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— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:
20 January 2011

(54) Title: VARIANTS OF C-TYPE NATRIURETIC PEPTIDE

(57) Abstract: The present disclosure provides variants of C-type natriuretic peptide (CNP), pharmaceutical compositions comprising CNP variants, and methods of making CNP variants. The CNP variants are useful as therapeutic agents for the treatment of diseases responsive to CNP, including but not limited to bone-related disorders, such as skeletal dysplasias (e.g., achondroplasia), and vascular smooth muscle disorders (e.g., restenosis and arteriosclerosis).
**A. CLASSIFICATION OF SUBJECT MATTER**
IPC(8): A61K 38/00; G01N 33/53 (2010.01)
USPC: 514/12; 530/324; 435/7.1
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(8): A61K 38/00; G01N 33/53 (2010.01)
USPC: 514/12; 530/324; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/7.5

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (PGPB, USPT, EPAB, JPAB): natriuretic, CNP, variant, bone, skeletal dysplasia, cartilage, osteoarthritis, achondroplasia, dwarfism, kidney, dysplasia, cGMP, collagen type, osteocalcin, PCNA, biomarker
--- Please see continuation on attached additional sheet ---

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>US 2007/0197434 A1 (NAKAO et al.) 23 August 2007 (23.08.2007), abstract; para [0089], [0116], [0117], [0131], [0132], [0164], [0165], [0169], [0170], [0181]; Table 1.</td>
<td>51-55</td>
</tr>
<tr>
<td>A</td>
<td>US 2007/0292966 A1 (PRICKETT et al.) 20 December 2007 (20.12.2007), abstract; para [0002], [0010], [0069], [0070], [0071], [0120], [0126], [0161]</td>
<td>51-55</td>
</tr>
<tr>
<td>A</td>
<td>EP 0 497 368 A1 (TANAKA et al.) 5 August 1992 (05.08.1992)</td>
<td>1, 51-55</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* 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 application or patent 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: 11 November 2010 (11.11.2010)
Date of mailing of the international search report: 24 Nov 2010

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Form PCT/ISA/210 (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

Box No. 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. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ 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:

3. ☒ Claims Nos.: 8-13,18-36, 43-50, 56-57
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. 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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: claim 1, drawn to a variant of C-type natriuretic peptide. The first invention encompasses a CNP of SEQ ID NO:145. Due to the number of sequences in this application, an additional invention(s) of Group I+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art.

--- Please see continuation on attached 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 additional fees, this Authority did not invite payment of additional fees.

3. ☒ 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.:
   claim 1, restricted to SEQ ID NO: 145; claims 51-55

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

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
Continuation of Box (III): Lack of Unity

Group II, claims 2-7, drawn to a pharmaceutical composition comprising a CNP variant, and a pharmaceutically acceptable excipient, carrier or diluent.

Group III, claims 14-17, 37-42, drawn to a method for recombinant production of a CNP variant.

Group IV, claims 51-55, drawn to a method comprising assaying the level of at least one bone- or cartilage-associated biomarker in a biological sample from a subject that has been administered a CNP peptide or variant.

The inventions listed as Groups I+ through IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I+ and III-IV do not include the inventive concept of a pharmaceutical composition comprising an excipient, carrier or diluent, as required by Group II.

The inventions of Groups I+, II and IV do not include the inventive concept of producing a CNP variant, as required by Group III.

The inventions of Groups I+ through III do not include the inventive concept of a method comprising assaying the level of at least one bone- or cartilage-associated biomarker in a biological sample from a subject that has been administered a CNP peptide or variant, as required by Group IV.

The inventions of Group I+ through IV share the technical feature of a CNP variant peptide. However, this shared technical feature does not represent a contribution over prior art. Specifically, EP0497368-A1 to Tanaka, et al. (05-AUG-1992) discloses a CNP variant peptide (Abstract, CNP analog). As said CNP variant peptide was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another technical feature of the inventions listed as Group I+ is the specific amino acid sequence recited therein. The inventions do not share a special technical feature, because Tanaka, et al. discloses a common structural core of said amino acid sequences, i.e. the claimed SEQ ID NO:178 (Tanaka, et al., pg 7, Table 2, compound 23). Without a shared special technical feature, the inventions lack unity with one another.

In addition, SEQ ID NO: 145-160, 179, 185-186, 190 share a bigger common structural core, specifically, aa 3-39 of SEQ ID NO:145. However, this shared technical feature does not represent a contribution over prior art. Specifically, US 2004/0009650 A1 to Moll, et al. discloses a polypeptide comprising said bigger common structural core, i.e. aa 3-39 of SEQ ID NO:145 (Moll, et al., aa 17-53 of SEQ ID NO 87). As said bigger common structural core was known at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I+ through IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

NOTE re item 4:
Claims 8-13, 18-36, 43-50, 56-57 are not drafted in accordance with the second and third sentences of Rule 6.4 (a). These claims are improper multiple dependent claims.
Continuation of (B): Fields Searched - Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Google Scholar: CNP natriuretic variant bone cartilage

est@cenet: Bi marin, CNP, natriuretic, bone, skeletal