



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : A61K 38/18, A61P 9/10</p>	<p>A3</p>	<p>(11) International Publication Number: WO 00/21548</p> <p>(43) International Publication Date: 20 April 2000 (20.04.00)</p>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/US99/22936</p> <p>(22) International Filing Date: 13 October 1999 (13.10.99)</p> <p>(30) Priority Data: 60/104,103 13 October 1998 (13.10.98) US</p> <p>(71) Applicants: CHIRON CORPORATION [US/US]; 4560 Horton Street, P.O. Box 8097, Intellectual Property R-440, Emeryville, CA 9662-8097 (US). WHITEHOUSE, Martha, Jo [-/US]; 151 Upper Terrace, San Francisco, CA 94117 (US).</p> <p>(72) Inventor: KAVANAUGH, William, M.; 205 Laverne Avenue, Mill Valley, CA 94941 (US).</p> <p>(74) Agents: DOLLARD, Anne; Chiron Corporation, 4560 Horton Street, P.O. Box 8097, Intellectual Property R-440, Emeryville, CA 94662-8097 (US) et al.</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 31 August 2000 (31.08.00)</p> </td> </tr> </table>			<p>(21) International Application Number: PCT/US99/22936</p> <p>(22) International Filing Date: 13 October 1999 (13.10.99)</p> <p>(30) Priority Data: 60/104,103 13 October 1998 (13.10.98) US</p> <p>(71) Applicants: CHIRON CORPORATION [US/US]; 4560 Horton Street, P.O. Box 8097, Intellectual Property R-440, Emeryville, CA 9662-8097 (US). WHITEHOUSE, Martha, Jo [-/US]; 151 Upper Terrace, San Francisco, CA 94117 (US).</p> <p>(72) Inventor: KAVANAUGH, William, M.; 205 Laverne Avenue, Mill Valley, CA 94941 (US).</p> <p>(74) Agents: DOLLARD, Anne; Chiron Corporation, 4560 Horton Street, P.O. Box 8097, Intellectual Property R-440, Emeryville, CA 94662-8097 (US) et al.</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 31 August 2000 (31.08.00)</p>
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<p>(54) Title: ANGIOGENICALLY EFFECTIVE UNIT DOSE OF FGF AND METHOD OF ADMINISTERING</p> <div style="text-align: center; margin: 20px 0;"> <p>Legend for graph:</p> <ul style="list-style-type: none"> —●— 0.33 µg/kg —○— 0.65 µg/kg ---△--- 2 µg/kg ---▲--- 6 µg/kg ---◇--- 12 µg/kg ---◊--- 24 µg/kg ---●--- 36 µg/kg ---■--- 48 µg/kg </div>				
<p>(57) Abstract</p> <p>The present invention has multiple aspects. In particular, in one aspect, the present invention is directed to a unit dose comprising 0.2 µg/kg to 36 µg/kg of a recombinant FGF or an angiogenically active fragment or mutein thereof. In another aspect, the present invention is directed to a pharmaceutical composition comprising an angiogenically effective dose of an FGF or an angiogenically active fragment or mutein thereof, and a pharmaceutically acceptable carrier. Typically, the angiogenically effective dose comprises 0.2 µg/kg to 36 µg/kg of an FGF of any one of SEQ ID NOS: 1-3, 5, 8-10 or 12-14 or and angiogenically active fragment or mutein thereof. In yet another aspect, the present invention is directed to a method for treating a human patient for coronary artery disease, comprising administering into at least one coronary vessel of a human patient in need of treatment for coronary artery disease a safe and angiogenically effective dose of a recombinant FGF of any one of SEQ ID NOS: 1-3, 5, 8-10 or 12-14, or an angiogenically active fragment or mutein thereof.</p>				

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/22936

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/18 A61P9/10

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 A61K

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 WPI MEDLIN BIOSIS CA EMBASE LIFESC SCISEA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIRSCHNER PAMELA B ET AL: "Basic fibroblast growth factor protects against excitotoxicity and chemical hypoxia in both neonatal and adult rats." JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM 1995, vol. 15, no. 4, 1995, pages 619-623, XP000906721 ISSN: 0271-678X the whole document ----- -/--	1,2, 13-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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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.

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Date of the actual completion of the international search

26 April 2000

Date of mailing of the international search report

12/05/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/22936

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SELLKE FRANK W ET AL: "Angiogenesis induced by acidic fibroblast growth factor as an alternative method of revascularization for chronic myocardial ischemia." SURGERY (ST LOUIS) 1996, vol. 120, no. 2, 1996, pages 182-188, XP000891931 ISSN: 0039-6060 the whole document</p>	1,2, 13-31
X	<p>US 4 378 347 A (FRANCO W.P.) 29 March 1983 (1983-03-29) the whole document</p>	1,2,13, 21
X	<p>FOLKMAN J.: "Angiogenic therapy for the human heart" CIRCULATION, vol. 97, 1998, pages 628-629, XP000891914 the whole document</p>	1,2, 11-31

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 22936

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:
Remark: Although claims 21-32 are directed to a method 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.:
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 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:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/22936

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4378347 A	29-03-1983	US 4296100 A	20-10-1981
		AU 7416981 A	02-02-1982
		GB 2090528 A,B	14-07-1982
		JP 57500878 T	20-05-1982
		WO 8200098 A	21-01-1982
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