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- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only)**: **REBAR, Edward** [US/US]; 1609 Roger Court, El Cerrito, CA 94530 (US). **JAMIESON, Andrew** [GB/US]; 2528 Sutter Street, San Francisco, CA 94115 (US). **LIU, Qiang** [US/US]; 55 Williams Lane, Foster City, CA 94404 (US). **LIU, Pei-Qi** [CN/US]; 2266 Bristlecone Drive, Richmond, CA 94803 (US). **WOLFFE, Alan** [GB/US]; 155 Alice Lane, Orinda, CA 94563 (US). **EISENBERG, Stephen, P.** [US/US]; 5664 Pennsylvania Place, Boulder, CO 80303 (US). **JARVIS, Eric** [US/US]; 2265 Dartmouth Avenue, Boulder, CO 80305 (US).
- (74) **Agents**: **SERAFINI, Andrew, T.** et al.; TOWNSEND AND TOWNSEND AND CREW LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111 (US).
- (84) **Designated States (regional)**: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declaration under Rule 4.17:**  
— of inventorship (Rule 4.17(iv)) for US only
- Published:**  
— with international search report  
— with sequence listing part of description published separately in electronic form and available upon request from the International Bureau
- (88) **Date of publication of the international search report:**  
13 March 2003
- 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**: REGULATION OF ANGIOGENESIS WITH ZINC FINGER PROTEINS

(57) **Abstract**: Provided herein are a variety of methods and compositions for regulating angiogenesis, such methods and compositions being useful in a variety of applications where modulation of vascular formation is useful, including, but not limited to, treatments for ischemia and wound healing. Certain of the methods and compositions accomplish this by using various zinc finger proteins that bind to particular target sites in one or more VEGF genes. Nucleic acids encoding the zinc finger proteins are also disclosed. Methods for modulating the expression of one or more VEGF genes with the zinc finger proteins and nucleic acids are also disclosed. Such methods can also be utilized in a variety of therapeutic applications that involve the regulation of endothelial cell growth. Pharmaceutical compositions including the zinc finger proteins or nucleic acids encoding them are also provided.



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## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/US 01/46861

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 C12N15/12 C07K14/47 A61K48/00 A61K38/17

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 7 C07K C12N

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 practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, CHEM ABS Data

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 Further documents are listed in the continuation of box C.

 Patent family members are listed in 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 document 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

21 November 2002

Date of mailing of the international search report

20/12/2002

Name and mailing address of the ISA

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Y	CHOO Y ET AL: "IN VIVO REPRESSION BY A SITE-SPECIFIC DNA-BINDING PROTEIN DESIGNED AGAINST AN ONCOGENIC SEQUENCE" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 372, 15 December 1994 (1994-12-15), pages 642-645, XP000986225 ISSN: 0028-0836 the whole document ---	1-98

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 In International Application No  
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P,X	LIU P-Q ET AL: "REGULATION OF AN ENDOGENOUS LOCUS USING A PANEL OF DESIGNED ZINC FINGER PRTEINS TARGETED TO ACESSIBLE CHROMATIN REGIONS ACTIVATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR A" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 276, no. 14, 6 April 2001 (2001-04-06), pages 11323-11334, XP000999288 ISSN: 0021-9258 cited in the application the whole document	1-98
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P,X	WO 01 83819 A (SANGAMO BIOSCIENCES INC) 8 November 2001 (2001-11-08) The whole document, see in particular figure 27	1-66, 83-97
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## INTERNATIONAL SEARCH REPORT

International Application No

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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.
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Y	RICHARD D E ET AL: "ANGIOGENESIS: HOW A TUMOR ADAPTS TO HYPOXIA" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 266, no. 3, 1999, pages 718-722, XP000938559 ISSN: 0006-291X the whole document	67-82,98
Y	YAO FENG ET AL: "Gene therapy in wound repair and regeneration." WOUND REPAIR AND REGENERATION, vol. 8, no. 6, November 2000 (2000-11), pages 443-451, XP001119979 ISSN: 1067-1927 the whole document	67-82,98
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In International Application No  
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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.
P, X	<p>POLLOCK ROY ET AL: "Regulation of the endogenous VEGF gene by small molecule dimerizers." BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), page 746a XP009001400 43rd Annual Meeting of the American Society of Hematology, Part 1; Orlando, Florida, USA; December 07-11, 2001, November 16, 2001 ISSN: 0006-4971 the whole document -----</p>	1-98

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/46861

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:  
Although claims 67-82, and 98 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 1-98  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:✓

see 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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-98 (all partially)

The zinc finger pretein BVO 13A and compositions and uses involving this protein.

2. Claims: 1-98 (all partially)

Each of the particular zinc finger proteins disclosed in the present application (as for example the ones mentioned in claims 4, 8), together with their uses, and any of the fussions of such proteins to activation or represion domains would correspond to a separate potential invention.

Listing here all these potential inventions is for technical reasons not feasible. Thus, such potential inventions are here listed as the second group of inventions, but each of them would constitute a different potential invention.

3. Claim : 98 (partially)

Method to treat a wound comprising introducing a zinc finger protein into an animal having a genome comprising a target site within a VEGF gene (wherein the target site or zinc fingers are not the ones specified in Tables 3 and 4 of the present application).

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1-98

Present claims 1-98 relate to a proteins defined by reference to a desirable characteristic or property, namely, which are able to bind to a big number of possible target sites.

The claims cover all proteins having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such proteins. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the products by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, on these claims making reference to particular zinc finger proteins, arbitrary designations are given which do not have any meaning for the skill reader. In contrast to a particular SEQ ID NO:, a mere arbitrary designation does not allow the search examiner to carry out a meaningful search of said protein.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed. Search has been done for the concept of using hybrid proteins containing zinc finger domains in order to alter the expression of a given gene, and also in particular of the VEGF gene.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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 International Application No  
 PCT/US 01/46861

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