Title: PEPTIDES ENHANCING CEH ACTIVITY OR ACAT INHIBITORY ACTIVITY. PHARMACEUTICAL COMPOSITIONS COMPRISING THESE PEPTIDES AND THEIR USE IN THE TREATMENT OF ATHEROSCLEROSIS

Abstract: Peptides and mimetics of selected domains of mammalian serum amyloid A isoform 2.1 (SAA2.1) and compounds and compositions thereof are provided that enhance the effect on macrophage cholesterol ester hydrolyse activity and/or inhibit acyl CoA:cholesterol acyl transferase activity. Methods of using these compositions in the treatment and/or prevention of atherosclerosis as well as coronary heart disease and cardiovascular disease are also provided.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7  C07K14/47  C07K7/08  A61K38/10  A61K38/17  A61K47/48

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

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, EMBASE, Sequence Search, WPI Data, BIOSIS, MEDLINE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of box C.

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 document 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.

*P 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.

**X 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.

*Y document member of the same patent family.

Date of the actual completion of the international search: 18 February 2005

Date of mailing of the international search report: 31.03.05

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-5016

Authorized officer

Döpfer, K-P

Form PCT/ISA/210 (second sheet) (January 2004)
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<td>X</td>
<td>WO 01/21188 A (OPPENHEIM JOOST J; GONG WANG HUA (US); US HEALTH (US); GAO JI LIANG (US)) 29 March 2001 (2001-03-29)</td>
<td>1-9</td>
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<td>LINDHORST E ET AL: &quot;Acute inflammation, acute phase serum amyloid A and cholesterol metabolism in the mouse&quot; 1997, BIOCHIMICA ET BIOPHYSICA ACTA - PROTEIN STRUCTURE AND MOLECULAR ENZYMOLGY 1997 NETHERLANDS, VOL. 1339, NR. 1, PAGE(S) 143-154, XP004281641 the whole document</td>
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<td>Y</td>
<td>WO 96/38166 A (UNIV KINGSTON) 5 December 1996 (1996-12-05)</td>
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<td>1,6</td>
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</table>
## INTERNATIONAL SEARCH REPORT

**Box 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. **X** Claims Nos.: 11
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Although claims 22-40 (60-78, 89-105 as not yet searched further non-unitarian subject-matter) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: 11
   - 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 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 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.:
   - 1-10, 12, 18-23, 25-29, 31-40 (all partially)

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.
Continuation of Box II.1

Although claims 22-40 (60-78, 89-105 as not yet searched further
non-unitarian subject-matter) are directed to a method of treatment of
the human/animal body, the search has been carried out and based on the
alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 11

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by
therapy

Continuation of Box II.2

Claims Nos.: 11

The subject-matter claimed addresses peptides, variants, portions and
mimetics thereof. This leads to an indefinite number of compounds
claimed whereas enabling support can be found for an only very limited
number of peptides in the sense of Article 5 PCT. The term mimetic as "a
small organic molecule" in claim 11 renders the claim so unclear that a
meaningful search is impossible. The usual meaning of a peptide
mimetic, i.e. the modification of a peptide bond to e.g. NH-CH2- or
substitution by a phosph(on)ate group has been taken into consideration.
The terms variants and portions are not well defined either and the
skilled person is let alone to which extent variations and truncations
can be performed without losing the desired activity.
The search is therefore to be restricted to the peptides explicitly
disclosed and their conservative mutants.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase
before the EPO, the applicant is reminded that a search may be carried
out during examination before the EPO (see EPO Guideline C-VI, 8.5),
should the problems which led to the Article 17(2) declaration be
overcome.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-12, 18-23, 25-29, 31-40 (all part)

Peptides of the general sequence according to SEQ ID No 29 or mimetics thereof having stimulating effect on the activity of the cholesterol ester hydrolase, pharmaceutical compositions comprising these peptides and their therapeutic use

Inventions 2-53: Claims 1-12, 18-23, 25-29, 31-40 (all part)

Peptides of SEQ ID Nos: 4, 8, 9, 10, 11, 12, 24, 25 or 26 with sequence identities of at least 80%, 90%, 95%, 99%, or 100% or mimetics thereof having stimulating effect on the activity of the cholesterol ester hydrolase, pharmaceutical compositions comprising these peptides and their therapeutic use

Invention 54: Claims 13-17 (complete), 18-23, 25-29, 31-40 (all part)

Conjugates of the formula Y-Z (Y: peptide which enhances cholesterol ester hydrolase activity) the moiety Z linked to Y enhances the performance of Y

Invention 55: Claims 41-78, 106

Peptides inhibiting the acyl CoA:cholesterol acyl transferase comprising the formula (X)1-2FX1FX2X3X4X5FX6; conjugates Y-Z and pharmaceutical compositions comprising these peptides or conjugates and their therapeutic use

Invention 56: Claims 79-105

Pharmaceutical compositions comprising a peptide which enhances cholesterol ester hydrolase activity and a peptide which inhibits acyl CoA: cholesterol acyl transferase and their therapeutic use
<table>
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