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(54) Title: PEPTIDES THAT BIND TO ATHEROSCLEROTIC LESIONS

(57) Abstract: The present invention provides peptides that selectively bind to mammalian atherosclerotic lesions. The present invention also provides methods for *in vivo* identification of peptides capable of binding to biomolecules as well as methods for identifying the targets of such binding moieties. Methods to diagnose or treat pathologic conditions that involve atherosclerotic lesions are also provided by the invention that involve administering to a mammal a peptide attached to a reporter molecule or a therapeutic agent, respectively.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K4/00 C07K7/06 C07K19/00 A61K38/00 C07H21/00
G01N33/68 //A61K38/03,A61K38/08,C07C233/00

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)
IPC 7 C07K A61K C07H G01N

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 practical, search terms used)
EPO-Internal, SEQUENCE SEARCH, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 827 516 A (VIGNALI DARIO A A ET AL) 27 October 1998 (1998-10-27) column 123, paragraph 245 -column 126, paragraph 246; table 8 ---	7,10
A	LUU T N ET AL: "Calcitonin gene-related peptide in healthy and atheromatous human epicardial coronary arteries: Function and receptor characterization." JOURNAL OF VASCULAR RESEARCH, vol. 32, no. 2, 1995, pages 93-99, XP009010613 ISSN: 1018-1172 abstract page 98, column 1, line 23 - line 26 --- -/--	7-9,11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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	Date of mailing of the international search report
16 September 2003	02.10.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jenn, T

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FRANK, RONALD: "Spot-synthesis: an easy technique for the positionally addressable, parallel chemical synthesis on a membrane support" TETRAHEDRON, vol. 48, no. 42, 16 October 1992 (1992-10-16), pages 9217-9232, XP000353580 Oxford, GB, ISSN: 0040-4020 figure 3 ---	1,2,5
X	WO 94 29333 A (BLACK CHRISTOPHER D V ;BURROUGHS WELLCOME CO (US); SNOW ROBERT ALL) 22 December 1994 (1994-12-22) page 47, line 1 - line 21 ---	1,2,5
X	WO 01 32853 A (INST APPLIED BIOMEDICINE) 10 May 2001 (2001-05-10) page 29, column 3, paragraph 5 ---	1-5,10, 12
E	WO 02 094854 A (BRIGHAM & WOMENS HOSPITAL; BETH ISRAEL HOSPITAL (US)) 28 November 2002 (2002-11-28) claim 1 ---	1,2,4,5
A	FAVRE ET AL.: "STRUCTURAL MIMICRY OF CANONICAL CONFORMATIONS IN ANTIBODY HYPERVARIABLE LOOPS USING CYCLIC PEPTIDES CONTAINING A HETEROCHIRAL DIPROLINE TEMPLATE" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 121, no. 12, 31 March 1999 (1999-03-31), pages 2679-2685, XP002137023 ISSN: 0002-7863 page 2681, column 1; example 6 page 2679, column 1, line 1 - line 3 ---	1-6
A	WO 94 13327 A (BLACK CHRISTOPHER D V ;STERLING WINTHROP INC (US); SNOW ROBERT A) 23 June 1994 (1994-06-23) page 42; example 11 ---	1-6
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A	WO 00 51971 A (DOW ROBERT LEE ;PFIZER PROD INC (US); CHIANG YUAN CHING PHOEBE (US) 8 September 2000 (2000-09-08) cited in the application the whole document -----	48

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

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 fee, this Authority did not invite payment of any additional fee.

3. [X] 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.:

1-6,7-17(part),22-49(part)

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.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 27-32 are directed to a diagnostic method practised on the human/animal body, the search could only be carried out and based on the alleged effects of the compound/composition.

Although claims 14 and 33-49 are directed to a method of treatment of the human/animal body, the search could only be carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

1. Present claims 1-6 relate to an extremely large number of possible compounds/products. In fact, the claims contain so many variables that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method/apparatus by reference to a result to be achieved ("can bind with specificity to a biomolecule or tissue in vivo"). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search could only be carried out for those parts of the application which do appear to be clear (and/or concise), namely an isolated peptide of formula APGPSK (SEQ ID NO:462), which is the only peptide according to claim 1 for which a sequence listing is provided.

2. Present claims 7-9 relate to a product/compound defined by reference to a desirable characteristic or property, namely "which is capable of binding to an atherosclerotic lesion in a mammal".
Said claims lack clarity (Article 6 PCT): an attempt is made to define the product/compound by reference to a result to be achieved. This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search can be carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds comprising SEQ ID NO:2N (N is an integer of 1 to 237).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 7-17(in part), 22-49(in part)

Invention 1:

An isolated peptide comprising SEQ ID NO:2 and which is capable of binding to an atherosclerotic lesion in a mammal;
Said peptide conjugated to a therapeutic agent or a reporter molecule;
The use of said peptide for the manufacture of a medicament for the treatment of atherosclerosis in a mammal;
A pharmaceutical composition comprising said peptide;
The use of said pharmaceutical composition for the treatment of atherosclerosis in a mammal;
An isolated nucleic acid encoding said peptide;
An isolated nucleic acid comprising SEQ ID NO:1;
An isolated nucleic acid capable of hybridizing the isolated nucleic acid encoding said peptide;
A method of identifying a protein bound by said peptide;
The use of said peptide conjugated to a reporter molecule in a method of identifying a location/the severity of an atherosclerotic lesion in a mammal;
The use of said peptide conjugated to a therapeutic agent for the manufacture of a medicament for the treatment of atherosclerosis in a mammal or for preventing heart attack in a mammal.

2. Claims: 7-17(in part), 22-49(in part)

Inventions 2-112:

An isolated peptide comprising one of SEQ ID NO:X (wherein X=4n+2 and n is an integer from 1 to 111) and which is capable of binding to an atherosclerotic lesion in a mammal;
Said peptide conjugated to a therapeutic agent or a reporter molecule;
The use of said peptide for the manufacture of a medicament for the treatment of atherosclerosis in a mammal;
A pharmaceutical composition comprising said peptide;
The use of said pharmaceutical composition for the treatment of atherosclerosis in a mammal;
An isolated nucleic acid encoding said peptide;
An isolated nucleic acid comprising SEQ ID NO:Z (wherein Z=X-1);
An isolated nucleic acid capable of hybridizing the isolated nucleic acid encoding said peptide;
A method of identifying a protein bound by said peptide;
The use of said peptide conjugated to a reporter molecule in a method of identifying a location/the severity of an atherosclerotic lesion in a mammal;
The use of said peptide conjugated to a therapeutic agent

for the manufacture of a medicament for the treatment of atherosclerosis in a mammal or for preventing heart attack in a mammal.

3. Claims: 7-17(in part), 22-49(in part)

Inventions 113-124:

An isolated peptide comprising one of SEQ ID NO:Y (wherein Y=2m and m is an integer from 225 to 237 with the proviso that Y is not 462) and which is capable of binding to an atherosclerotic lesion in a mammal;
Said peptide conjugated to a therapeutic agent or a reporter molecule;
The use of said peptide for the manufacture of a medicament for the treatment of atherosclerosis in a mammal;
A pharmaceutical composition comprising said peptide;
The use of said pharmaceutical composition for the treatment of atherosclerosis in a mammal;
An isolated nucleic acid encoding said peptide;
An isolated nucleic acid capable of hybridizing the isolated nucleic acid encoding said peptide;
A method of identifying a protein bound by said peptide;
The use of said peptide conjugated to a reporter molecule in a method of identifying a location/the severity of an atherosclerotic lesion in a mammal;
The use of said peptide conjugated to a therapeutic agent for the manufacture of a medicament for the treatment of atherosclerosis in a mammal or for preventing heart attack in a mammal.

4. Claims: 1-6(full), 7-17(in part), 22-49(in part)

Invention 125:

An isolated peptide having any one of formulae I-IV as defined in claim 1 and which is capable of binding with specificity to a biomolecule or tissue in vivo (Obs: SEQ ID NO:462 is of formula I as defined in claim 1);
Said peptide conjugated to a therapeutic agent or a reporter molecule;
The use of said peptide for the manufacture of a medicament for the treatment of atherosclerosis in a mammal;
A pharmaceutical composition comprising said peptide;
The use of said pharmaceutical composition for the treatment of atherosclerosis in a mammal;
An isolated nucleic acid encoding said peptide;
An isolated nucleic acid comprising SEQ ID NO:Z (wherein Z=X-1);
An isolated nucleic acid capable of hybridizing the isolated nucleic acid encoding said peptide;
A method of identifying a protein bound by said peptide;
The use of said peptide conjugated to a reporter molecule

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

in a method of identifying a location/the severity of an atherosclerotic lesion in a mammal;
The use of said peptide conjugated to a therapeutic agent for the manufacture of a medicament for the treatment of atherosclerosis in a mammal or for preventing heart attack in a mammal.

5. Claims: 18-19(full)

Invention 126:

A method of identifying a peptide capable of binding to a mammalian vascular tissue

6. Claims: 20-21(full)

Invention 127:

A method of identifying a peptide capable of binding to an atherosclerotic lesion in a mammal.

7. Claims: 9(part), 22-24(in part), 27-30(in part), 33-43(in part), 46-49(in part)

Invention 128:

A method of identifying a protein bound by a peptide, wherein the peptide is different to the peptides of inventions 1-126;
The use of said peptide conjugated to a reporter molecule in a method of identifying a location/the severity of an atherosclerotic lesion in a mammal;
The use of said peptide conjugated to a therapeutic agent for the manufacture of a medicament for the treatment of atherosclerosis in a mammal or for preventing heart attack in a mammal.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/08942

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