



KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

24 December 2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/029318

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C07K 14/47 (2014.01) USPC - 530/333 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; C07K 14/00, 14/435, 14/46, 14/47 (2014.01) USPC - 514/19.2, 19.3; 530/300, 317, 333 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched CPC - A61K 38/00; C07K 14/435, 14/46, 14/47, 14/4747 (2014.09) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Google Patents, PubMed, Google		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,789,201 A (GUASTELLA) 04 August 1998 (04.08.1998) entire document	1-6, 47
A	LABELLE et al. "A stapled BIM peptide overcomes apoptotic resistance in hematologic cancers," The Journal of Clinical Investigation, 01 June 2012 (01.06.2012), Vol. 122, No. 6, Pgs. 2018-2031. entire document	1-6, 47
A	US 7,723,469 B2 (WALENSKY et al) 25 May 2010 (25.05.2010) entire document	1-6, 47
A	US 2010/0273704 A1 (KORSMEYER et al) 28 October 2010 (28.10.2010) entire document	1-6, 47
A	US 2012/0270800 A1 (VERDINE et al) 25 October 2012 (25.10.2012) entire document	1-6, 47
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* 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 03 October 2014		Date of mailing of the international search report 29 OCT 2014
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		Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/029318

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.: 21-24, 29-46, 48, 49
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.:
1-6 and 47 to the extent that they read on SEQ ID NO:1 comprising an internal staple and/or an internal stitch at amino acid positions 5 and 9.

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 1-20, 25-28, and 47 are drawn to an internally cross-linked polypeptide.

The first invention of Group I+ is restricted to an internally cross-linked polypeptide, wherein the internally cross-linked polypeptide is selected to be EIVMKYIHYKLSQRGYEWDA (SEQ ID NO: 1), wherein the side chains of amino acid positions 5 and 9 of SEQ ID NO:1 are replaced by an internal staple and/or an internal stitch. It is believed that claims 1-6 and 47 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:1 comprising an internal staple and/or an internal stitch at amino acid positions 5 and 9.

Applicant is invited to elect additional internally cross-linked polypeptides with specified SEQ ID NO and/or amino acid positions comprising an internal staple and/or an internal stitch within a specified SEQ ID NO to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an internally cross-linked polypeptide, wherein the internally cross-linked polypeptide is selected to be EIVMKYIHYKLSQRGYEWDA (SEQ ID NO: 1), wherein the side chains of amino acid positions 13 and 17 of SEQ ID NO:1 are replaced by an internal staple and/or an internal stitch. Additional internally cross-linked polypeptides with specified SEQ ID NO and/or amino acid positions comprising an internal staple and/or an internal stitch within a specified SEQ ID NO 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. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

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 internally cross-linked polypeptide and amino acid positions comprising an internal staple and/or an internal stitch, where "an internally cross-linked polypeptide comprising between 15 to 24 contiguous amino acids of the amino acid sequence

A0B0C0D0E0F0G0H0I0J0K0L0M0N0O0P0Q0R0S0T0 U0V0W0X0 wherein: A0 is Asn, or a conservative amino acid substitution thereof, B0 is Arg or Cys, or a conservative amino acid substitution thereof, C0 is Glu or Ala, or a conservative amino acid substitution thereof, D0 is Ile, Ala, or selenocysteine, or a conservative amino acid substitution thereof, E0 is Val or Ala, or a conservative amino acid substitution thereof, F0 is Met, Asp, Asn, Ala, or Cys, or selenocysteine, or a conservative amino acid substitution thereof, G0 is Lys, Ala, or Asp, or a conservative amino acid substitution thereof, H0 is Tyr or Ala, or a conservative amino acid substitution thereof, I0 is Ile, Ala, or selenocysteine, or a conservative amino acid substitution thereof, J0 is His, Ala, or selenocysteine, or a conservative amino acid substitution thereof, K0 is Tyr or Ala, or a conservative amino acid substitution thereof, L0 is Lys, or a conservative amino acid substitution thereof, M0 is Leu or Ala, or a conservative amino acid substitution thereof, N0 is Ser or Ala, or a conservative amino acid substitution thereof, O0 is Gin, or a conservative amino acid substitution thereof, P0 is Arg, Ala, or Glu, or a conservative amino acid substitution thereof, Q0 is Gly, Ala, or Glu, or a conservative amino acid substitution thereof, R0 is Tyr, Ala, Arg, or selenocysteine, or a conservative amino acid substitution thereof, S0 is Glu, or a conservative amino acid substitution thereof, T0 is Trp, Ala, Arg, or selenocysteine, or a conservative amino acid substitution thereof, U0 is Asp or Ala, or a conservative amino acid substitution thereof, V0 is Ala or Glu, or a conservative amino acid substitution thereof, W0 is Gly or Cys, or a conservative amino acid substitution thereof, and X0 is Asp, or a conservative amino acid substitution thereof" and "the side chains of two amino acids separated by two to six amino acids are replaced by an internal staple; the side chains of three amino acids are replaced by internal staples and/or an internal stitch; the side chains of four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches; or the side chains of at least four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches".

The Groups I+ share the technical features of an internally cross-linked polypeptide comprising the amino acid sequence of EIVMKYIHYKLSQRGYEWDA (SEQ ID NO:1); the amino acid sequence of RELVVDFLSYKLSQKGYWSWSQF (SEQ ID NO:2); and the amino acid sequence of ALVADFGYKLRQKGYVCGA (SEQ ID NO:3), wherein the side chains of two amino acids of the internally cross-linked polypeptide are separated by two to six amino acids are replaced by an internal staple; the side chains of three amino acids are replaced by internal staples and/or an internal stitch; the side chains of four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches; or the side chains of at least four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches. However, these shared technical features do not represent a contribution over the prior art.

US 5,789,201 A to Guastella discloses a BCL-2 polypeptide comprising the amino acid sequence of EIVMKYIHYKLSQRGYEWDA (SEQ ID NO:1) (human bcl-2, SEQ ID NO:11, Col. 3, Lns. 22-23; where SEQ ID NO:11 of Guastella comprises SEQ ID NO:1 of the instant application) and the amino acid sequence of ALVADFGYKLRQKGYVCGA (SEQ ID NO:3) (SEQ ID NO:5; where SEQ ID NO:5 of Guastella comprises SEQ ID NO:3 of the instant application); and a BCL-XL polypeptide comprising the amino acid sequence of RELVVDFLSYKLSQKGYWSWSQF (SEQ ID NO:2) (Bcl-XL, SEQ ID NO:16; where SEQ ID NO:15 of Guastella comprises SEQ ID NO:2 of the instant application).

"A stapled BIM peptide overcomes apoptotic resistance in hematologic cancers" to LaBelle et al. discloses an internally cross-linked BCL-2 polypeptide (a stapled BCL-2-interacting mediator of cell death (BIM) BH3 helix that contains an i, i+4 all-hydrocarbon crosslink spanning positions 154 and 158, Pg. 2018, right-hand column, first full paragraph) comprising wherein the side chains of two amino acids of the internally cross-linked polypeptide are separated by two to six amino acids are replaced by an internal staple; the side chains of three amino acids are replaced by internal staples and/or an internal stitch; the side chains of four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches; or the side chains of at least four amino acids are replaced by internal staples, internal stiches, or a combination of internal staples and stiches (a stapled BCL-2-interacting mediator of cell death (BIM) BH3 helix that contains an i, i+4 all-hydrocarbon crosslink spanning positions 154 and 158, Pg. 2018, right-hand column, first full paragraph; see also Fig. 1A, where amino acid side chains of Arg and Glu of BIM BH3 have been replaced by the non-natural staple forming amino acid, see Fig. 1A and caption).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the structure of the BCL-2 family polypeptides of Guastella with an internal staple as taught by LaBelle as a staple introduced into the alpha helical polypeptide chain helps to maintain the peptide in a helical conformation, which is thought to convey higher affinity for its target, as well as greater stability and perhaps cell penetration.

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