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A61K 38/16 (2006.01) C07K 14/435 (2006.01)
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EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,
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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
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(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declarations under Rule 4.17:

[Continued on next page]

(54) **Title:** COMPOSITIONS AND METHODS UTILIZING FIBRIN BETA CHAIN FRAGMENTS OF THE BBETA CHAIN OF FIBRINOGEN

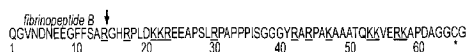


FIG. 1A

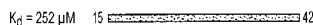


FIG. 1B

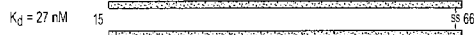


FIG. 1C

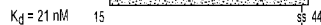


FIG. 1D

(57) **Abstract:** A composition including a peptide sequence of the formula βX1-X2, the peptide sequence corresponding to an amino acid sequence of a fibrin beta chain fragment of a Bbeta chain of fibrinogen, wherein X1 represents an N-terminal end of the peptide sequence, and X2 represents a C-terminal end of the peptide sequence, wherein the peptide sequence includes additional amino acids between X1 and X2, wherein the peptide sequence may contain a non-naturally occurring amino acid residue, wherein the peptide sequence is other than a wild-type β15-42 monomer sequence per se, and wherein the peptide sequence is other than (β15-66)₂ dimer having two chains with each chain limited to wild type amino acids β15-65 and each chain further including a non-naturally occurring Gly at position 66 of each chain. Methods for treatment and pharmaceutical combinations may include a polypeptide agent such as Thymosin beta 4. In such methods and combinations, a dimer of the peptide sequence may include amino acids 15-66 of the fibrin beta chain.



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— *of inventorship (Rule 4.17(iv))*

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/10832

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 38/16; C07K 14/435 (2009.01) USPC - 514/2; 514/12; 530/382 According to International Patent Classification (IPC) or to both national classification and IPC</p>																	
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) USPC- 514/2; 514/12; 530/382</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC- 435/69.1; 530/382</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST (PGPB,USPT,USOC,EPAB,JPAB), Google (Patents, Scholar, and Web); peptide sequence fibrin fibrinogen position glycine dimer pegylate\$ disulfide (cys-gly OR gly-cys) cadherin GenCore 6.3: SEQ ID NO:5</p>																	
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <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 ---- Y</td> <td>GORLATOV et al. Interaction of Fibrin(ogen) with the Endothelial Cell Receptor VE-Cadherin: Mapping of the Receptor-Binding Site in the NH2-Terminal Portions of the Fibrin B Chains. Biochemistry 2002, 41:4107-4116; pg 4108, col 2, para 2; pg 4110, col 2, para 3; pg 4111, Fig 1; pg 4113, col 2, para 2</td> <td>1-6 ----- 8-14, 16-18, 27-30, 32, 33, 35, 37, 38, and 40</td> </tr> <tr> <td>Y</td> <td>US 2006/0263360 A1 (GOLDSTEIN) 23 Nov 2006 (23.11.2006), para [0011], [0014], [0021], [0035], [0036]</td> <td>8, 10-14, 16-18, 27-30, 32, 33, 35, 37, 38, and 40</td> </tr> <tr> <td>Y</td> <td>US 2007/0048383 A1 (HELMUS) 1 Mar 2007 (01.03.2007), para [0052]</td> <td>9, 18</td> </tr> <tr> <td>A</td> <td>WO 2007/095660 A1 (PETZELBAUER et al.) 30 Aug 2007 (30.08.2007)</td> <td>7, 15, 31, 34, 36, 39</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X ---- Y	GORLATOV et al. Interaction of Fibrin(ogen) with the Endothelial Cell Receptor VE-Cadherin: Mapping of the Receptor-Binding Site in the NH2-Terminal Portions of the Fibrin B Chains. Biochemistry 2002, 41:4107-4116; pg 4108, col 2, para 2; pg 4110, col 2, para 3; pg 4111, Fig 1; pg 4113, col 2, para 2	1-6 ----- 8-14, 16-18, 27-30, 32, 33, 35, 37, 38, and 40	Y	US 2006/0263360 A1 (GOLDSTEIN) 23 Nov 2006 (23.11.2006), para [0011], [0014], [0021], [0035], [0036]	8, 10-14, 16-18, 27-30, 32, 33, 35, 37, 38, and 40	Y	US 2007/0048383 A1 (HELMUS) 1 Mar 2007 (01.03.2007), para [0052]	9, 18	A	WO 2007/095660 A1 (PETZELBAUER et al.) 30 Aug 2007 (30.08.2007)	7, 15, 31, 34, 36, 39
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>																	
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>													
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<p>Date of the actual completion of the international search</p> <p>31 March 2009 (31.03.2009)</p>		<p>Date of mailing of the international search report</p> <p>22 APR 2009</p>															
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201</p>		<p>Authorized officer:</p> <p>Lee W. Young</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/10832

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.:
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:

***** Please see Supplemental 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.: 1-18 and 27-40, wherein claims 7, 15, 31, 36 and 39 are restricted to SEQ ID NO: 5.

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/10832

***** SUPPLEMENTAL SHEET *****

Box III: Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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+: Claims 1-18, 27-40 are directed to an isolated peptide sequence, and a pharmaceutical composition comprising an amino acid sequence of a fibrin beta chain fragment of a Bbeta chain of fibrinogen, wherein claims 7, 15, 31, 36 and 39 are restricted to SEQ ID NO: 5. Additional sequences(s) may be searched upon payment of additional fee(s).

Group II: Claims 10, 13, 19-26 are directed to a method of treating inflammation and cell damage in a subject in need thereof, wherein claims 20 and , are directed to SEQ ID NO: 7.

Group III+: Claims 41-47 are directed to an isolated nucleic acid sequence encoding a peptide sequence, wherein claim 47 is restricted to SEQ ID NO: 11. Additional sequences(s) may be searched upon payment of additional fee(s).

The special technical feature linking Groups I-XXIII is a fibrin beta chain fragment of a Bbeta chain of fibrinogen; however, this does not represent an improvement over US 2007/0037749 A1 to Petzelbauer et al., which teaches fibrin Bbeta chains, and pharmaceutical preparations of the same (para [0034]; para [0020]).

Further, there is no special technical feature shared by the Groups based on the amino acid and nucleotide sequences of the claimed inventions. The amino acid sequences represented by SEQ ID NOs:5-9 and the nucleotide sequences represented by SEQ ID NOs: 11-15 are unique sequences and do not relate to a single general inventive concept because, under PCT Rule 13.2, the different peptides and amino acids represented by the amino acid and nucleotide sequences are not common to one another but are different because they are composed of unique amino acid and nucleotide sequences.

Accordingly, unity of invention is lacking under PCT Rule 13.1.