Title: STABILIZED POLYPEPTIDES AND USES THEREOF

Abstract: The present invention provides inventive stabilized STAT polypeptides, pharmaceutical compositions thereof, and methods of making and using inventive stabilized STAT polypeptides. The provided polypeptides may have good cell-penetrating capability. In certain embodiments, the provided polypeptides are capable of binding a target and/or disrupting native or aberrant protein/protein interactions. In certain embodiments, the provided polypeptides are capable of disrupting STAT protein homodimerization. The present invention provides pharmaceutical compositions comprising a polypeptide as described herein, and optionally a pharmaceutically acceptable carrier. In one aspect, the present invention provides a method of treating a disorder in a subject in need thereof, comprising administering an effective amount of a provided polypeptide, or pharmaceutical composition thereof, to the subject.
(15) Information about Correction:

Previous Correction:

see Notice of 7 May 2015
A. CLASSIFICATION OF SUBJECT MATTER
   IPC(8) - C07K1 4/435 (2015.01)
   CPC - C07K1 4/435 (2015.04)

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) - C07K 14/47, 14/435 (2015.01)
   CPC - A61K38/00, 38/1709, 47/48338, C07K 1/13, 14/001, 14/47, 14/435, 2319/00; C12N 2501/60 (2015.04)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
   CPC - A61K38/00, 38/1709, 47/48338, C07K 1/13, 14/001, 14/47, 14/435, 2319/00, C12N 2501/60 (2015.04) (keyword delimited)
   USPC - 530/324, 345

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

Search terms used: polypeptide helix hairpin STAT3 SH2

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>X</td>
<td>US 201 1/0144306 A1 (VERDINE et al) 16 June 201 1 (16.06.201 1) entire document</td>
<td>1, 2</td>
</tr>
<tr>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>US 2012/0082636 A1 (WALENSKY et al) 05 April 201 2 (05.04.201 2) entire document</td>
<td>1, 2, 22-24</td>
</tr>
<tr>
<td>A</td>
<td>US 2006/014871 S A1 (TWERALDY) 06 July 2006 (06.07.200 6) entire document</td>
<td>22-24</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
"S" document member of the same patent family

Date of the actual completion of the international search
02 April 2015

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of mailing of the international search report
23 APR 2015

Authorized officer:
Blaine R. Copenheaver
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774
Box No. 1  Nucleotide and/or amino acid sequence(s) (Continuation item 1 of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:
   a. (means)
      ♦ on paper
      • in electronic form
   b. (time)
      ❌ in the international application as filed
      ❌ together with the international application in electronic form
      □ subsequently to this Authority for the purposes of search

2. ❌ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs:1-20 were searched.
### 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:

   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:

See Extra 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.:

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.: 1, 2, and 22-24 restricted to a polypeptide and a method of making the same, wherein the polypeptide comprises a stabilized alpha helix and a stabilized beta hairpin, wherein the polypeptide is selected to be STAT3 SH2 peptide of SEQ ID NO:1.

### 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.
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 need to be paid.

Group I+: claims 1-3, 22-25, 29-32, 62-64, and 67-70 are drawn to a polypeptide comprising a stabilized alpha helix and at least one other stabilized structural motif that is not an alpha helix, and a method of making the same.

The first invention of Group I+ is restricted to a polypeptide and a method of making the same, wherein the polypeptide comprises a stabilized alpha helix and a stabilized beta hairpin, wherein the polypeptide is selected to be SABS1 peptide, wherein SABS1 is understood to be SEQ ID NO:1 comprising amino acid substitutions S2S5 and E6E6 wherein amino acid S5 is the structure represented as S5 in Figure 5 of the instant application, further wherein the alpha helix comprises two cross-linked amino acids at position 2 and 6. Additional polypeptides with specific SEQ ID NO and crosslinks will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group.

The inventions listed in Groups I+ 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 Groups I+ formulas do not share a significant structural element, requiring the selection of alternatives for the polypeptide, where “the peptide is a STAT3 SH2 peptide or SABS1, SABS2, SABS3, SABS4, SABS5, SABS6, SABS7,” “a polypeptide of Formula I (see structure of claim 29),” and “a polypeptide of one of the following formulae (see structures of claim 30).”

The Groups I+ share the technical features of a polypeptide, a method of making a polypeptide having a stabilized alpha helix and a stabilized beta hairpin, and a polypeptide having a stabilized alpha helix and a stabilized beta hairpin, wherein the alpha helix has two cross-linked amino acids, and a STAT peptide or a derivative thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2011/0144306 A1 to Verdine et al. discloses a polypeptide (the present invention provides technology for making large (e.g., greater than 50 amino acids), semi-synthetic, stapled or stitched proteins, Abstract), a method of making a polypeptide having a stabilized alpha helix (a method of preparing a stapled or stitched protein, Para. [0145]: One or both of the targeting domain and effector domain of the bifunctional peptide are stapled or stitched to stabilize the conformation of the peptide, Para. [0010]; Stapling provides a constraint on a secondary structure, such as an alpha-helical structure, Para. [0014]) and a stabilized beta hairpin (in certain embodiments, the stapled or stitched secondary structural motif is a beta-hairpin, Para. [0194]), wherein the alpha helix has two cross-linked amino acids (“stitched” peptide, as used herein, is a stapled peptide comprising more than one, that is multiple (two, three, four, five, six, etc.) cross-links (i.e., staples), Para. [0015]), and a STAT peptide or a derivative thereof (activator of transcription-6 (STAT-6), Para. [0004]; STAT-6, Para. [0222]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.