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(54) **Cross beta structure comprising amyloid binding proteins and methods for detection of the cross beta structure, for modulating cross beta structures fibril formation and for modulating cross beta structure-mediated toxicity**

(57) The present invention relates to modulating extracellular protein degradation and/or protein clearance by modulating the cross-beta structure formation or tissue plasminogen activator-like activity, treatment of amy-

loidosis-type diseases by modulating the cross-beta structure, and diagnosis of amyloidosis-type diseases by visualising cross-beta structure.



EUROPEAN SEARCH REPORT

Application Number
EP 08 15 3132

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	<p>CHAUHAN A ET AL: "Media from rhabdomyosarcoma and neuroblastoma cell cultures stimulate in vitro aggregation and fibrillization of amyloid beta-protein." NEUROCHEMICAL RESEARCH FEB 1997, vol. 22, no. 2, February 1997 (1997-02), pages 227-232, XP002498010 ISSN: 0364-3190 * abstract * * page 228, paragraph "Thioflavin T Fluorescence Spectroscopy" *</p> <p>-----</p>	1-5,53,54	<p>INV. A61K31/00 A61K31/7004 A61K31/195 A61K31/197 A61K31/198 A61K39/395 A61K38/49 G01N33/53 C12N9/72 A61P9/10 A61P3/10 A61P7/04 A61P35/00 A61P31/00 A61P37/00 A61P25/28 A61P25/16</p>
X	<p>ELGHETANY M T ET AL: "METHODS FOR STAINING AMYLOID IN TISSUES A REVIEW" STAIN TECHNOLOGY, WILLIAMS AND WILKINS, BALTIMORE, US, vol. 63, no. 4, 1 January 1988 (1988-01-01), pages 201-212, XP008051786 ISSN: 0038-9153 * abstract * * page 201, line 1 - page 202, line 16 *</p> <p>-----</p>	7	<p>TECHNICAL FIELDS SEARCHED (IPC)</p> <p>A61K A61M G01N</p>
X	<p>KLUNK W E ET AL: "DEVELOPMENT OF SMALL MOLECULE PROBES FOR THE BETA-AMYLOID PROTEIN OF ALZHEIMER'S DISEASE" NEUROBIOLOGY OF AGING, TARRYTOWN, NY, US, vol. 15, no. 6, 1 January 1994 (1994-01-01), pages 691-698, XP000602786 ISSN: 0197-4580 * abstract * * paragraphs "Binding Assay to Synthetic Abeta(10-43)" and "Discussion" * * figure 7 *</p> <p>-----</p> <p style="text-align: center;">-/--</p>	7,8,53,54	
-The present search report has been drawn up for all claims			
9	Place of search The Hague	Date of completion of the search 1 October 2008	Examiner Adida, Anne
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>	

EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 08 15 3132

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	US 6 136 548 A (ANDERSON STEPHEN) 24 October 2000 (2000-10-24) * the whole document *		A61M1/36 A61P7/02 A61P29/00 A61P25/08 G01N33/68
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			TECHNICAL FIELDS SEARCHED (IPC)
----- -/--			
-The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 1 October 2008	Examiner Adida, Anne
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 08 15 3132

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	HUBBARD G B ET AL: "Spontaneous pancreatic islet amyloidosis in 40 baboons." JOURNAL OF MEDICAL PRIMATOLOGY APR 2002, vol. 31, no. 2, April 2002 (2002-04), pages 84-90, XP002498011 ISSN: 0047-2565 * abstract *	7,8	
A	----- US 5 750 349 A (SUZUKI NOBUHIRO [JP] ET AL) 12 May 1998 (1998-05-12) * the whole document * -----		
			TECHNICAL FIELDS SEARCHED (IPC)
-The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 1 October 2008	Examiner Adida, Anne
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EPO FORM 1503 03.02 (F04C01)



Application Number

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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

- Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
1-5, 7, 8 (partially), 6 (entirely) + 53-55 (partially)
- The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 08 15 3132

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-5, 7, 8 (partially), 6 (entirely) + 53-55 (partially)

Claims 1-5, 7, 8 (partially), 6 (entirely)
Method for detecting cross-beta structures using a compound capable of binding cross-beta structures and use of a cross-beta structure binding domain for determining the presence of plaque involved in a conformational disease, wherein the compound/domain is an antibody.

- 1.1. claims: 53-55 (partially)

A diagnostic device for carrying out a method according to any of the claims 1-5, wherein the compound/domain is an antibody.

2. claims: 1-5, 7, 8 (partially)

Method for detecting cross-beta structures using a compound capable of binding cross-beta structures and use of a cross-beta structure binding domain for determining the presence of plaque involved in a conformational disease, wherein the compound/domain is a tPA finger domain.

3. claims: 1-5, 7, 8 (partially)

Method for detecting cross-beta structures using a compound capable of binding cross-beta structures and use of a cross-beta structure binding domain for determining the presence of plaque involved in a conformational disease, wherein the compound/domain is a multiligand receptor for cross-beta structures.

4. claims: 9 (partially), 10-13 (entirely), 34 (entirely), 43 (partially), 49 (partially)

A method for modulating, which is increasing, extracellular protein degradation and/or protein clearance and its use in therapy or dialysis, comprising providing a compound capable of increasing cross-beta structure formation or a compound which is capable of stabilising cross-beta structure of said protein present in the circulation.

5. claims: 9 (partially), 16 (partially), 17-20 (entirely), 35-42 (entirely), 43 (partially), 44-45 (entirely), 47-48 (entirely), 49 (partially)



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number
EP 08 15 3132

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

A method for modulating, which is increasing, extracellular protein degradation and/or protein clearance and its use in therapy or dialysis, comprising providing a compound capable of increasing tPA-like activity or a compound capable of binding to a cross-beta structure or a compound capable of increasing or stabilising an interaction of a compound comprising a cross-beta structure and a compound comprising tPA-like activity.

6. claims: 9 (partially), 32 (entirely), 49 (partially)

A method for modulating extracellular protein degradation and/or protein clearance and its use in dialysis, comprising modulating an interaction of a compound comprising tPA-like activity and the substrate of said activity.

7. claims: 9 (partially), 33 (entirely), 49 (partially)

A method for modulating extracellular protein degradation and/or protein clearance and its use in dialysis, comprising modulating the activity of a receptor for cross-beta forming proteins.

8. claims: 9 (partially), 14-15 (entirely), 49 (partially)

A method for modulating, which is decreasing, extracellular protein degradation and/or protein clearance and its use in dialysis, comprising providing a compound capable of decreasing cross-beta structure formation of said protein present in the circulation.

9. claims: 9 (partially), 16 (partially), 21-25 (entirely), 46 (entirely), 49 (partially)

A method for modulating, which is decreasing, extracellular protein degradation and/or protein clearance and its use in dialysis, comprising providing a compound capable of decreasing tPA-like activity.

10. claims: 9 (partially), 26-31 (entirely), 49 (partially)



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number
EP 08 15 3132

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

A method for modulating, which is decreasing, extracellular protein degradation and/or protein clearance and its use in dialysis, comprising providing a compound capable of decreasing an interaction of a compound comprising a cross-beta structure and a compound comprising tPA-like activity.

11. claims: 50-52 (entirely)

A separation device for carrying out a method according to any of the claims 9-33 or 45-49.

12. claims: 53-55 (partially)

A diagnostic device for carrying out a method according to any of the claims 1-5, wherein the compound/domain is a tPA finger domain.

13. claims: 53-55 (partially)

A diagnostic device for carrying out a method according to any of the claims 1-5, wherein the compound/domain is a multiligand receptor for cross-beta structures.

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 08 15 3132

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

01-10-2008

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	包含淀粉样蛋白结合蛋白的交叉β结构和用于检测交叉β结构的方法，用于调节交叉β结构的原纤维形成和用于调节交叉β结构介导的毒性		
公开(公告)号	EP1978362A3	公开(公告)日	2009-02-11
申请号	EP2008153132	申请日	2003-07-08
申请(专利权)人(译)	交叉βBIOSCIENCES B.V.		
当前申请(专利权)人(译)	交叉βBIOSCIENCES B.V.		
[标]发明人	GEBBINK MARTIJN FRANS BEN GERARD BOUMA BAREND KRANENBURG ONNO WOUTER KROON LOUISE MARIA JOHANNA		
发明人	GEBBINK, MARTIJN FRANS BEN GERARD BOUMA, BAREND KRANENBURG, ONNO WOUTER KROON, LOUISE MARIA JOHANNA		
IPC分类号	A61K31/00 A61K31/7004 A61K31/195 A61K31/197 A61K31/198 A61K39/395 A61K38/49 G01N33/53 C12N9/72 A61P9/10 A61P3/10 A61P7/04 A61P35/00 A61P31/00 A61P37/00 A61P25/28 A61P25/16 A61M1/36 A61P7/02 A61P29/00 A61P25/08 G01N33/68 G01N33/50 A61K38/00 A61K45/00 A61P25 /00 A61P31/04 A61P37/06 G01N33/15		
CPC分类号	A61K31/00 A61K31/195 A61K31/197 A61K31/198 A61K31/7004 A61K38/49 A61P3/00 A61P3/10 A61P19/00 A61P19/02 A61P25/00 A61P25/08 A61P25/16 A61P25/28 A61P29/00 A61P31/00 A61P31 /04 A61P35/00 C07K16/18 C07K2319/23 C12N9/6459 C12Y304/21069 G01N33/6854 G01N33/6896 G01N2333/9726 G01N2800/042 G01N2800/2821		
优先权	2002077797 2002-07-09 EP		
其他公开文献	EP1978362A2		
外部链接	Espacenet		

摘要(译)

本发明涉及通过调节交叉β结构形成或组织纤溶酶原激活物样活性调节细胞外蛋白质降解和/或蛋白质清除，通过调节交叉β结构治疗淀粉样变性疾病和诊断淀粉样变性类型通过可视化交叉β结构的疾病。

				Application Number EP 08 15 3132	
DOCUMENTS CONSIDERED TO BE RELEVANT					
Category	Classification of documents with translation, where appropriate, of relevant passages.	Relevant to claim	Classification of the APPLICATION (IPC)		
X	CHAURAN A ET AL: "Media from rhabdomyosarcoma and neuroblastoma cell cultures stimulate in vitro aggregation and fibrillation of amyloid beta-protein." NEUROCHEMICAL RESEARCH FEB 1997, vol. 22, no. 2, February 1997 (1997-02), pages 227-232, XP002498010 ISSN: 0364-2190 * abstract * * page 228, paragraph "Thioflavin T Fluorescence Spectroscopy" *	1-5, 53, 54	A61K31/00 A61K31/7004 A61K31/195 A61K31/197 A61K31/198 A61K39/395 A61K38/49 G01N33/53 C12N9/72 A61P9/10 A61P37/00		
X	ELGHETANY M T ET AL: "METHODS FOR STAINING AMYLOID IN TISSUES A REVIEW" STAIN TECHNOLOGY, WILLIAMS AND WILKINS, BALTIMORE, US, vol. 63, no. 4, 1 January 1988 (1988-01-01), pages 201-212, XP008051786 ISSN: 0038-9153 * abstract * * page 201, line 1 - page 202, line 16 *	7	A61P35/00 A61P31/00 A61P37/00 A61P25/28 A61P25/16		
X	KLUNG W E ET AL: "DEVELOPMENT OF SMALL MOLECULE PROBES FOR THE BETA-AMYLOID PROTEIN OF ALZHEIMER'S DISEASE" NEUROBIOLOGY OF AGING, TARRYTOWN, NY, US, vol. 15, no. 6, 1 January 1994 (1994-01-01), pages 691-699, XP00602786 ISSN: 0197-4580 * abstract * * paragraphs "Binding Assay to Synthetic Aβ(1-42)" and "Discussion" * * figure 33 * *-----* *-----* *-----*	7, 8, 53, 54	A61K A61M G01N		
The present search report has been drawn up for all claims					
Page of search: 9 The Hague CATEGORY OF CITED DOCUMENTS C: particularly relevant if taken alone D: particularly relevant if considered with another document A: technological background B: intermediate documents		Date of completion of the search: 1 October 2008 Adida, Anne I: theory or principle underlying the invention J: prior art documents (EP, US, national or other) K: the filing date L: document cited for other reasons M: inventor of the same patent family, corresponding documents			