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(54) Title: COMPOSITIONS AND METHODS FOR TREATING AGE-RELATED MACULAR DEGENERATION AND GEOGRAPHIC ATROPHY

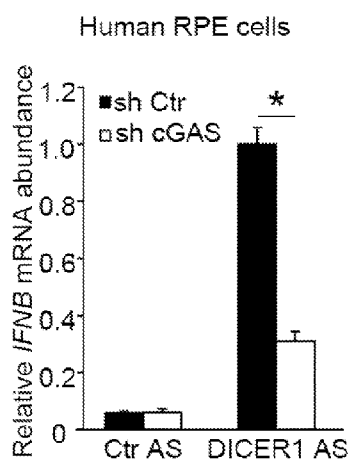


FIG. 4E

(57) Abstract: It is disclosed herein that RPE degeneration in human cell culture and in mouse models is driven by a non-canonical inflammasome pathway that results in activation of caspase-4 (also known as caspase-11 in mouse) and caspase-1, and requires cyclic GMP-AMP synthase (cGAS)-dependent interferon- $\beta$  (IFN- $\beta$ ) production and gasdermin D-dependent interleukin-18 (IL-18) secretion. Reduction of DICER1 or accumulation of Alu RNA triggers cytosolic escape of mitochondrial DNA, which engages cGAS. Collectively, these data highlight an unexpected role for cGAS in responding to mobile element transcripts, reveal cGAS-driven interferon signaling as a conduit for mitochondrial damage-induced NLRP3 activation, and expand the immune sensing repertoire of cGAS and caspase-4 to non-infectious human disease. Coupled with the unexpected result that caspase-4, gasdermin D, IFN- $\beta$ , and cGAS are elevated in the RPE of human eyes with geographic atrophy, these findings also identify new targets for a major cause of blindness.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/054941

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a.  forming part of the international application as filed:
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3. Additional comments:

SEQ ID NOs: 1, 2, and 9-21 were searched.

## INTERNATIONAL SEARCH REPORT

International application No.

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 31/00; A61K 39/395; A61P 27/02; C12N 15/113 (2018.01) CPC - A61K 31/00; A61K 2039/505; C12N 2310/14 (2018.08)		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) See Search History document		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 424/130.1; 435/375; 514/44A; 514/20.8; 536/24.5 (keyword delimited)		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) See Search History document		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/138425 A1 (UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION) 01 September 2016 (01.09.2016) entire document	1, 3, 4, 14-18
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Y		2, 5-7, 11, 12, 19-27, 31, 32, 34-42, 46, 47, 49-51
Y	KAYAGAKI et al. "Caspase-11 cleaves gasdermin D for non-canonical inflammasome signaling," Nature, 16 September 2015 (16.09.2015), Vol. 526, Pgs. 666-671 (Pgs. 1-18 for citations), entire document	2, 20-27, 31, 32, 34-42, 46, 47, 49-51
Y	US 2016/0068595 A1 (DEVELOPMENT CENTER FOR BIOTECHNOLOGY et al) 10 March 2016 (10.03.2016) entire document	5, 6, 25, 26, 40, 41
Y	KNODLER et al. "Noncanonical inflammasome activation of caspase-4/caspase-11 mediates epithelial defenses against enteric bacterial pathogens," Cell Host Microbe, 13 August 2014 (13.08.2014), Vol. 16, Pgs. 249-256 (Pgs. 1-16 for citations), entire document	7, 11, 12, 20-27, 31, 32, 34-42, 46, 47, 49-51
Y	US 2005/0255487 A1 (KHVOROVA et al) 17 November 2005 (17.11.2005) entire document	12, 32, 47
Y	US 2014/0178309 A1 (AMBATI et al) 26 June 2014 (26.06.2014) entire document	19, 35
A	US 9,707,235 B1 (AMBATI) 18 July 2017 (18.07.2017) entire document	1-57
A	GAO et al. "NLRP3 inflammasome: activation and regulation in age-related macular degeneration," Mediators Inflamm, 27 January 2015 (27.01.2015), Vol. 2015, Pgs. 1-11, entire document	1-57
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Date of the actual completion of the international search 25 November 2018		Date of mailing of the international search report <b>27 DEC 2018</b>
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300		Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US2018/054941

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/0263114 A1 (UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION) 15 September 2016 (15.09.2016) entire document	1-57
P, A	KERUK et al. "cGAS drives noncanonical-inflammasome activation in age-related macular degeneration," Nat Med, 27 November 2017 (27.11.2017), Vol. 24, Pgs. 50-61. entire document	1-57