CLAIMS

1. An isolated polypeptide fragment comprising an amino-terminal fragment of the PA subunit of a viral RNA-dependent RNA polymerase possessing endonuclease activity, wherein said PA subunit is from Influenza A 2009 pandemic H1N1 virus according to SEQ ID NO: 2 wherein the N-terminus is identical to or corresponds to amino acid position 1 and the C-terminus is identical to or corresponds to an amino acid at a position selected from positions 190 to 198 of the amino acid sequence of the PA subunit according to SEQ ID NO: 2, or is a variant thereof, wherein said variant comprises the amino acid serine at an amino acid position 186 according to SEQ ID NO: 2 or at an amino acid position corresponding thereto and retains the endonuclease activity.

2. The polypeptide fragment of claim 1, which is soluble.

3. The polypeptide fragment of claim 1 or 2, which is crystallizable.

~~4. The polypeptide fragment of any one of claims 1 to 3, wherein the amino terminal fragment corresponds to at least amino acids 1 to 190 of the PA subunit of the RNA-dependent RNA polymerase of Influenza A 2009 pandemic H1N1 virus according to SEQ ID NO: 2.~~

~~5~~4. The polypeptide fragment of any one of claims 1 to ~~4~~3, wherein said polypeptide fragment is purified to an extent to be suitable for crystallization.

~~6~~5. The polypeptide fragment of any one of claims 1 to ~~5~~ 4 to which two divalent cations are bound, wherein the divalent cation is preferably manganese and/or magnesium**.**

~~7. The polypeptide fragment of any one of claims 1 to 6, wherein the N-terminus is identical to or corresponds to amino acid position 1 and the C-terminus is identical to or corresponds to an amino acid at a position selected from positions 190 to 198 of the amino acid sequence of the PA subunit according to SEQ ID NO: 2, or is a variant thereof, wherein said variant comprises the amino acid serine at an amino acid~~

~~position 186 according to SEQ ID NO: 2 or at an amino acid position corresponding thereto and retains the endonuclease activity.~~

~~8~~6. The polypeptide fragment of any one of claims 1 to ~~7~~5, which

(a) consists of amino acids 1 to 198 of the amino acid sequence set forth in SEQ ID NO: 2 and optionally of an amino-terminal linker having the amino acid sequence MGSGMA (SEQ ID NO: 3) and which has the structure defined by (i) the structure coordinates as shown in Figure 1, (ii) the structure coordinates as shown in Figure 2, (iii) the structure coordinates as shown in Figure 3, (iv) the structure coordinates as shown in Figure 4, or (v) the structure coordinates as shown in Figure 5, or

(b) consists of amino acids 1 to 198 of the amino acid sequence set forth in SEQ ID NO: 2 with amino acids 52 to 64 replaced by the amino acid glycine and optionally of an amino-terminal linker having the amino acid sequence MGSGMA (SEQ ID NO: 3) and which has the structure defined by (vi) the structure coordinates as shown in Figure 15, or (vii) the structure coordinates as shown in Figure 16.

~~9~~7. The polypeptide fragment of claim ~~8~~6, wherein the polypeptide fragment having the structure defined by (i) has a crystalline form with space group *C*2 and unit cell dimensions of a = 26.36 nm ± 0.5 nm, b = 6.62 nm ± 0.3 nm, c = 6.63 nm ± 0.3 nm, α = 90 deg, β = 96 ± 2 deg, γ = 90 deg, (ii) to (v) has a crystalline form with space group $P2_12_12_1$ and unit cell dimensions of a = 5.46 ± 0.3 nm, b= 12.25 ± 0.4 nm, c=13.0 ± 0.3 nm, α = 90 deg, β = 90 deg, γ = 90 deg, (vi) has a crystalline form with space group *P* $6_2$22 and unit cell dimensions of a = 7.50 nm ± 0.3 nm, b = 7.50 nm ± 0.3 nm, c = 12.00 nm ± 0.5 nm, α = 90 deg, β = 90 deg, γ = 120 deg, or (vii) has a crystalline form with space group *P6$_4$22* and unit cell dimensions of a = 9.99 nm ± 0.5 nm, b = 9.99 nm ± 0.5 nm, c = 8.27 nm ± 0.3 nm, α = 90 deg, β = 90 deg, γ = 120 deg.

~~10~~8. The polypeptide fragment of claims ~~8~~ 6 or ~~9~~7, wherein the crystal diffracts X-rays to a resolution of 2.6 Å or higher, preferably 2.1 Å or higher or 1.9 Å or higher.

~~11~~9. An isolated polynucleotide coding for an isolated polypeptide fragment of any one of claims 1 to ~~10~~8.

~~12~~10. A recombinant vector comprising said isolated polynucleotide of claim ~~11~~9.

~~13~~11. A recombinant host cell comprising said isolated polynucleotide of claim ~~11~~ 9 or said recombinant vector of claim ~~12~~10.

~~14~~12. A method for identifying compounds, which modulate the endonuclease activity of the PA subunit of a RNA-dependent RNA polymerase from Influenza A 2009 pandemic H1N1 virus or a variant thereof comprising the steps of:

(a) constructing a computer model of the active site defined by (i) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 1, (ii) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 2, (iii) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 3, (iv) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 4, (v) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 5, (vi) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 15, or (vii) the structure coordinates of the polypeptide fragment of claim ~~8~~ 6 as shown in Figure 16,

(b) selecting a potential modulating 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 active site in order to provide an energy-minimized configuration of the said compound in the active site; and

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

~~15~~13. The method of claim ~~14~~12, wherein said active site comprises amino acids Glu80, Glu119, Asp108, Ile120, and His41 of the PA subunit according to SEQ ID NO: 2 or amino acids corresponding thereto.

~~16~~14. The method of claim ~~15~~13, wherein said active site further comprises amino acids Lys34, Tyr24, Arg84, Phe105, Tyr130, Ile38, and Arg124 of the PA subunit according to SEQ ID NO: 2 or amino acids corresponding thereto.

~~17~~15. The method of claims ~~15~~ 13 or ~~16~~14, wherein said active site further comprises amino acids Glu26, Lys134, Leu106, and Lys137 of the PA subunit according to SEQ ID NO: 2 or amino acids corresponding thereto.

~~18~~16. The method of claim ~~14~~12, wherein said active site is defined by the structure coordinates of the PA subunit SEQ ID NO: 2 amino acids Glu80, Glu119, Asp108, Ile120, and His41 according to Figures 1 to 5 or by the structure coordinates of the PA subunit amino acids Glu, Glu, Asp, Ile, and His corresponding to amino acids Glu80, Glu119, Asp108, Ile120, and His41 of SEQ ID NO: 2, respectively, according to Figures 15 or 16.

~~19~~17. The method of claim ~~18~~16, wherein said active site is further defined by the structure coordinates of the PA subunit SEQ ID NO: 2 amino acids Lys34, Tyr24, Arg84, Phe105, Tyr130, Ile38, and Arg124 according to Figures 1 to 5 or by the structure coordinates of the PA subunit amino acids Lys, Tyr, Arg, Phe, Tyr, Ile, and Arg corresponding to amino acids Lys34, Tyr24, Arg84, Phe105, Tyr130, Ile38, and Arg124 of SEQ ID NO: 2, respectively, according to Figures 15 or 16.

~~20~~18. The method of claims ~~18~~ 16 or ~~19~~17, wherein said active site is further defined by the structure coordinates of the PA subunit SEQ ID NO: 2 amino acids Glu26, Lys134, Leu106, and Lys137 according to Figures 1 to 5 or by the structure coordinates of the PA subunit amino acids Glu, Lys, Leu, and Lys corresponding to amino acids Glu26, Lys134, Leu106, and Lys137 of SEQ ID NO: 2, respectively, according to Figures 15 or 16.

~~21~~19. The method of any one of claims ~~14~~ 12 to ~~20~~ 18 further comprising the 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).

~~22~~20. The method of claim ~~21~~ 19 further comprising the step of:

(f) contacting said compound and said polypeptide fragment or variant thereof of any one of claims 1 to ~~10~~ 8 or said recombinant host cell according to claim ~~13~~ 11 and determine the ability of said compound to modulate the endonuclease activity of said PA subunit polypeptide fragment or variant thereof.

~~23~~21. A method for identifying compounds, which modulate the endonuclease activity of the PA subunit of a RNA-dependent RNA polymerase from Influenza A 2009 pandemic H1N1 virus or a variant thereof comprising the steps of:

(i) contacting said polypeptide fragment or variant thereof of any one of claims 1 to ~~10~~ 8 or said recombinant host cell of claim ~~13~~ 11 with a test compound, and

(ii) analyzing the ability of said test compound to modulate the endonuclease activity of said PA subunit polypeptide fragment or variant thereof.

~~24~~22. The method of claim ~~23~~21, wherein the ability of said test compound to inhibit the endonuclease activity of said PA subunit polypeptide fragment or variant thereof is analyzed.

~~25~~23. The method of claims ~~23~~ 21 or ~~24~~22, wherein said method is performed in a high-throughput setting.

~~26~~24. The method of any one of claims ~~23~~ 21 to ~~25~~23, wherein said test compound is a small molecule.

~~27~~25. The method of any of one claims ~~23~~ 21 to ~~26~~24, wherein said test compound is a peptide or protein.

~~28~~26. The method of any one of claims ~~23~~ 21 to ~~27~~25, 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).

~~29. A compound which is able to modulate, preferably to inhibit, the endonuclease activity of the PA subunit polypeptide fragment or variant thereof of any one of claims 1 to 10.~~

~~30. The compound of claim 29, wherein said compound is identifiable by the method of any one of claims 14 to 22 or by the method of any one of claims 23 to 28.~~

~~31. A pharmaceutical composition comprising the compound of claims 29 or 30 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipient(s) and/or carrier(s).~~

~~32. The pharmaceutical composition of claim 31, wherein said pharmaceutical composition is producible according to the method of claims 21 or 28.~~

~~33~~27. An isolated antibody directed against the active site of the PA subunit of the Influenza A 2009 pandemic H1N1 virus according to SEQ ID NO: 2 or a variant thereof, wherein said variant comprises the amino acid serine at an amino acid position 186 according to SEQ ID NO: 2 or at an amino acid position corresponding thereto.

~~34~~28. The antibody of claim ~~33~~27, wherein said antibody recognizes a polypeptide fragment of a length between 5 and 15 amino acids of the amino acid sequence as set forth in SEQ ID NO: 2, wherein the polypeptide fragment comprises one or more amino acid residues selected from the group consisting of Lys34, Glu26, Ile38,

Tyr24, His41, Glu80, Arg84, Leu106, Asp108, Glu119, Ile120, Tyr130, Lys134, Phe105, Lys137, and Arg124.

3529. Use of ~~a compound according to claims 29 or 30, a pharmaceutical composition according to claims 31 or 32, or~~ an antibody according to claims ~~33~~ 27 or ~~34~~ 28 for the manufacture of a medicament for treating, ameliorating, or preventing disease conditions caused by viral infections with viruses of the Orthomyxoviridae family, Bunyaviridae family and/or Arenviridae family, preferably caused by viral infections with Influenza A 2009 pandemic H1N1 virus.

~~36. Use of 4-[3-[(4-chlorophenyl)methyl]-1-(phenylmethyl)-3-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-3), 4-[4-[(4-chlorophenyl)methyl]-1-(cyclohexylmethyl)-4-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-2), 4-[3-[(4-chlorophenyl)methyl]-1-(phenylmethylsulpho)-3-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-1), or [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl]3,4,5-trihydroxybenzoate (EGCG) for the manufacture of a medicament for treating, ameliorating, or preventing disease conditions caused by viral infections with Influenza A 2009 pandemic H1N1 virus.~~

3730. ~~A compound according to claims 29 or 30, a pharmaceutical composition according to claims 31 or 32, or a~~n antibody according to claims ~~33~~ 27 or ~~34~~ 28 for treating, ameliorating, or preventing disease conditions caused by viral infections with viruses of the Orthomyxoviridae family, Bunyaviridae family and/or Arenviridae family, preferably caused by viral infections with Influenza A 2009 pandemic H1N1 virus.

~~38. 4-[3-[(4-chlorophenyl)methyl]-1-(phenylmethyl)-3-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-3), 4-[4-[(4-chlorophenyl)methyl]-1-(cyclohexylmethyl)-4-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-2), 4-[3-[(4-chlorophenyl)methyl]-1-(phenylmethylsulpho)-3-piperidinyl]-2-hydroxy-4-oxo-2-butenoic acid (EMBL-R05-1), or [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl]3,4,5-trihydroxybenzoate (EGCG) for treating, ameliorating, or preventing disease conditions caused by viral infections with Influenza A 2009 pandemic H1N1 virus.~~