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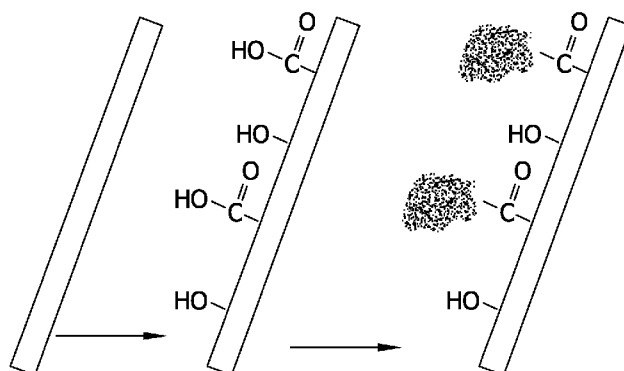
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[Continued on next page]

(54) Title: ALTERING PROTEIN CONCENTRATIONS IN CEREBROSPINAL FLUID AND/OR BRAIN INTERSTITIAL FLUID

FIG. 2



(57) Abstract: Devices and methods of altering protein concentrations in cerebrospinal fluid and/or brain interstitial fluid are disclosed. Devices include a support having at least one protease attached to the support. The device may further include a housing. Devices may be implantable for use in an in vivo active flow system or for use in an in vivo passive system. Devices may also be used in an ex vivo active flow system. Devices may also be used in a passive system to treat cerebrospinal fluid and/or brain interstitial fluid that is withdrawn, or in a passive system that is implanted surgically. Methods include contacting cerebrospinal fluid and/or brain interstitial fluid with a support including at least one protease attached to the support. Proteins contained in the cerebrospinal fluid and/or brain interstitial fluid are cleaved by the protease resulting in the reduction of protein in cerebrospinal fluid and/or brain interstitial fluid. Additionally, methods are disclosed for treating neurodegenerative diseases and neurological disorders.



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LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

A61M 37/00; C07K 19/00; A61K 38/43; A61K 38/02; A61M 1/00; C12N 11/02; A61M 36/14; A61K 38/48

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: protease, Alzheimer, cerebrospinal, zinc, metalloprotease

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008-0242590 A1 (ANDERSSON et al.) 02 October 2008 See the abstract; claims 1-2 and 30;	1-4, 14-16, 18, 24 , 26-27, 30-31
A	and paragraphs [0002]-[0003], [0104], [0113] and [0128].	5-13, 17, 19-23, 25 , 28-29, 32-34
A	US 2009-0131850 A1 (GEIGER) 21 May 2009 See the abstract; claims 1, 9-10, 12 and 18; and fig. 1.	1-34
A	US 6471960 B1 (ANDERSON) 29 October 2002 See the abstract; and claims 1-2.	1-34
A	US 2010-0260857 A1 (FALLON et al.) 14 October 2010 See the abstract; and claims 1-2.	1-34

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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**PCT/US2012/034120**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0242590 A1	02.10.2008	AU 2008-230177 A1	02.10.2008
		CA 2681404 A1	02.10.2008
		CN 101668545 A	10.03.2010
		EP 2139525 A1	06.01.2010
		EP 2139525 A4	18.08.2010
		JP 2010-522559 A	08.07.2010
		TW 200907056 A	16.02.2009
		WO 2008-118093 A1	02.10.2008
US 2009-0131850 A1	21.05.2009	US 7887503 B2	15.02.2011
US 6471960 B1	29.10.2002	EP 0792156 A1	22.10.2003
		EP 0792156 A4	01.03.2000
		EP 0792156 B1	12.05.2004
		JP 10-509457 A	14.09.1998
		US 05589154 A	31.12.1996
		US 06136548 A	24.10.2000
		WO 96-15799 A1	30.05.1996
US 2010-0260857 A1	14.10.2010	AU 2010-236628 A1	03.11.2011
		CA 2758257 A1	21.10.2010
		CN 102421284 A	18.04.2012
		EP 2418941 A1	22.02.2012
		GB 201117669 D0	23.11.2011
		GB 2480987 A	07.12.2011
		JP 2012-523462 A	04.10.2012
		KR 10-2012-0006052 A	17.01.2012
		US 2012-027848 A1	02.02.2012
		WO 2010-120781 A1	21.10.2010