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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,

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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— 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:

28 March 2013

(54) Title: METHODS AND COMPOSITIONS FOR INHIBITING NEDDYLYATION OF PROTEINS

(57) Abstract: Provided herein is a novel binding pocket within NEDD8 co-E3 proteins that binds NEDD8 E2 enzymes. Particularly at its M-Terminus. Methods are provided for screening for compounds that bind to the disclosed E2-binding pocket in NEDD8 co-E3 proteins. Compounds that bind to the E2-binding pocket and optionally inhibit the activity of NEDD8 co-E3 proteins and pharmaceutical compositions comprising the same are further provided. The NEDD8 co-E3 inhibitors find use, as agents preventing the NEDDylation of a target protein, in inhibiting cell growth and methods for treating cancers, inflammatory disorders, and pathogenic infections. The preferred inhibitors are peptides corresponding to a M-terminal fragment of Dncl, e.g. MTLASKLKRDD, MLKLRQLQKKKQ, and MIKLFSLKQKKK, which are substituted at the M-Terminus with an uncharged group (e.g. acyl).



WO 2012/158789 A3

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
 INV. G01N33/573 C12N9/00
 ADD. A61K38/00 A61P31/00 A61P35/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 G01N C12N C12Y

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EPO-Internal, Sequence Search, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	D. C. SCOTT ET AL: "N-Terminal Acetylation Acts as an Avidity Enhancer Within an Interconnected Multiprotein Complex", SCIENCE, vol. 334, no. 6056, 22 September 2011 (2011-09-22), pages 674-678, XP055033393, ISSN: 0036-8075, DOI: 10.1126/science.1209307 abstract; figures 2-4 ----- -/--	1-43, 51-57

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 20 July 2012	Date of mailing of the international search report 21/01/2013
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Fausti, Simone
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/038127

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DANIEL C. SCOTT ET AL: "A Dual E3 Mechanism for Rub1 Ligation to Cdc53", MOLECULAR CELL, vol. 39, no. 5, 1 September 2010 (2010-09-01), pages 784-796, XP055033282, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2010.08.030 abstract; from the second full paragraph of the right-hand column on page 789 to the first paragraph of the right-hand column on page 790; figure 5 -----	1-43, 51-57
X	EP 2 182 006 A2 (GENENTECH INC [US]) 5 May 2010 (2010-05-05) abstract; paragraph [0125]; claim 8; sequence 802 -----	1-8, 16-43, 52,53
X	THIMO KURZ ET AL: "Dcn1 Functions as a Scaffold-Type E3 Ligase for Cullin Neddylation", MOLECULAR CELL, vol. 29, no. 1, 1 January 2008 (2008-01-01), pages 23-35, XP055033471, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2007.12.012 abstract; second and third full paragraphs of the right-hand column on page 29 -----	1-8, 16-43, 52-57
X	DANNY T HUANG ET AL: "A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8", NATURE STRUCTURAL & MOLECULAR BIOLOGY, vol. 11, no. 10, 1 October 2004 (2004-10-01), pages 927-935, XP055033432, ISSN: 1545-9993, DOI: 10.1038/nsmb826 abstract -----	1-43, 52-57
T	TOMOAKI TANAKA ET AL: "Inhibition of NEDD8-conjugation pathway by novel molecules: Potential approaches to anticancer therapy", MOLECULAR ONCOLOGY, vol. 6, no. 3, 1 June 2012 (2012-06-01), pages 267-275, XP055033291, ISSN: 1574-7891, DOI: 10.1016/j.molonc.2012.01.003 abstract; the second and the third full paragraphs of the left-hand column on page 270 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038127

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-43(completely); 51-57(partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-43(completely); 51-57(partially)

Peptides binding to NEDD8 co-E3 at its E2-binding pocket bearing an R group at the N-terminus, as well as medical and pharmaceutical uses/compositions thereof.

2. claims: 44-50(completely); 51-57(partially)

Small molecules binding to NEDD8 co-E3 at its E2-binding pocket bearing an R group at the N-terminus, as well as medical and pharmaceutical uses/compositions thereof.

3. claims: 58-64

Screening method exploiting the E2-binding pocket of NEDD8 co-E3.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/038127

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2182006	A2	05-05-2010	
		EP 1654278 A2	10-05-2006
		EP 2014675 A1	14-01-2009
		EP 2182006 A2	05-05-2010
		US 2007184444 A1	09-08-2007
		US 2010034817 A1	11-02-2010
		US 2011245090 A1	06-10-2011
		WO 2005016962 A2	24-02-2005
		WO 2005019258 A2	03-03-2005
