Claims

1. A soluble polypeptide fragment, wherein said polypeptide fragment is (i) derived from the Influenza virus RNA-dependent RNA polymerase subunit PB2 or variant thereof and (ii) capable of binding to a RNA cap or analog thereof.

2. The polypeptide fragment of claim 1, wherein said polypeptide fragment is purified to an extent to be suitable for crystallization.

3. The polypeptide fragment of claims 1 or 2, wherein the Influenza virus RNA-dependent RNA polymerase subunit PB2 is from an Inluenza A, B, or C virus or variant thereof.

4. The polypeptide fragment of any of claims 1 to 3, wherein

(i) the N-terminus is identical to or corresponds to amino acid position 220 or higher and the C-terminus is identical to or corresponds to amino acid position 510 or lower of the amino acid sequence of PB2 according to SEQ ID NO: 1,

(ii) the N-terminus is identical to or corresponds to amino acid position 222 or higher and the C-terminus is identical to or corresponds to amino acid position 511 or lower of the amino acid sequence of PB2 according to SEQ ID NO: 2, or

(iii) wherein the N-terminus is identical to or corresponds to amino acid position 227 or higher and the C-terminus is identical to or corresponds to amino acid position 528 or lower of the amino acid sequence of PB2 according to SEQ ID NO: 3

and variants thereof, which retain the ability to associate with an RNA cap or analog thereof.

5. The polypeptide fragment of claim 4, wherein said polypeptide fragment has or corresponds to an amino acid sequence selected from the group of amino acid sequences according to SEQ ID NO: 4 to 13 and variants thereof, which retain the ability to associate with an RNA cap or analog thereof.

6. A complex comprising the polypeptide fragment of any of claims 1 to 5 and a RNA cap or analog thereof.

7. The complex of claim 6, wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, and $m^7GpppUm$.

8. The complex of claim 6, wherein said polypeptide fragment consists of an amino acid sequence according to SEQ ID NO: 11 and said cap analog is m^7GTP, having the structure defined by the structure coordinates as shown in Figure 18.

9. The complex of claim 8, wherein said complex has a crystalline form with space group $C222_1$ and unit cell dimensions of a = 9.2 nm, b = 9.4 nm; c = 22.0 nm (± 0.3 nm)

10. The complex of claims 8 and 9, wherein the crystal diffracts X-rays to a resolution of 3.0 Å or higher, preferably 2.4 Å or higher.

11. An isolated polynucleotide coding for an isolated polypeptide of any of claims 1 to 5.

12. A recombinant vector comprising said isolated polynucleotide of claim 11.

13. A recombinant host cell comprising said isolated polynucleotide of claim 11 or said recombinant vector of claim 12.

14. A method for identifying compounds which associate with all or part of the RNA cap binding pocket of PB2 or the binding pocket of a PB2 polypeptide variant, comprising the steps of

(a) constructing a computer model of said binding pocket defined by the structure coordinates of the complex of claim 8 as shown in Figure 18;

(b) selecting a potential binding compound by a method selected from the group consisting of:

(i) assembling molecular fragments into said compound,

(ii) selecting a compound from a small molecule database, and

(iii) de novo ligand design of said compound;

(c) employing computational means to perform a fitting program operation between computer models of the said compound and the said binding pocket in order to provide an energy-minimized configuration of the said compound in the binding pocket; and

(d) evaluating the results of said fitting operation to quantify the association between the said compound and the binding pocket model, whereby evaluating the ability of said compound to associate with the said binding pocket.

15. The method of claim 14, wherein said binding pocket comprises amino acids Phe323, His357, and Phe404 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto.

16. The method of claim 15, wherein said binding pocket further comprises amino acids Phe325, Phe330, and Phe363 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto.

17. The method of claims 15 or 16, wherein said binding pocket further comprises amino acids Glu361, and Lys376 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto.

18. The method of any of claims 15 to 17, wherein said binding pocket further comprises amino acids Ser320, Arg332, Ser337, and Gln406

19. The method of any of claims 15 to 18, wherein said binding pocket further comprises amino acids Lys339, Arg355, Asn429, and His432 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto.

20. The method of claim 14, wherein said binding pocket is defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Phe323, His357, and Phe404 according to Figure 18.

21. The method of claim 20, wherein said binding pocket is further defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Phe325, Phe330, and Phe363 according to Figure 18.

22. The method of claims 20 or 21, wherein said binding pocket is further defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Glu361, and Lys376 according to Figure 18.

23. The method of any of claims 20 or 22, wherein said binding pocket is further defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Ser320, Arg332, Ser337, and Gln406 according to Figure 18.

24. The method of any of claims 20 to 23, wherein said binding pocket is further defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Lys339, Arg355, Asn429, and His432 according to Figure 18.

25. The method of claim 20, wherein the binding pocket of a PB2 polypeptide variant has a root mean square deviation from the backbone atoms of the amino acids Phe323, His357, and Phe404 of said binding pocket of not more than 2.5 Å.

26. The method of any of claims 14 to 25 comprising the further step of

(e) synthesizing said compound and optionally formulating said compound or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

27. The method of claim 26 comprising the further step of

(f) contacting said compound, said polypeptide fragment of any of claims 1 to 4 or said recombinant host cell according to claim 12 and a RNA cap or analog thereof to determine the ability of said compound to inhibit binding between said PB2 polypeptide fragment and said RNA cap or analog thereof.

28. A compound identifiable by the method of claims 14 to 27, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1\text{-}15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um and is able to bind to the RNA cap binding pocket of PB2 or variant thereof.

29. A compound identifiable by the method of claims 14 to 27, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1\text{-}15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um

and is able to inhibit binding between the PB2 polypeptide, variant thereof or fragment thereof and the RNA cap or analog thereof.

30. A method for identifying compounds which associate with the RNA cap binding pocket of PB2 or binding pockets of PB2 polypeptide variants, comprising the steps of (i) contacting said polypeptide fragment of claims 1 to 4 or said recombinant host cell according to claim 13 with a test compound and (ii) analyzing the ability of said test compound to bind to PB2.

31. The method of claim 30, comprising the further step of adding a RNA cap or analog thereof.

32. The method of claim 31, wherein the ability of said test compound to bind to PB2 or a variant thereof in presence of said RNA cap or analog thereof or the ability of said test compound to inhibit binding of said RNA cap or analog thereof to PB2 or a variant thereof is analyzed.

33. The method of claims 31 or 32, wherein said RNA cap or analog thereof is added prior, concomitantly, or after addition of said test compound.

34. The method of any of claims 30 to 33 performed in a high-throughput setting.

35. The method of any of claims 30 to 34, wherein said test compound is a small molecule.

36. The method of any of claims 30 to 34, wherein said test compound is a peptide or protein.

37. The method of any of claims 26, 27, or 30 to 36, wherein said method further comprises the step of formulating said compound or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

38. A pharmaceutical composition producible according to the method of claims 27 or 37.

39. A compound identifiable by the method of any of claims 30 to 37, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um and is able to bind to the PB2 polypeptide, variant thereof or fragment thereof.

40. A compound identifiable by the method of any of claims 29 to 36, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6-one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um, and is able to inhibit binding between the PB2 polypeptide, variant thereof or fragment thereof and the RNA cap or analog thereof.

41. An antibody directed against the RNA cap binding domain of PB2.

42. The antibody of claim 41, wherein said antibody recognizes a polypeptide fragment selected from the group of polypeptides defined by SEQ ID NO: 14 to 22.

43. Use of a compound according to claims 28, 29, 39, or 40, a pharmaceutical composition according to claim 36, or an antibody according to claims 41 or 42 for the manufacture of a medicament for treating, ameliorating, or preventing disease conditions caused by viral infections with negative-sense ssRNA viruses.

44. The use of claim 43, wherein said disease condition is caused by viral infections of the Mononegavirales order comprising the Bornaviridae, Filoviridae, Paramyxoviridae, and Rhabdoviridae families.

45. The use of claim 43, wherein said disease condition is caused by the Orthomyxoviridae, Arenaviridae, or Bunyaviridae families.

46. The use of claim 43, wherein said disease condition is caused by a virus selected from the group consisting of Borna disease virus, Marburg virus, Ebola virus, Sendai virus, Mumps virus, Measles virus, Human respiratory syncytial virus, Turkey rhinotracheitis virus,

Vesicular stomatitis Indiana virus, Nipah virus, Henda virus, Rabies virus, Bovine ephemeral fever virus, Infectious hematopoietic necrosis virus, Thogoto virus, Influenza A virus, Influenza B virus, Influenza C virus, Hantaan virus, Crimean-congo hemorrhagic fever virus, Rift Valley fever virus, and La Crosse virus.

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47. The use of claim 43, wherein said disease condition is caused by a virus selected from the group consisting of Influenza A virus, Influenza B virus, Influenza C virus, Thogoto virus, and Hantaan virus.

Claims

1. A soluble polypeptide fragment of an Influenza virus RNA-dependent RNA polymerase subunit PB2, wherein said soluble polypeptide fragment is selected from the group consisting of:

(i) a polypeptide fragment in which the N-terminus is located at amino acid position 220 of the PB2 polypeptide according to SEQ ID NO: 1 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 510 of the PB2 polypeptide according to SEQ ID NO: 1 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

(ii) a polypeptide fragment in which the N-terminus is located at amino acid position 222 of the PB2 polypeptide according to SEQ ID NO: 2 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 511 of the PB2 polypeptide according to SEQ ID NO: 2 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

(iii) a polypeptide fragment in which the N-terminus is located at amino acid position 227 of the PB2 polypeptide according to SEQ ID NO: 3 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 528 of the PB2 polypeptide according to SEQ ID NO: 3 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

variants thereof, which retain the ability to associate with an RNA cap or analog thereof; wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppN, $m^7GpppNm$ and optionally comprises additional nucleotides, and wherein the variant has at least 80% sequence identity to said soluble polypeptide fragment according to (i), (ii), or (iii).

2. The polypeptide fragment of claim 1, wherein said polypeptide fragment is selected from the group consisting of:

(i) a polypeptide fragment with an amino acid sequence according to one of SEQ ID NO: 4 to 13;

(ii) a polypeptide fragment with an amino acid sequence that spans analogous positions in a PB2 polypeptide aligned to one of SEQ ID NO: 4 to 13; or

(iii) a variant polypeptide fragment, which has at least 80% sequence identity to the PB2 polypeptid fragment according to (i) or (ii);

and wherein the polypeptide fragment according to (i) or (ii) or the variant polypeptide fragment according to (iii) retains the ability to associate with an RNA cap or analog thereof, wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppN, $m^7GpppNm$ and optionally comprises additional nucleotides.

3. A complex comprising the polypeptide fragment of claim 1 or 2 and a RNA cap or analog thereof, wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppN, $m^7GpppNm$ and optionally comprises additional nucleotides.

4. The complex of claim 3, wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, and $m^7GpppUm$.

5. The complex of claim 4, wherein said polypeptide fragment consists of an amino acid sequence according to SEQ ID NO: 11 and said cap analog is m^7GTP, having the structure defined by the structure coordinates as shown in Figure 18.

6. An isolated polynucleotide coding for an isolated polypeptide of claim 1 or 2.

7. A recombinant vector comprising the isolated polynucleotide of claim 6.

8. A recombinant host cell comprising the isolated polynucleotide of claim 6 or the recombinant vector of claim 7.

9. A method for identifying compounds which associate with all or part of the RNA cap binding pocket of PB2 or the binding pocket of a PB2 polypeptide variant as defined in claims 1 or 2, comprising the steps of

(a) constructing a computer model of said binding pocket defined by the structure coordinates of the complex of claim 5 as shown in Figure 18;

(b) selecting a potential binding compound by a method selected from the group consisting of:

(i) assembling molecular fragments into said compound,

(ii) selecting a compound from a small molecule database, and

(iii) de novo ligand design of said compound;

(c) employing computational means to perform a fitting program operation between computer models of the said compound and the said binding pocket in order to provide an energy-minimized configuration of the said compound in the binding pocket; and

(d) evaluating the results of said fitting operation to quantify the association between the said compound and the binding pocket model, whereby evaluating the ability of said compound to associate with the said binding pocket.

10. The method of claim 9, wherein said binding pocket comprises:
amino acids Phe323, His357, and Phe404 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and wherein said binding pocket optionally further comprises amino acids Phe325, Phe330, and Phe363 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Glu361, and Lys376 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Ser320, Arg332, Ser337, and Gln406 of SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Lys339, Arg355, Asn429, and His432 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto

11. A method for identifying compounds which associate with the RNA cap binding pocket of PB2 or binding pockets of PB2 polypeptide variants as defined in claims 1 or 2, comprising the steps of (i) contacting said polypeptide fragment of claim 1 or 2 or said recombinant host cell according to claim 8 with a test compound and (ii) analyzing the ability of said test compound to bind to PB2.

12. The method of claim 11, comprising the further step of adding a RNA cap or analog thereof.

13. An antibody directed against the RNA cap binding domain of PB2, wherein said antibody recognizes a polypeptide fragment selected from the group of polypeptides defined by SEQ ID NO: 14 to 22.

14. A compound identifiable by a method comprising the steps of

(a) constructing a computer model of a binding pocket defined by the structure coordinates of a complex comprising a polypeptide fragment consisting of an amino acid sequence according to SEQ ID NO: 11 and an RNA cap or analog thereof, wherein the cap analog is m^7GTP, having the structure defined by the structure coordinate as shown in Figure 18;

(b) selecting a potential binding compound by a method selected from the group consisting of:

(i) assembling molecular fragments into said compound,

(ii) selecting a compound from a small molecule database, and

(iii) de novo ligand design of said compound;

(c) employing computational means to perform a fitting program operation between computer models of the said compound and the said binding pocket in order to provide an energy-minimized configuration of the said compound in the binding pocket; and

(d) evaluating the results of said fitting operation to quantify the association between the compound and the binding pocket model, whereby evaluating the ability of said compound to associate with the said binding pocket,

under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um and is able to bind to the RNA cap binding pocket of PB2 or variant thereof.

15. A compound identifiable by a method comprising the steps of

(a) constructing a computer model of said binding pocket defined by the structure coordinates of a complex comprising a polypeptide fragment consisting of an amino acid sequence according to SEQ ID NO: 11 and an RNA cap or analog thereof, wherein the cap analog is m^7GTP, having the structure defined by the structure coordinate as shown in Figure 18;

(b) selecting a potential binding compound by a method selected from the group consisting of:

(i) assembling molecular fragments into said compound,

(ii) selecting a compound from a small molecule database, and

(iii) de novo ligand design of said compound;

(c) employing computational means to perform a fitting program operation between computer models of the said compound and the said binding pocket in order to provide an energy-minimized configuration of the said compound in the binding pocket; and

(d) evaluating the results of said fitting operation to quantify the association between the said compound and the binding pocket model, whereby evaluating the ability of said compound to associate with the said binding pocket,

under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um and is able to inhibit binding between the PB2 polypeptide, variant thereof or fragment thereof and the RNA cap or analog thereof.

16. The compound of claim 14 or 15, wherein said binding pocket comprises: amino acids Phe323, His357, and Phe404 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and wherein said binding pocket optionally further comprises amino acids Phe325, Phe330, and Phe363 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Glu361, and Lys376 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Ser320, Arg332, Ser337, and Gln406 of SEQ ID NO: 1 or amino acids corresponding thereto and/or amino acids Lys339, Arg355, Asn429, and His432 of PB2 according to SEQ ID NO: 1 or amino acids corresponding thereto

17. The compound of any of claims 14 to 16, wherein said binding pocket is defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Phe323, His357, and Phe404 according to Figure 18., and/or wherein said binding pocket is optionally further defined by the structure coordinates of PB2 SEQ ID NO: 1 amino acids Phe325, Phe330, and Phe363 according to Figure 18 and/or amino acids Glu361, and Lys376 according to Figure 18 and/or amino acids Ser320, Arg332, Ser337, and Gln406 according to Figure 18 and/or amino acids Lys339, Arg355, Asn429, and His432 according to Figure 18.

18. The compound of any of claims 14 to 17, wherein said binding pocket of a PB2 polypeptide variant has a root mean square deviation from the backbone atoms of the amino acids Phe323, His357, and Phe404 of said binding pocket of not more than 2.5 Å.

19. The compound of any of claims 14 to 18, wherein said method further comprises step (e) synthesizing said compound and optionally formulating said compound or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

20. The compound of claim 19, wherein said method further comprises step (f) contacting said compound, said polypeptide fragment, or a recombinant host cell comprising a

polynucleotide coding for said polypeptide, and a RNA cap or analog thereof to determine the ability of said compound to inhibit binding between said PB2 polypeptide fragment and said RNA cap or analog thereof.

21. A method for identifying compounds which associate with the RNA cap binding pocket of PB2 or binding pockets of PB2 polypeptide variants, comprising the steps of

(i) contacting a soluble polypeptide fragment of an Influenza virus RNA-dependent RNA polymerase subunit PB2, wherein said soluble polypeptide fragment is selected from the group consisting of:

(a) a polypeptide fragment in which the N-terminus is located at amino acid position 220 of the PB2 polypeptide according to SEQ ID NO: 1 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 510 of the PB2 polypeptide according to SEQ ID NO: 1 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

(b) a polypeptide fragment in which the N-terminus is located at amino acid position 222 of the PB2 polypeptide according to SEQ ID NO: 2 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 511 of the PB2 polypeptide according to SEQ ID NO: 2 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

(c) a polypeptide fragment in which the N-terminus is located at amino acid position 227 of the PB2 polypeptide according to SEQ ID NO: 3 or at an amino acids residue that occupies an analogous position in a PB2 polypeptide aligned thereto or at a higher amino acid position; and the C-terminus is located at amino acid position 528 of the PB2 polypeptide according to SEQ ID NO: 3 or at an amino acids residue that occupies an

analogous position in a PB2 polypeptide aligned thereto or at a lower amino acid position; or

variants thereof, which retain the ability to associate with an RNA cap or analog thereof; wherein the cap analog is selected from the group consisting of m^7G, m^7GMP, m^7GTP, m^7GpppN, $m^7GpppNm$ and optionally comprises additional nucleotides, and wherein the variant has at least 80% sequence identity to said soluble polypeptide fragment according to (a), (b), or (c),

or a recombinant host cell comprising a polynucleotide coding for said polypeptide,

with a test compound and

(ii) analyzing the ability of said test compound to bind to PB2.

22. The method of claim 21, comprising the further step of adding a RNA cap or analog thereof.

23. The method of claim 22, wherein the ability of said test compound to bind to PB2 or a variant thereof in presence of said RNA cap or analog thereof or the ability of said test compound to inhibit binding of said RNA cap or analog thereof to PB2 or a variant thereof is analyzed.

24. The method of claims 22 or 23, wherein said RNA cap or analog thereof is added prior, concomitantly, or after addition of said test compound.

25. The method of any of claims 22 to 24 performed in a high-throughput setting.

26. The method of any of claims 22 to 25, wherein said test compound is a small molecule.

27. The method of any of claims 22 to 26, wherein said test compound is a peptide or protein.

28. The method of any of claims 22 to 27, further comprising the step of formulating said compound or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipient(s) and/or carrier(s).

29. A pharmaceutical composition producible according to the method of claim 28.

30. A compound identifiable by the method of any of claims 21 to 28, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6- one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um and is able to bind to the PB2 polypeptide, variant thereof or fragment thereof.

31. A compound identifiable by the method of any of claims 21 to 28, under the provision that the compound is not m^7G, m^7GMP, m^7GTP, m^7GpppG, $m^7GpppGm$, m^7GpppA, $m^7GpppAm$, m^7GpppC, $m^7GpppCm$, m^7GpppU, $m^7GpppUm$, 2-Amino-7-benzyl-9-(4-hydroxy-butyl)-1,9-dihydro-purin-6-one, T-705 or $m^7Gppp(N)_{1-15}$, wherein N is A, Am, G, Gm, C, Cm, U or Um, and is able to inhibit binding between the PB2 polypeptide, variant thereof or fragment thereof and the RNA cap or analog thereof.

32. Use of a compound according to any of claims 14 to 20, 30, or 31, or a pharmaceutical composition according to claim 16, for the manufacture of a medicament for treating, ameliorating, or preventing disease conditions caused by viral infections with negative-sense ssRNA viruses.

33. The use of claim 32, wherein said disease condition is caused by viral infections of the Mononegavirales order comprising the Bornaviridae, Filoviridae, Paramyxoviridae, and Rhabdoviridae families.

34. The use of claim 33, wherein said disease condition is caused by the Orthomyxoviridae, Arenaviridae, or Bunyaviridae families.

35. The use of claim 33, wherein said disease condition is caused by a virus selected from the group consisting of Borna disease virus, Marburg virus, Ebola virus, Sendai virus, Mumps virus, Measles virus, Human respiratory syncytial virus, Turkey rhinotracheitis virus, Vesicular stomatitis Indiana virus, Nipah virus, Henda virus, Rabies virus, Bovine ephemeral fever virus, Infectious hematopoietic necrosis virus, Thogoto virus, Influenza A virus, Influenza B virus, Influenza C virus, Hantaan virus, Crimean-congo hemorrhagic fever virus, Rift Valley fever virus, and La Crosse virus.

36. The use of claim 33, wherein said disease condition is caused by a virus selected from the group consisting of Influenza A virus, Influenza B virus, Influenza C virus, Thogoto virus, and Hantaan virus.