(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 June 2010 (24.06.2010)

PCT

(10) International Publication Number
WO 2010/069600 A3

(51) International Patent Classification:
C12N 9/12 (2006.01)

(21) International Application Number:
PCT/EP2009/009161

(22) International Filing Date:
18 December 2009 (18.12.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/203,259 19 December 2008 (19.12.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
5 August 2010

(54) Title: POLYPEPTIDE FRAGMENTS COMPRISING ENDONUCLEASE ACTIVITY AND THEIR USE

(57) Abstract: The present invention relates to polypeptide fragments comprising an amino-terminal fragment of the PA subunit of a viral RNA-dependent RNA polymerase or variants thereof possessing endonuclease activity, wherein said PA subunit is from a virus belonging to the Orthomyxoviridae family. This invention also relates to (i) crystals of the polypeptide fragments which are suitable for structure determination of said polypeptide fragments using X-ray crystallography and (ii) computational methods using the structural coordinates of said polypeptide to screen for and design compounds that modulate, preferably inhibit the endonucleolytically active site within the polypeptide fragment. In addition, this invention relates to methods identifying compounds that bind to the PA polypeptide fragments possessing endonuclease activity and preferably inhibit said endonucleolytic activity, preferably in a high throughput setting. This invention also relates to compounds and pharmaceutical compositions comprising the identified compounds for the treatment of disease conditions due to viral infections caused by viruses of the Orthomyxoviridae family.

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