

tively inhibit replication of the Ebola virus for use in treating pathological processes mediated by Ebola infection.

#### SUMMARY OF THE INVENTION

**[0016]** The invention provides double-stranded ribonucleic acid (dsRNA), as well as compositions and methods for inhibiting the expression of the Ebola virus in a cell or mammal using such dsRNA. The invention also provides compositions and methods for treating pathological conditions and diseases caused by Ebola viral infection, such as systemic hemorrhage and multi-organ failure. The dsRNA featured in the invention includes an RNA strand (the antisense strand) having a region which is less than 30 nucleotides in length, generally 19-24 nucleotides in length, and is substantially complementary to at least part of an mRNA transcript of a gene from the Ebola virus.

**[0017]** In one embodiment, the invention provides dsRNA molecules for inhibiting the expression of a gene of the Ebola virus and viral replication. The dsRNA comprises at least two sequences that are complementary to each other. The dsRNA comprises a sense strand comprising a first sequence and an antisense strand comprising a second sequence. The antisense strand comprises a nucleotide sequence which is substantially complementary to at least part of an mRNA encoded by a gene from the Ebola virus, and the region of complementarity is less than 30 nucleotides in length, generally 19-24 nucleotides in length. The dsRNA, upon contact with a cell infected with the Ebola virus, inhibits the expression of a gene from the Ebola virus by at least 40%.

**[0018]** For example, the dsRNA molecules of the invention can include a first sequence of the dsRNA that is selected from the group consisting of the sense sequences of Table 2 and the second sequence selected from the group consisting of the antisense sequences of Table 2. The dsRNA molecules featured in the invention can include naturally occurring nucleotides or can include at least one modified nucleotide, such as a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative. Alternatively, the modified nucleotide may be chosen from the group of: a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide. Generally, such modified sequence will be based on a first sequence of said dsRNA selected from the group consisting of the sense sequences of Table 2 and a second sequence selected from the group consisting of the antisense sequences of Table 2.

**[0019]** In another embodiment, the invention provides a cell having a dsRNA of the invention. The cell is generally a mammalian cell, such as a human cell.

**[0020]** In another embodiment, the invention provides a pharmaceutical composition for inhibiting the replication of the Ebola virus in an organism, generally a human subject. The composition includes one or more of the dsRNA of the invention and a pharmaceutically acceptable carrier or delivery vehicle.

**[0021]** In another embodiment, the invention provides a method for inhibiting the expression of a gene in the Ebola virus in a cell, including the following steps:

**[0022]** (a) introducing into the cell a double-stranded ribonucleic acid (dsRNA), wherein the dsRNA includes at least two sequences that are complementary to each

other. The dsRNA includes a sense strand having a first sequence and an antisense strand having a second sequence. The antisense strand includes a region of complementarity which is substantially complementary to at least a part of an mRNA encoded by the Ebola virus, and wherein the region of complementarity is less than 30 nucleotides in length, generally 19-24 nucleotides in length, and optionally, wherein the dsRNA, upon contact with a cell infected with the Ebola virus, inhibits expression of a gene from the Ebola virus by at least 40%, such as in an assay described herein (e.g., a fluorescence-based assay); and

**[0023]** (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a Ebola gene, thereby inhibiting expression of a gene from the Ebola virus in the cell.

**[0024]** In another embodiment, the invention provides methods for treating, preventing or managing pathological processes mediated by Ebola infection, such as systemic hemorrhage and multi-organ failure, comprising administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of one or more of the dsRNAs of the invention.

**[0025]** In another embodiment, the invention provides vectors for inhibiting the expression of a gene of the Ebola virus in a cell, comprising a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of a dsRNA of the invention.

**[0026]** In another embodiment, the invention provides a cell comprising a vector for inhibiting the expression of a gene of the Ebola virus in a cell. The vector comprises a regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of a dsRNA of the invention.

**[0027]** In one aspect, the invention provides for a method of increasing the life-span of a subject (e.g., a mammal, such as a human or nonhuman primate) infected with an Ebola virus. The method includes administering a dsRNA to the subject, where the dsRNA includes an antisense RNA strand having a region which is less than 30 nucleotides in length, generally 19-24 nucleotides in length, and is substantially complementary to at least part of an mRNA transcript of a gene from the Ebola virus. The dsRNA is administered in an amount sufficient to increase the lifespan of the subject. In one embodiment, the dsRNA includes an antisense RNA strand having a region that is substantially complementary to at least part of an mRNA transcript of a gene selected from the VP30, VP35, NP, L, VP24, VP40 and GP genes. In a preferred embodiment, the dsRNA includes an antisense RNA strand having a region that is substantially complementary to at least part of an mRNA transcript of the VP35 gene. In some embodiments, the subject does not experience a decrease in one or both of lymphocyte or platelet count after administration of the dsRNA. In other embodiments, the subject does not experience an increase in cytokine levels (e.g., IFN-alpha or TNF-alpha levels).

**[0028]** In another aspect, the invention features a method of decreasing viral titre in a subject (e.g., a mammal, such as a human or nonhuman primate) infected with an Ebola virus. The method includes administering a dsRNA to the subject, where the dsRNA includes an antisense RNA strand having a region which is less than 30 nucleotides in length, generally 19-24 nucleotides in length, and is substantially complementary to at least part of an mRNA transcript of a gene from the Ebola virus. In one embodiment, the dsRNA includes an