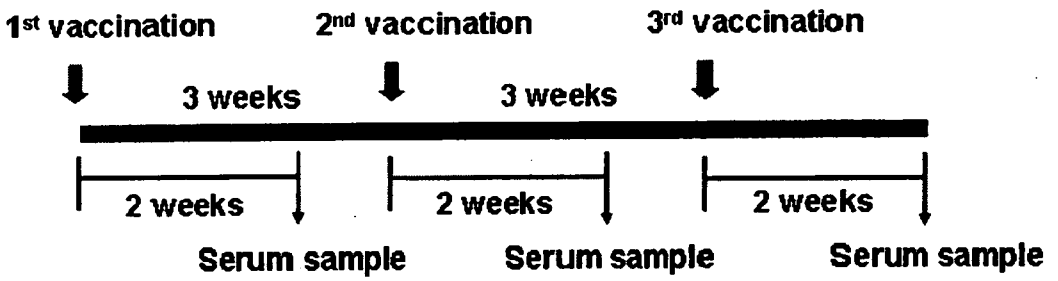


Fig. 1A

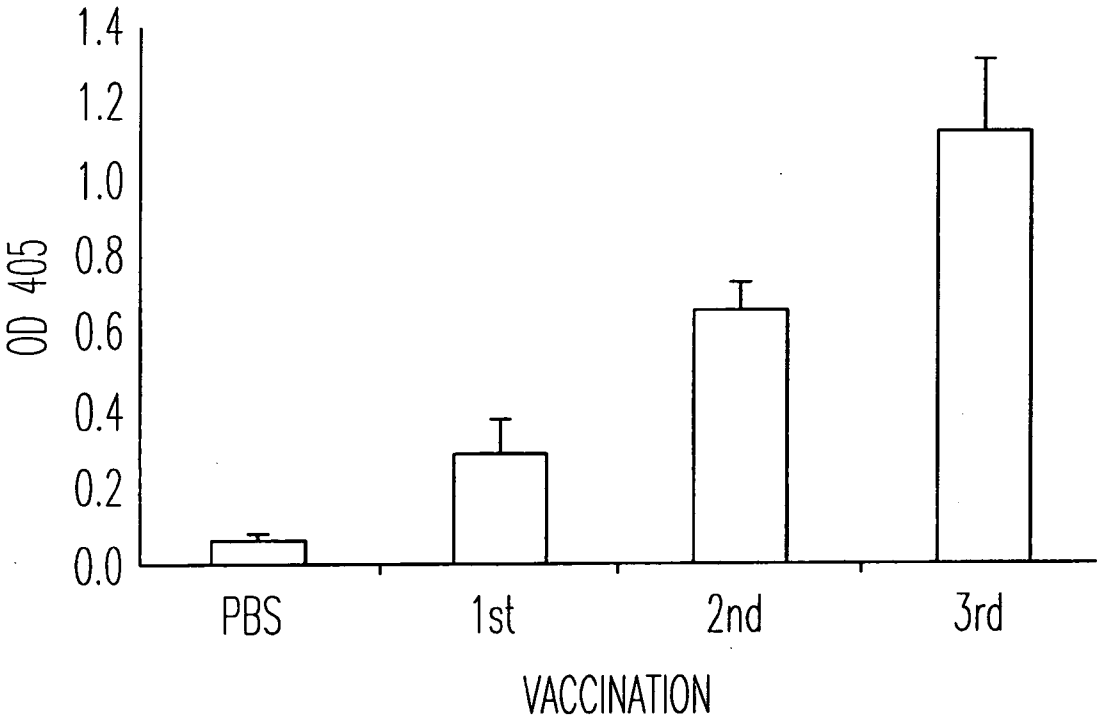


Fig. 1B

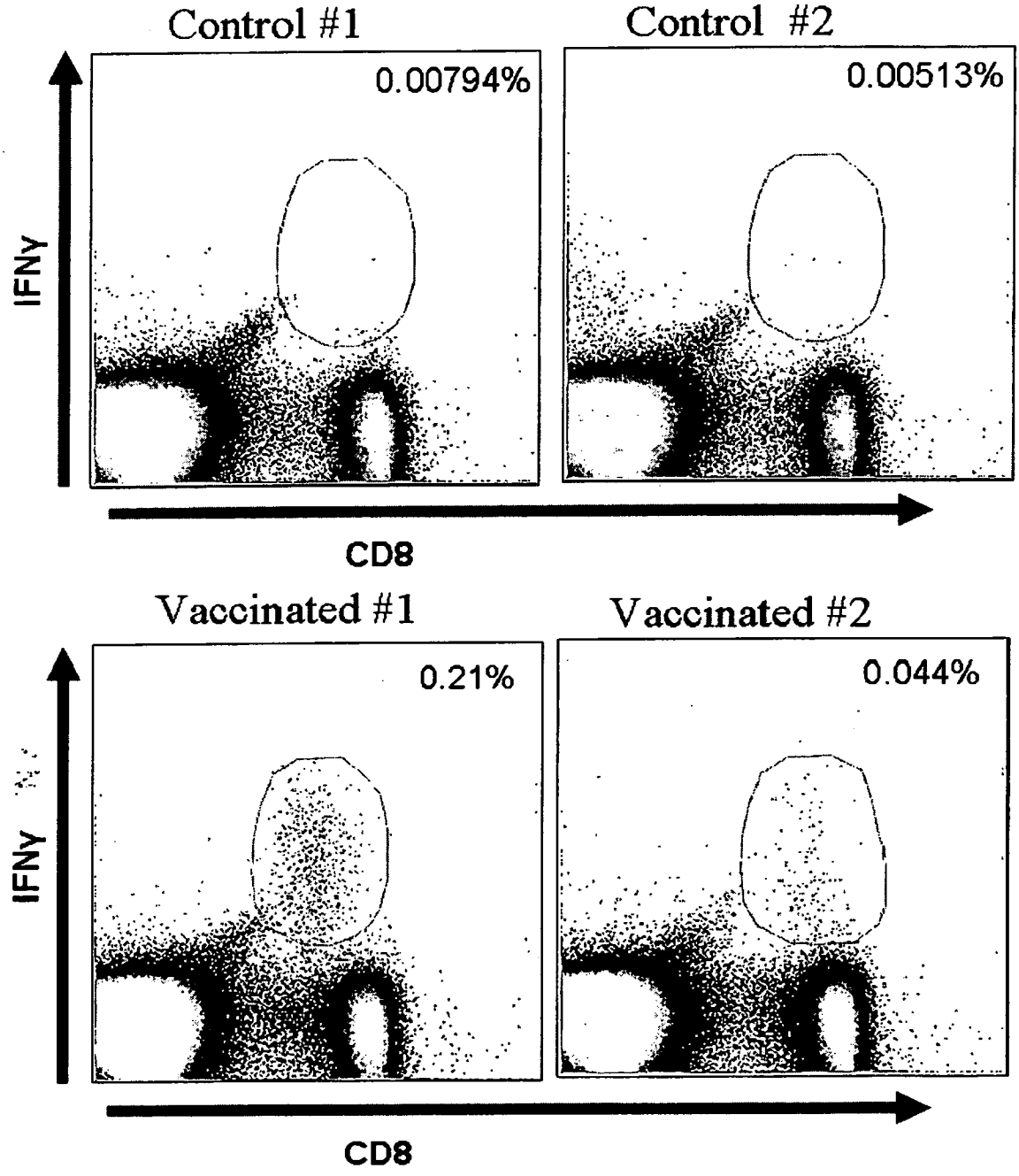

Control #1
0.00794%
Control #2
0.00513%
IFNγ
CD8
Vaccinated #1
0.21%
Vaccinated #2
0.044%
IFNγ
CD8

Fig.2

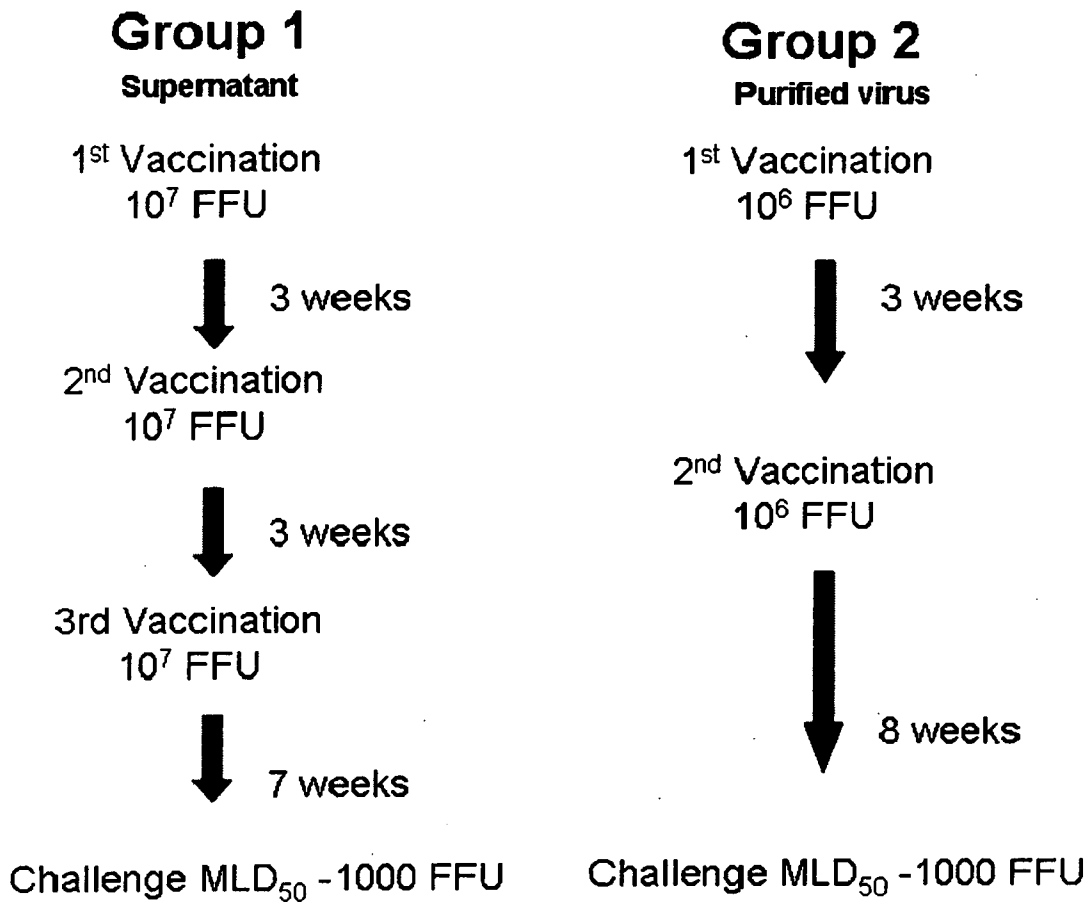

Group 1
Supernatant
1st Vaccination
10^7 FFU
3 weeks
2nd Vaccination
10^7 FFU
3 weeks
3rd Vaccination
10^7 FFU
7 weeks
Challenge MLD50 -1000 FFU
Group 2
Purified virus
1st Vaccination
10^6 FFU
3 weeks
2nd Vaccination
10^6 FFU
8 weeks
Challenge MLD50 -1000 FFU

Fig. 3

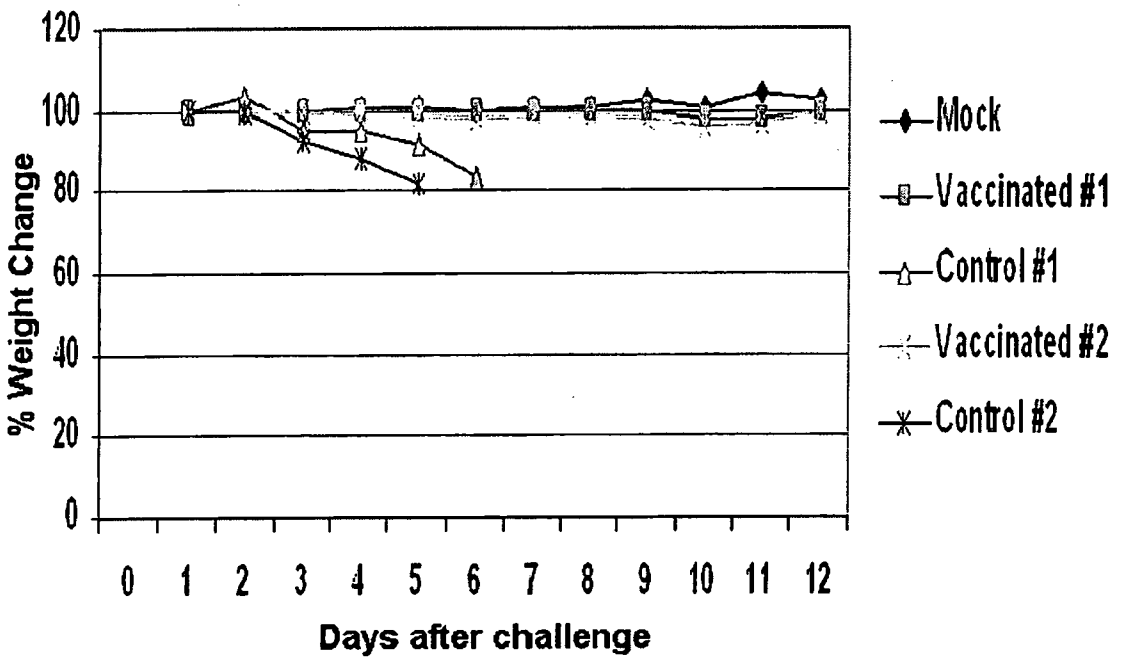

120
100
80
60
40
20
0
% Weight Change
0 1 2 3 4 5 6 7 8 9 10 11 12
Days after challenge
Mock
Vaccinated #1
Control #1
Vaccinated #2
Control #2

Fig. 4A

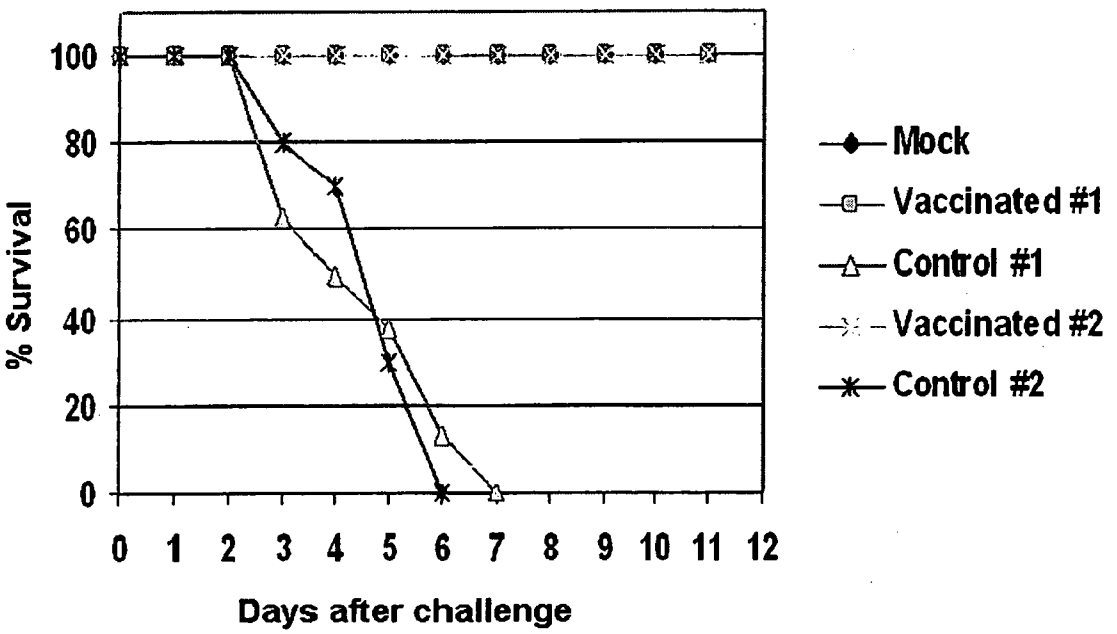
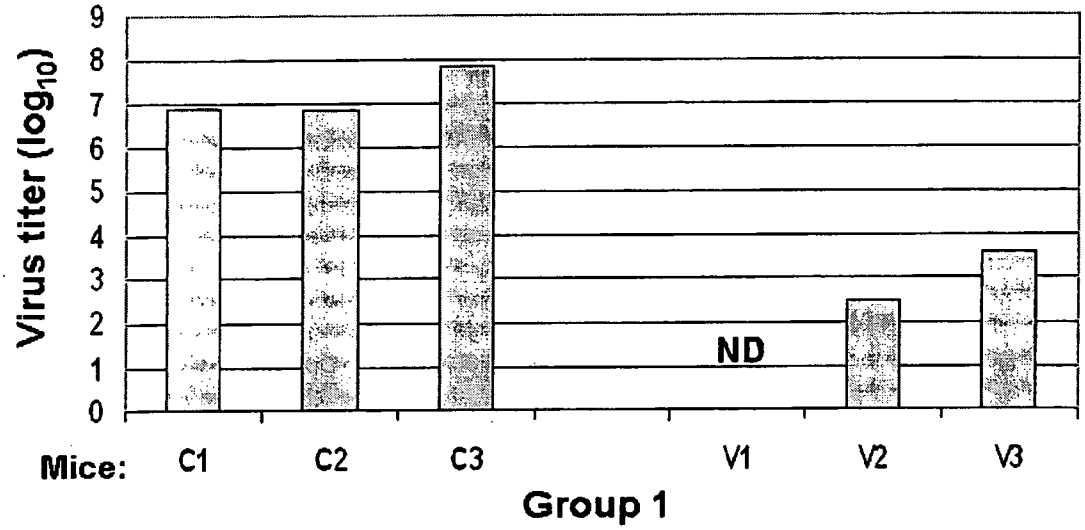

100
80
60
40
20
0
% Survival
0 1 2 3 4 5 6 7 8 9 10 11 12
Days after challenge
Mock
Vaccinated #1
Control #1
Vaccinated #2
Control #2

Fig. 4B


Virus titer (log_{10})
9
8
7
6
5
4
3
2
1
0
ND
Mice:
C1
C2
C3
V1
V2
V3
Group 1

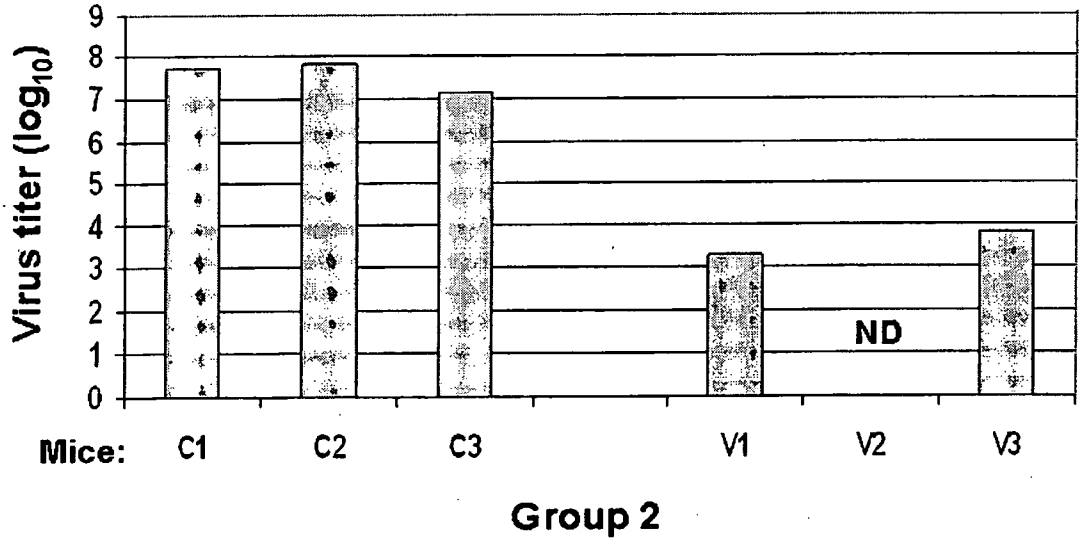

Virus titer (log_{10})
9
8
7
6
5
4
3
2
1
0
ND
Mice:
C1
C2
C3
V1
V2
V3
Group 2

Fig. 5

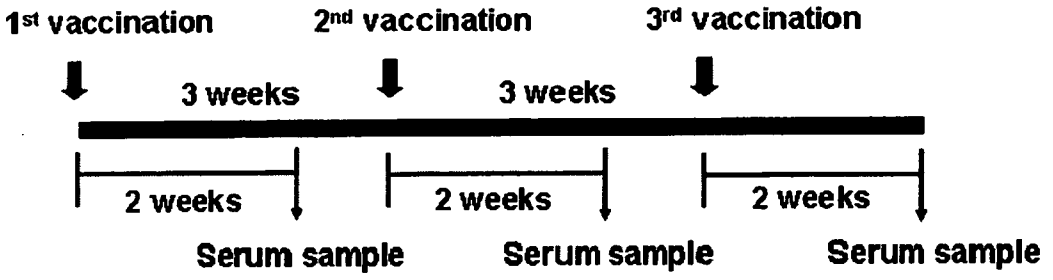

1st vaccination
2nd vaccination
3rd vaccination
3 weeks
3 weeks
2 weeks
2 weeks
2 weeks
Serum sample
Serum sample
Serum sample

Fig. 5A

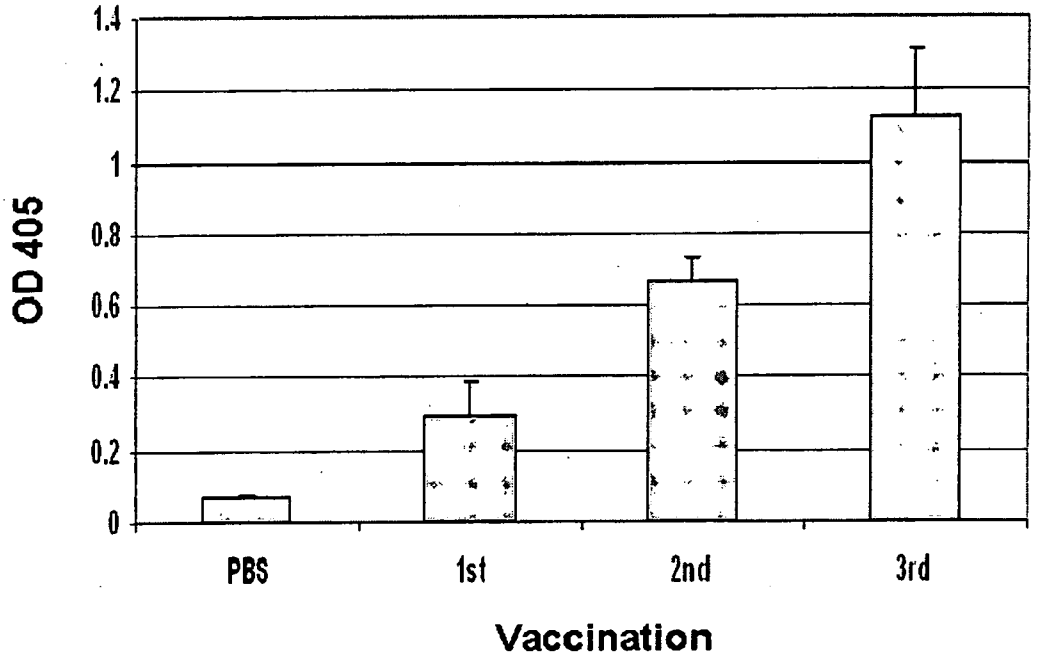

OD 405
1.4
1.2
1
0.8
0.6
0.4
0.2
0
PBS
1st
2nd
3rd
Vaccination

Fig. 5B

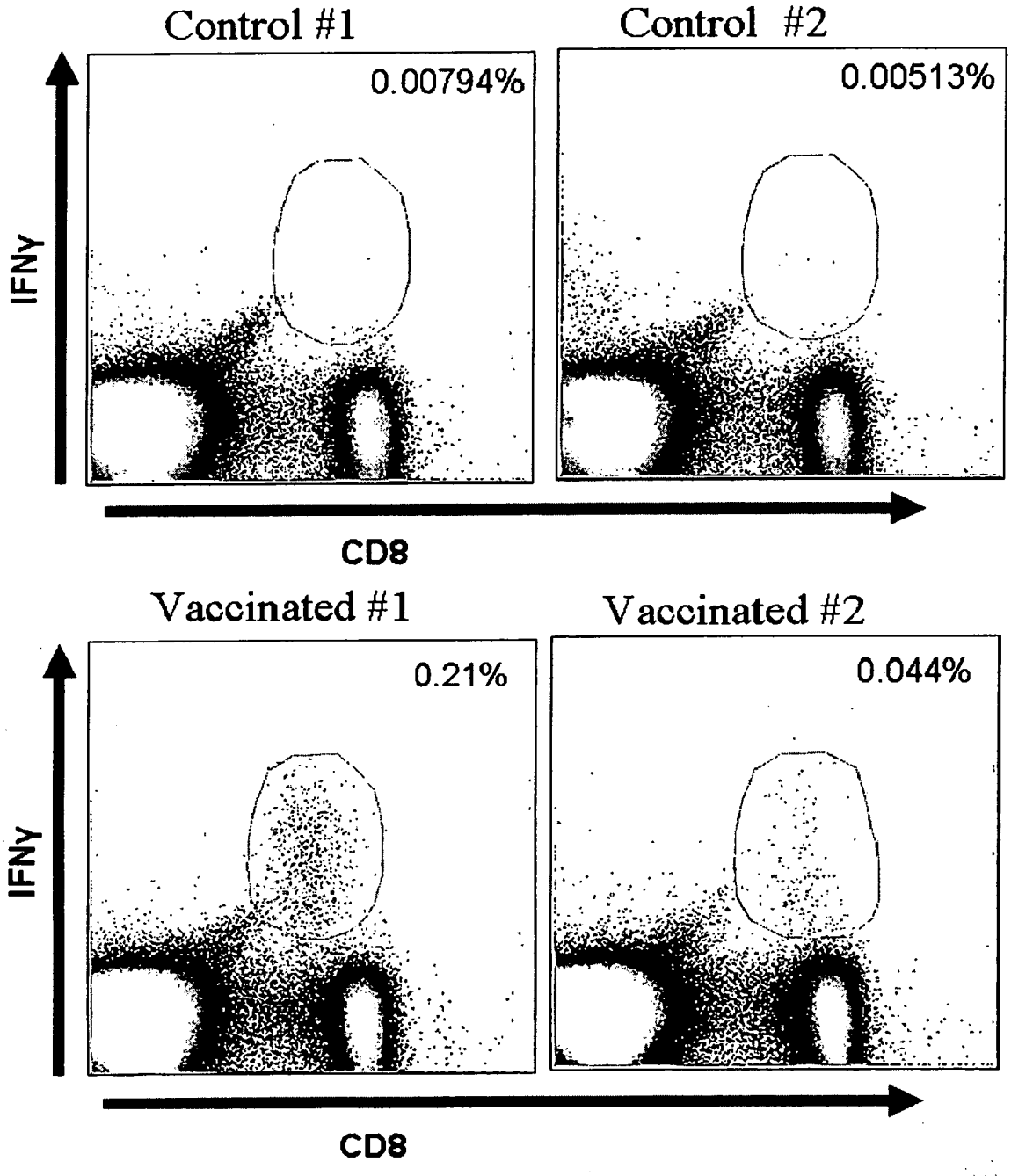

Control #1
0.00794%
Control #2
0.00513%
IFNγ
CD8
Vaccinated #1
0.21%
Vaccinated #2
0.044%
IFNγ
CD8

Fig. 6

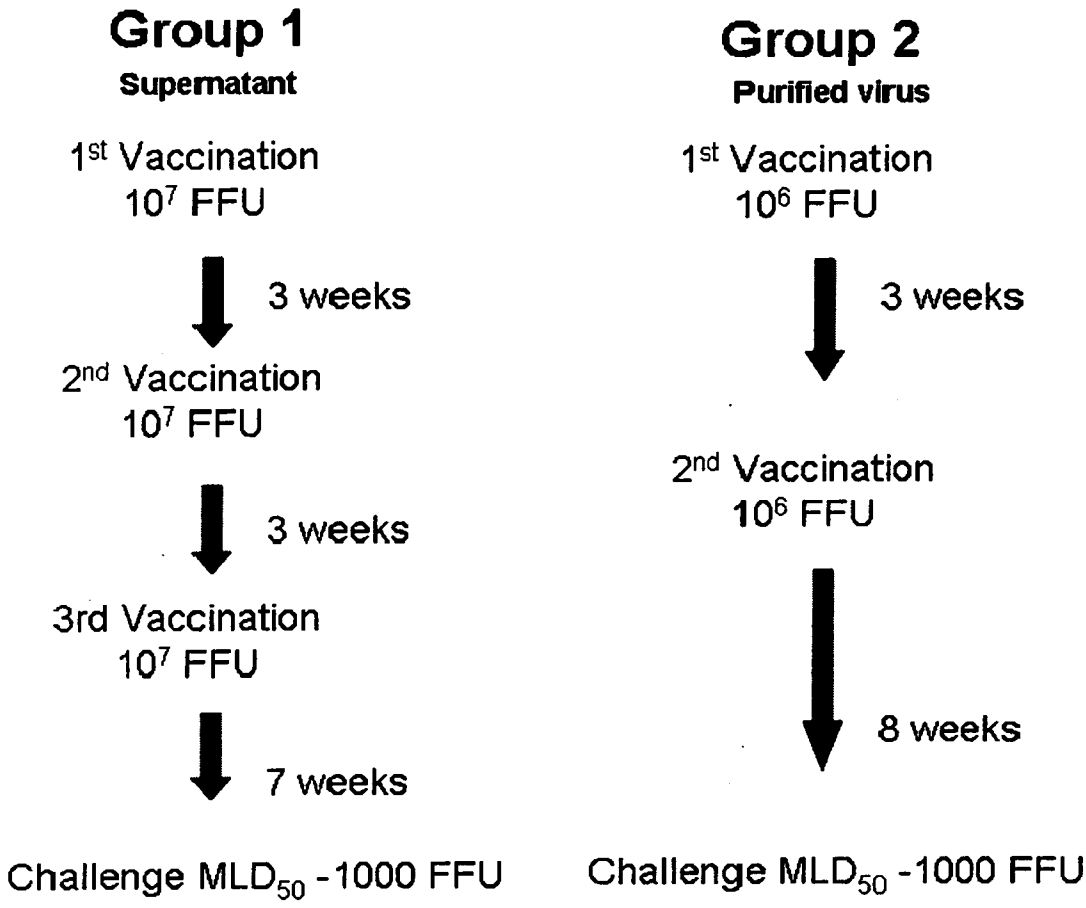

Group 1
Supernatant
1st Vaccination
10^7 FFU
3 weeks
2nd Vaccination
10^7 FFU
3 weeks
3rd Vaccination
10^7 FFU
7 weeks
Challenge MLD50 -1000 FFU
Group 2
Purified virus
1st Vaccination
10^6 FFU
3 weeks
2nd Vaccination
10^6 FFU
8 weeks
Challenge MLD50 -1000 FFU

Fig. 7

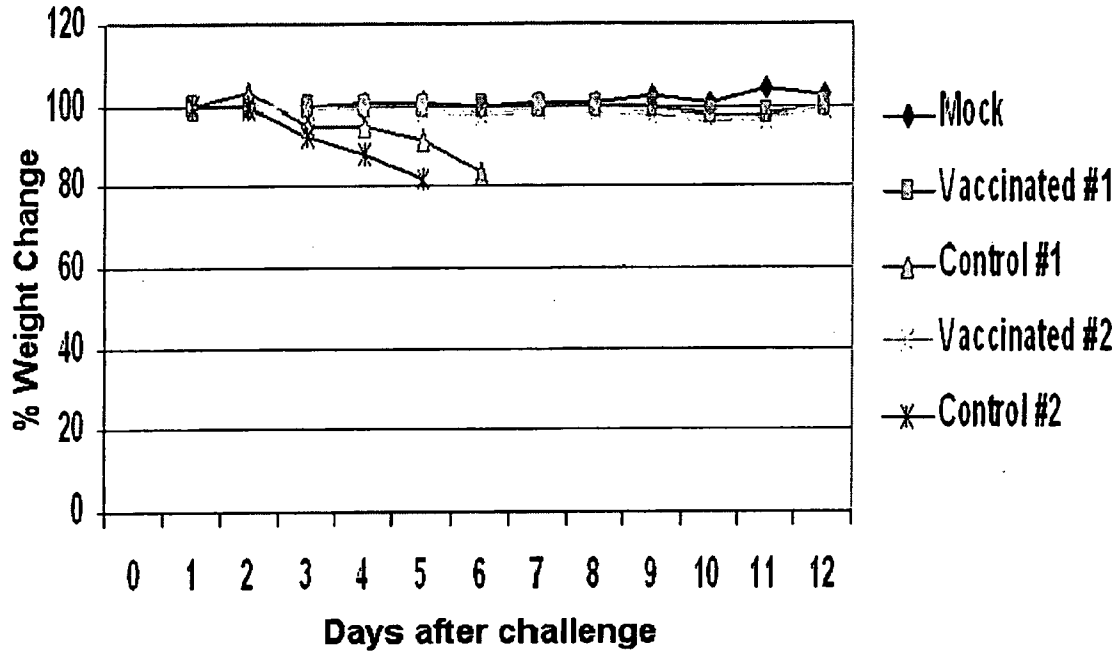

120
100
80
60
40
20
0
% Weight Change
0 1 2 3 4 5 6 7 8 9 10 11 12
Days after challenge
Mock
Vaccinated #1
Control #1
Vaccinated #2
Control #2

Fig. 8A

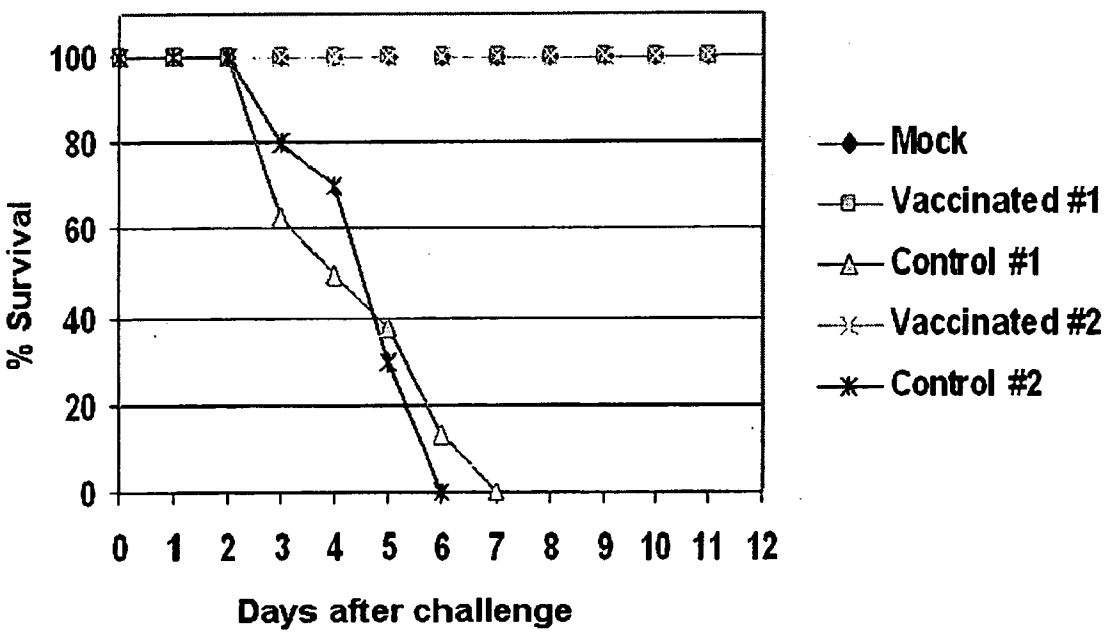
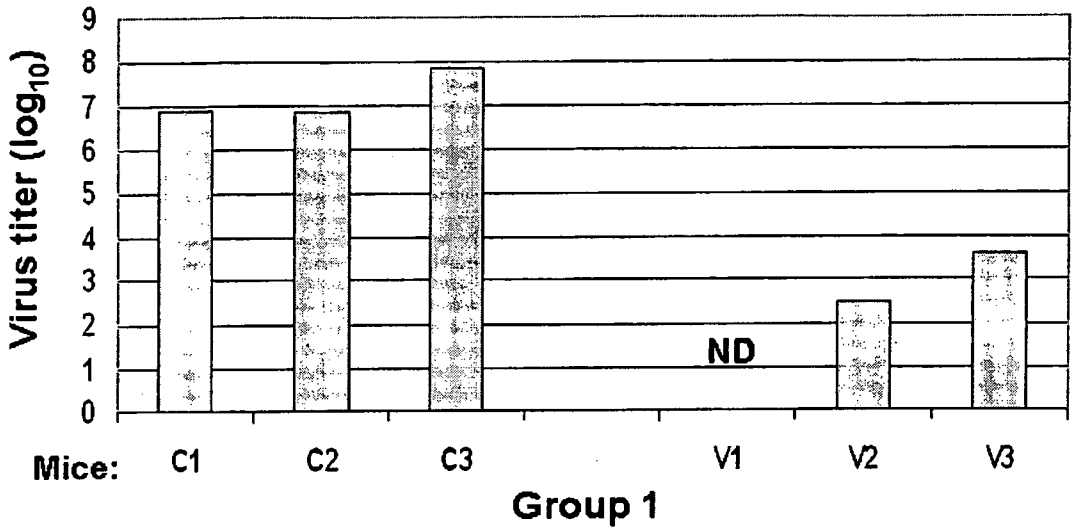

100
80
60
40
20
0
% Survival
0 1 2 3 4 5 6 7 8 9 10 11 12
Days after challenge
Mock
Vaccinated #1
Control #1
Vaccinated #2
Control #2

Fig. 8B


Virus titer (log_{10})
9
8
7
6
5
4
3
2
1
0
ND
Mice:
C1
C2
C3
V1
V2
V3
Group 1

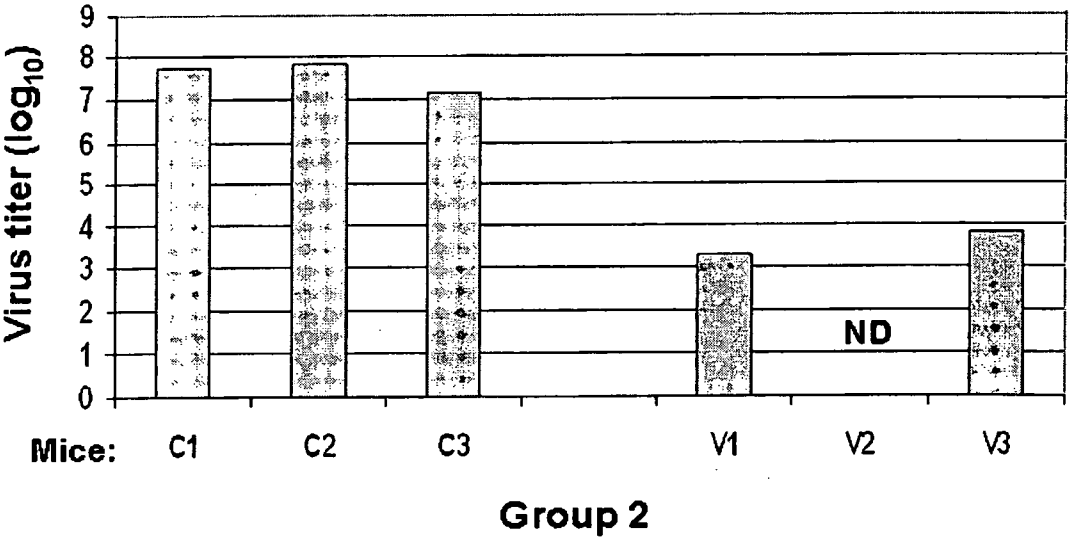

Virus titer (log_{10})
9
8
7
6
5
4
3
2
1
0
ND
Mice:
C1
C2
C3
V1
V2
V3
Group 2

Fig. 9

NC_006432

1 cggacacaca aaaagaaaga aaagtttttt atacttttttg tgtgcgaata actatgagga
61 agattaatca ttttcctcaa actcaaacta atattaacat tgagattgat ctcatcattt
121 accaattgga gacaatttaa ctagtcaatc ccccatttgg gggcattcct aaagtgttgc
181 aaaggtatgt gggtcgtatt gctttgcctt ttcctaacct ggctcctcct acaattctaa
241 cctgcttgat aagtgtgatt acctgagtaa tagactaatt tcgtcctggt aattagcatt
301 ttctagtaaa accaatacta tctcaagtcc taagagaagg tgagaagagg gtcccgaggt
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421 acgctaacta ctaagggttt acctgagagc ctacaacatg gataaacggg tgagaggttc
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1441 gagcacgctg gctggtgtta atgtagggga gcaatatcag caactgcgtg aggctgctac
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2521 cccagattct cttgaagaag cctacccgcc ttggttgagt gagaaggagg ccttagagaa
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3601 atggacaagc acctccaggc ccatcattgt acgaggatga tgctattaag gctaaattga
3661 aagatccgaa cgggaaggtt ccagaaagtg tcaaacaggc ctacataaat ctagatagca
3721 caagtgccct caatgaggaa aatttcgggc gaccttacat ttcagcaaaa gatctcaagg
3781 aaatcatcta tgaccatctc ccaggatttg ggacagcttt tcatcagttg gtgcaggtta
3841 tctgcaaaat tggtaaggat aataatatcc tagacataat tcatgcagaa ttccaagcaa
3901 gcttggctga gggagactcc ccccagtgtg cattaatcca gataacaaaa cggatccctg
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NC_004161

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(SEQ ID NO: 12)

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L11365

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VP30

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NC_001608

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NC002549

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AF272001

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18841 gacattgacc acgctcatca gaaggctcgc cagaataaac gttgcaaaaa ggattcctgg
18901 aaaaatggtc gcacacaaaa atttaaaaat aaatctattt cttctttttt gtgtgtcca (SEQ ID NO: 32)

VP30
MEASYERGRPRAARQHSRDGHDHHVRARSSSRENYRGEYRQSRSASQVRVPTV
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KLRALLTLCAVMTRKFSKSQLSLLCETHLRREGLGQDQAEPVLEVYQRLHSDKG
GSFEAALWQQWDRQSLIMFITAFLNIALQLPCESSAVVVSGLRTLVPQSDNEEAS
TNPGTCSWSDEGTP (SEQ ID NO: 33)

Known bioactive

Compound name	IC50 (μM)	CC50 (μM)
Bepridil Hydrochloride	1.8	>10
Clomiphene citrate	3.1	>10
Benzotropin mesylate	2.2	
7-Deacetoxy-3-deacetyl-7-Oxokhivorin	0.6	>10
1,2alpha-Epoxy-7-Deacetoxy-7-Oxodihxdrogedunin	<0.15	>10
Epoxygedunin	<0.15	>10
1,3-Dideacetly-7-Deacetoxy-7-Oxokhivorin	<0.15	>10
Gedunin	0.3	>10
Tamoxifen Citrate	0.5	9
Fluspirilene	2.5	9
Raloxifene hydrochloride	0.6	>10
Bromoenol lactone	8	>10
Cortexolone maleate	4	>10
(R,R)-cis-Diethyl tetrahydro-2,8-chrysenediol	5	>10
MK-866	8	>10
L-687,384 hydrochloride	<0.15	
Cycloheximide	0.15	1.25

Fig. 11

Maybridge

Compound name	IC_{50} (μM)	CC_{50} (μM)
HTS00384	1.15	49.3
NRB03063	<0.78	33.8
CD03565	0.64	8.7
KM0483	0.42	30.4
SPB06885	0.41	4.5
CD04265	0.28	12.0
CD02075	<0.78	12.5
PD00647	<0.78	>50
HTS07940	0.20	>50
HTS13483	<0.08	>50
JFD02423	0.28	>50
HTS04029	0.09	>50

Fig. 11 (Cont.)

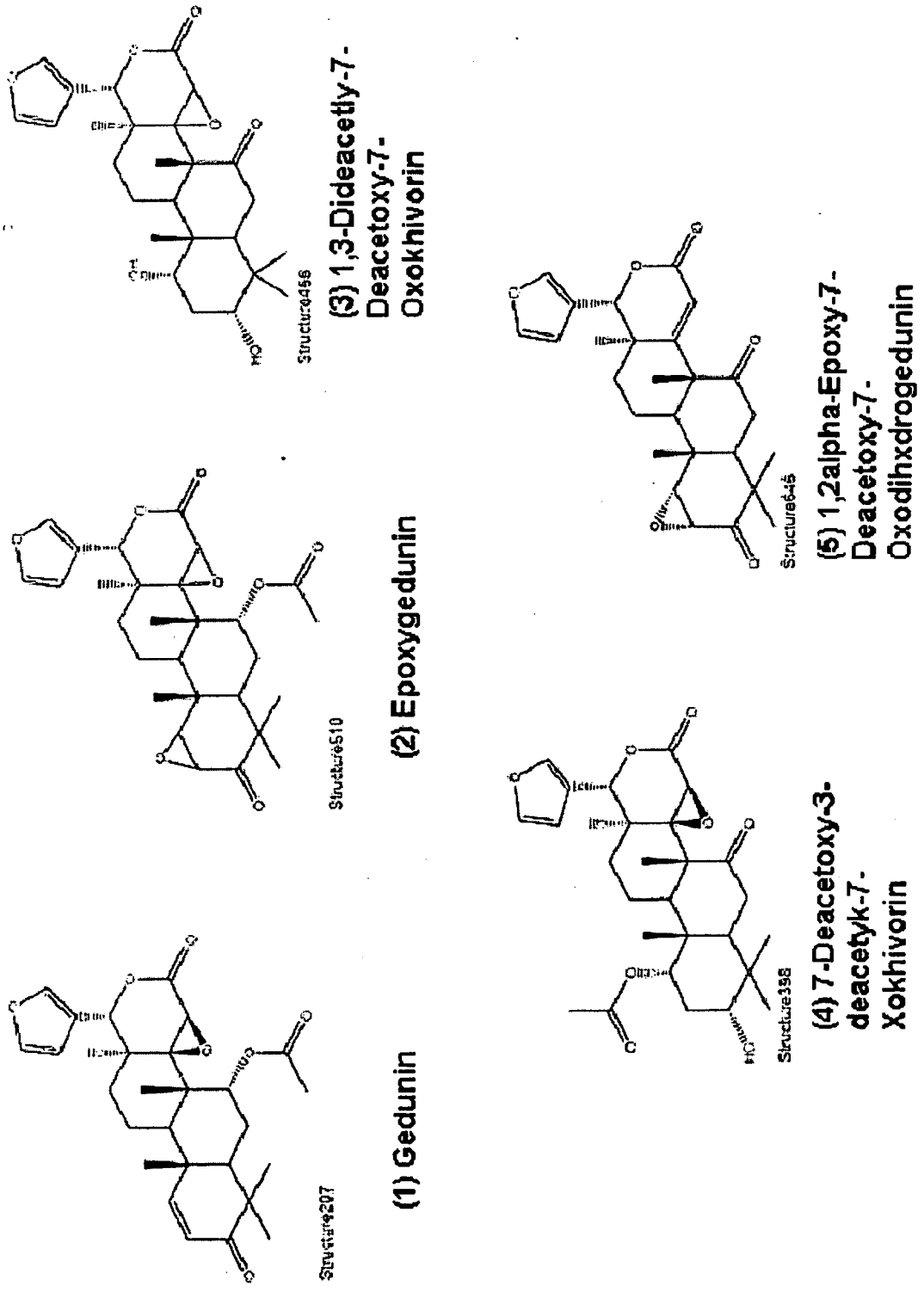
(1) Gedunin
(2) Epoxygedunin
(3) 1,3-Dideacetly-7-Deacetoxy-7-Oxokhivorin
(4) 7-Deacetoxy-3-deacetyk-7-Xokhivorin
(5) 1,2alpha-Epoxy-7-Deacetoxy-7-Oxodihxdrogedunin

Fig. 12

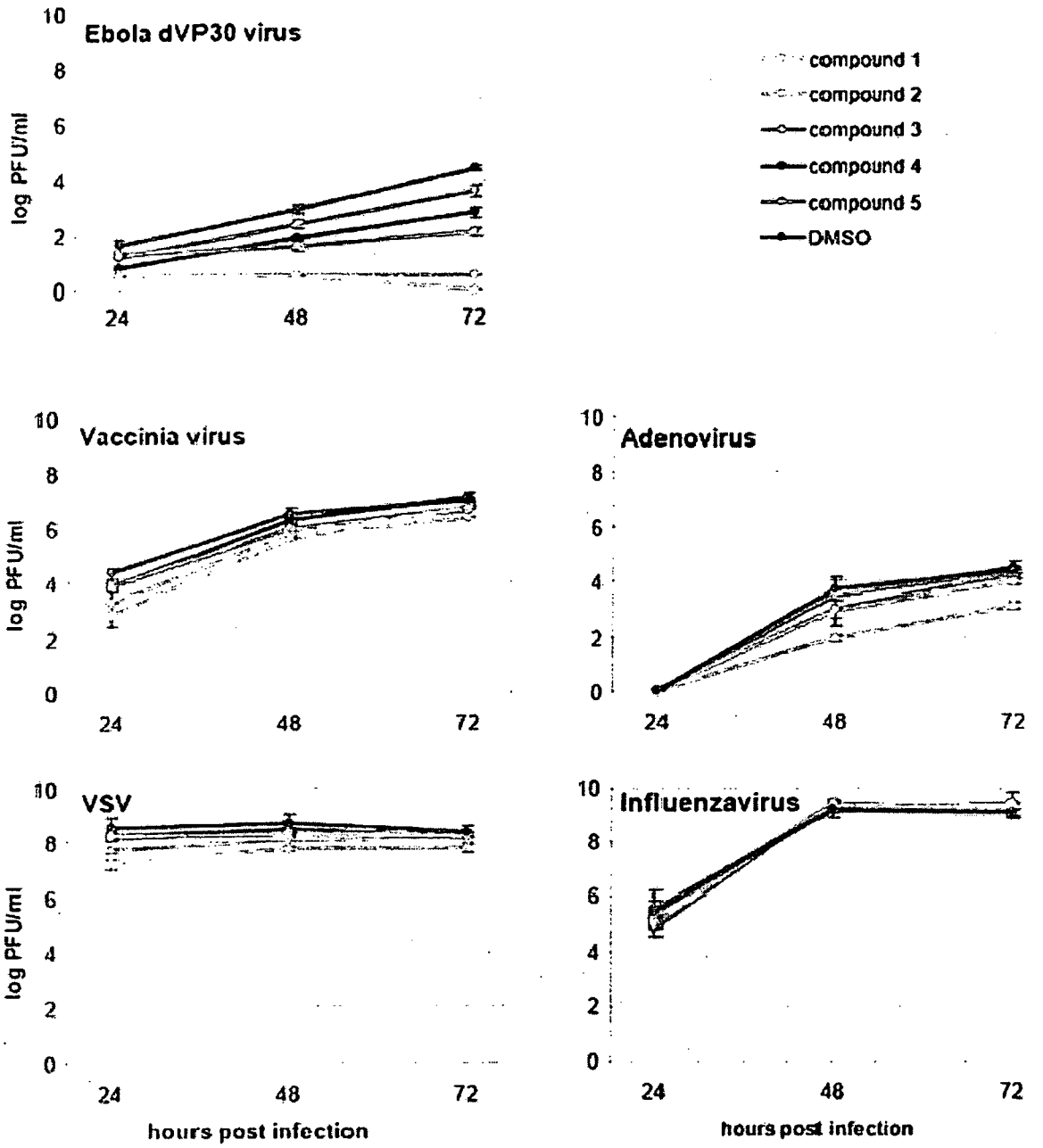
Ebola dVP30 virus
Vaccinia virus
Adenovirus
VSV
Influenzavirus
log PFU/ml
hours post infection
compound 1
compound 2
compound 3
compound 4
compound 5
DMSO

Fig. 13

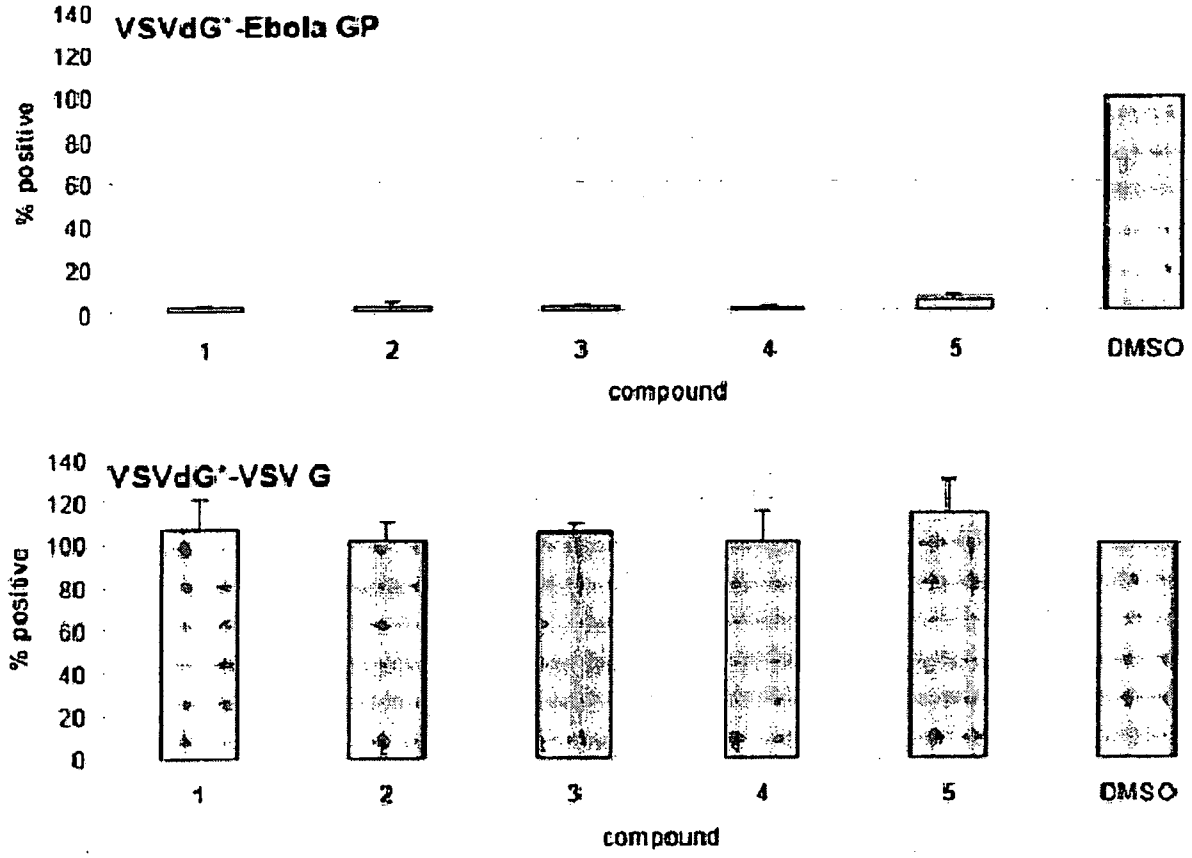
VSVdG*-Ebola GP
% positive
140
120
100
80
60
40
20
0
1
2
3
4
5
DMSO
compound
VSVdG*-VSV G
% positive
140
120
100
80
60
40
20
0
1
2
3
4
5
DMSO
compound

Fig. 14

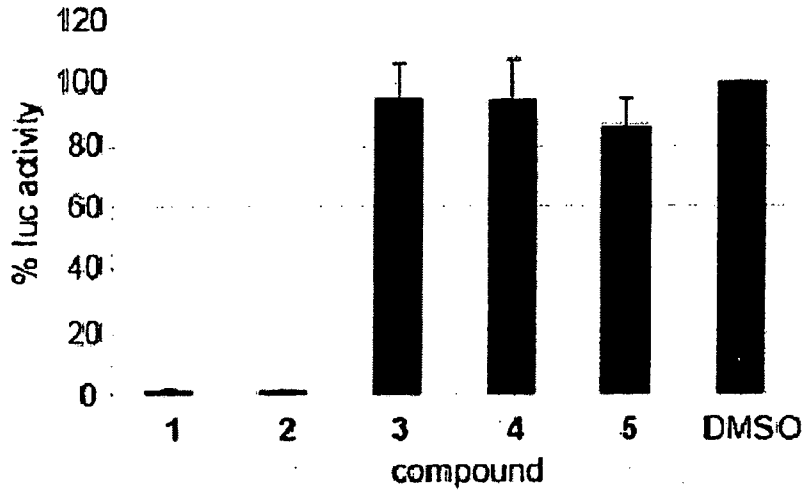

Fig. 15

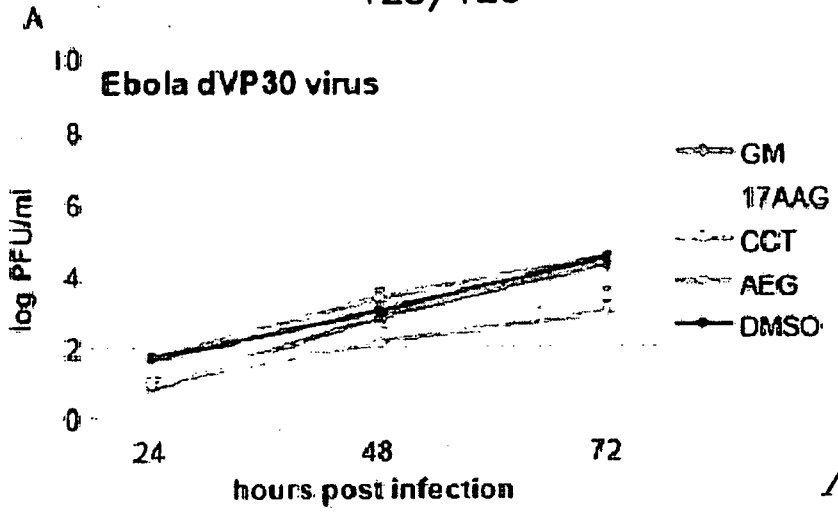

Fig. 16A

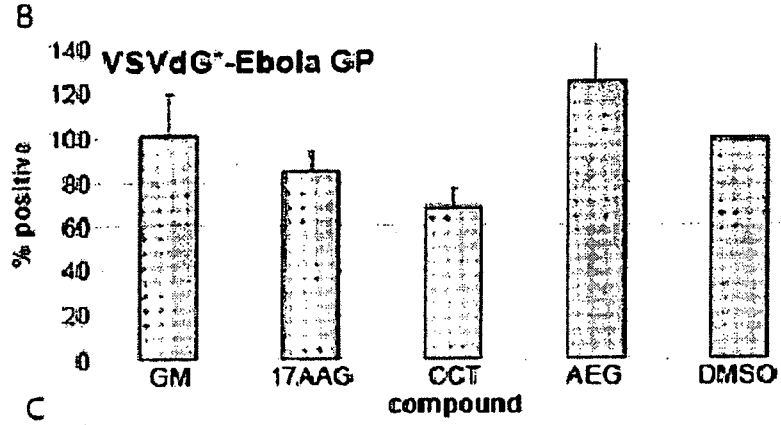

Fig. 16B

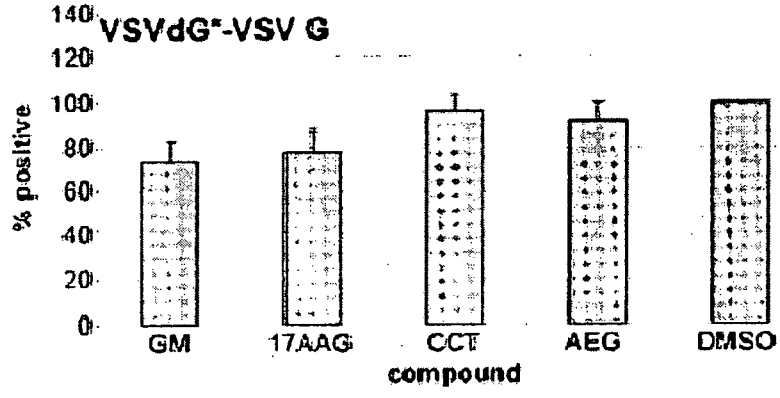

Fig. 16C

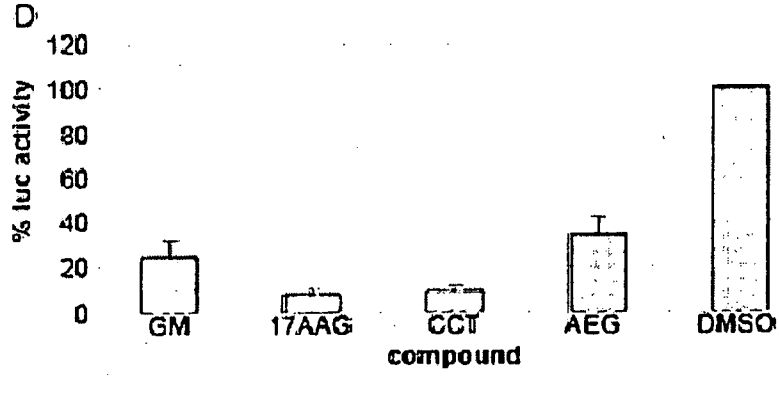

Fig. 16D