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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PF4 PHARMACOPHORES AND THEIR USES

(57) Abstract: The invention provides a novel PF4 pharmacophore that is useful, *inter alia,* for identifying peptidomimetics and other compounds capable of modulating PF4 activity *(e.g.,* as inhibitors, agonists or antagonists). Mutant PF4 polypeptide sequences are also provided that modulate PF4 activity in cells

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A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 51/00**(2006.01),**38/00**(2006.01)

USPC: 424/1.65;530/300
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)
U.S. : 424/1.65;530/300

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 practicable, search terms used)
Pubmed, STN-Caplus, WEST, Chemical search on Formula I in Registry by STIC, Sequence(s) searches on Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAGGIN et al. Neutralization of the Antiheparin Activity of Platelet Factor 4 by a Monoclonal Antibody. Thrombosis and Haemostasis. 23 January 1992, Vol. 67, pages 137-143, entire document.	1-8, 10, 11, 13-30
X	MAIONE et al. Inhibition of Tumor Growth in Mice by an Analogue of Platelet Factor 4 That Lacks Affinity for Heparin and Retains Potent Angiostatic Activity. Cancer Research. 15 April 1991, Vol. 51, pages 2077-2083, entire document.	1-9, 11, 13-27, 30 and 57-61
X	GREEN et al. Identification and Characterization of PF4var1, a Human Gene Variant of Platelet Factor 4. Molecular and Cellular Biology. April 1989, Vol. 9, pages 1445-1451, entire document.	57 and 58
X	EP 0 308 364 A2 (REPLIGEN CORPORATION) 18 July 1990, especially Sequence 70.	57-58 and 62

☒ Further documents are listed in the continuation of Box C. ☐ See patent family 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" earlier application or patent 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

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARONE et al. The Expression in Escherichia coli of Recombinant Human Platelet Factor 4, a Protein with Immunoregulatory Activity. The Journal of Biological Chemistry. 15 June 1986, Vol. 263, pages 8710-8715,	1-11,13-30,57-62 and 64-74
A	LU et al. Properties of Ets-1 Binding to Chromatin and Its Effect on Platelet Factor 4 Gene Expression. Molecular and Cellular Biology. January 2004, Vol. 24, pages 428-441.	1-11,13-30,57-62 and 64-74
A	LUSTER et al. The IP-10 Chemokine Binds to a Specific Cell Surface Heparan Sulfate Site Shared with Platelet Factor 4 and Inhibits Endothelial Cell Proliferation. J. Exp. Med. July 1995, Vol. 182, page 219-231.	1-11,13-30,57-62 and 64-74
A	LUO et al. Molecular modeling of interleukin-8 and analysisi of the receptor-ligand interaction. Protein engineering. 1997, Vol. 10, pages 1039-1045.	1-11,13-30,57-62 and 64-74
A	FIORE et al. Platelet factor 4 neutralizes heparan sulfate-enhanced antithrombin inactivation of factor Xa by preventing interaction(s) of enzyme with polysacharide. Biochemical and Biophysical Research Communications. 2003, Vol. 311, pages 71-76.	1-11,13-30,57-62 and 64-74
A	SLUNGAARD, A. Platelet factor 4: a chemokine enigma. The International Journal of Biochemistry and Cell Biology. 2005, Vol. 37, pages 1162-1167.	1-11,13-30,57-62 and 64-74
A	HAN et al. Platelet Factor 4 Inhibits Human Megakaryocytopoiesis In Vitro. Blood. 15 March 1990, Vol. 75, pages 1234-1239.	1-11,13-30,57-62 and 64-74
Y	LECOMTE-RACLET et al. New Insights Into the Negative Regulation of Hematopoiesis by Chemokine Platelet Factor 4 and Related Peptides. Blood. 15 April 1998, Vol. 91, pages 2772-2780.	1-11,13-30,57-62 and 64-74

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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:
See Continuation Sheet.
ustifying additional fees, this Authority did not invite payment of any 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.: Please See Continuation Sheet

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.

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Continuation of Box III Item 3:
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 1, claim(s) 1-31 and 64-66, drawn to PF4 modulating compound.

Group 2, claim(s) 32-56, drawn to a method for identifying a compound that modulates PF4 activity using a three-dimensional structure of a candidate compound and a three-dimensional structure of a PF4 pharmacophore.

Group 3, claim(s) 57-61, drawn to a PF4 polypeptide having the amino acid sequence SEQ ID NO: 1 and its point mutations.

Groups 4-32, claim(s) 62 and 67-74, drawn to a mutant PF4 polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 2-30, respectively.

Groups 33-36, claim(s) 63, drawn to an isolated polypeptide from selected from the group consisting of SEQ ID NO: 157-160.

Group 37, claim(s) 75, 78-81, drawn to a method for detecting PF4 binding sites in an individual.

Group 38, claim(s) 76, 78-81, drawn to a method for detecting sites of angiogenesis in an individual.

Group 39, claim(s) 77, 78-81, drawn to a method for detecting an infection in an individual.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

a) The species of compound is drawn to an agonist or an antagonist.

b) Applicants are required to further elect a species of compound which is a polypeptide or a small molecule.

c) If Applicants elect a polypeptide, Applicants are required to further elect SEQ ID NO: 157 or SEQ ID NO: 159.

d) If Applicants elect a small compound, Applicants are required to further elect one small molecule from Formula I to VII.
The inventions listed as Groups 1-39 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:

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The inventions are linked by the technical feature of a compound that modulates PF4 activity. However, this technical feature is not special because it does not constitute an advance over the prior art. Jordan et al. (1982, The Journal of Biological Chemistry) disclose a protein haparin which binds tightly to PF4 and "thereby prevents the complexing of mucopolysaccharide with the protease inhibitor" (see page 400, bottom of left column). Thus, the haparin of Jordan et al. is a PF4 polypeptide agonist that modulates PF4 activity. The invention of Group 1, a first product, requires as its special technical feature of a compound that modulates PF4 activity. This special technical feature is not required by Groups 2-39. The invention of Groups 2, 37, 38, and 39 are drawn to a method for identifying a compound, a method for detecting PF4 binding site, a method for detecting sites of angiogenesis, and a method for detecting an infection, respectively, do not require to use the compound that modulates PF4 activity of Group 1. The invention of Groups 3-36 has distinct structure, which is comprised of amino acids, compared to the PF4 modulator compound of Group 1 both structurally and functionally. Therefore, Groups 1-39 do not share the special technical feature of a PF4 activity modulating compound. Thus, Groups 2-39 do not relate to a single general inventive concept.

These species are related to PF4 modulating compounds. The species lack unity of invention because each compound's distinct structure, evidenced by a different chemical composition and/or different structures do not share a technical feature, much less a special technical feature. In addition to their distinctness, the search of each complex requires different search, thus searching species of Group I together would impose a serious search burden on the examination process.