



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/17 // (A61K 38/17, 31:505)	A3	(11) International Publication Number: WO 98/24463 (43) International Publication Date: 11 June 1998 (11.06.98)
(21) International Application Number: PCT/US97/22733 (22) International Filing Date: 8 December 1997 (08.12.97) (30) Priority Data: 60/032,587 6 December 1996 (06.12.96) US 60/036,355 23 January 1997 (23.01.97) US 60/039,315 7 February 1997 (07.02.97) US 60/052,023 9 July 1997 (09.07.97) US (71) Applicant (for all designated States except US): AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BENDELE, Alison, M. [US/US]; 6583 Magnolia Road, Nederland, CO 80466 (US). SENNELLO, Regina, M. [US/US]; 948 Deer Trail Road, Boulder, CO 80302 (US). EDWARDS, Carl, K. [US/US]; 1620 South Pitkin Avenue, Superior, CO 80301 (US). (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, 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, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 16 July 1998 (16.07.98)
(54) Title: COMBINATION THERAPY USING A TNF BINDING PROTEIN FOR TREATING TNF-MEDIATED DISEASES (57) Abstract The invention relates to methods for treating or preventing acute and/or chronic arthritis. The method comprises administering to patients in need thereof therapeutically effective amounts of a TNF binding protein and methotrexate (N-[4-[[[2,4-diamino-6-pteridiny]methylamino]benzoyl]-L-glutamic acid). In a preferred embodiment, the TNF binding protein is sTNFR-I or sTNFR-II. The invention also relates to pharmaceutical compositions containing a TNF binding protein and methotrexate useful in such methods.		

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22733

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K38/17 //(A61K38/17,31:505)		
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 6 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 20729 A (UNIVERSITY OF SOUTH FLORIDA)) 11 July 1996 see the whole document ---	1,9,15, 21
X	WO 94 06476 A (IMMUNEX CORPORATION) 31 March 1994 see the whole document ---	1,9,15, 21
X	WO 92 07585 A (CELLTECH LIMITED) 14 May 1992 see the whole document ---	1,9,15, 21
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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 28 April 1998		Date of mailing of the international search report 29. 05. 1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Moreau, J

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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.
X	KAVANAUGH A F ET AL: "ANTI-TNF-ALPHA MONOCLONAL ANTIBODY (MAB) TREATMENT OF RHEUMATOID ARTHRITIS (RA) PATIENTS WITH ACTIVE DISEASE ON METHOTREXATE (MTX); RESULTS OF A DOUBLE-BLIND, PLACEBO CONTROLLED MULTICENTER TRIAL" ARTHRITIS & RHEUMATISM, vol. 39, no. 9, September 1996, page S123 XP002048557 see the whole document ---	1-26
A	BARRERA P ET AL: "Circulating soluble tumor necrosis factor receptors, interleukin-2 receptors, tumor necrosis factor alpha, and interleukin-6 levels in rheumatoid arthritis. Longitudinal evaluation during methotrexate and azathioprine therapy [see comments]." ARTHRITIS AND RHEUMATISM, (1993 AUG) 36 (8) 1070-9, XP002063595 see the whole document ---	1-26
A	SEITZ M ET AL: "Methotrexate action in rheumatoid arthritis: stimulation of cytokine inhibitor and inhibition of chemokine production by peripheral blood mononuclear cells." BRITISH JOURNAL OF RHEUMATOLOGY, (1995 JUL) 34 (7) 602-9, XP002063596 see the whole document ---	1-26
A	SEITZ M ET AL: "Interleukin 1 (IL-1) receptor antagonist, soluble tumor necrosis factor receptors, IL-1 beta, and IL-8--markers of remission in rheumatoid arthritis during treatment with methotrexate." JOURNAL OF RHEUMATOLOGY, (1996 SEP) 23 (9) 1512-6, XP002063597 see the whole document ---	1-26
A	BOLOGNA C ET AL: "ASSOCIATION DES TRAITEMENTS DE FOND DANS LA POLYARTHRITE RHUMATOIDE" PRESSE MEDICALE, vol. 25, no. 19, 1 June 1996, pages 876-878, XP002048553 ---	1-26
A	BORIGINI M J ET AL: "COMBINATION THERAPY" BAILLIERE S CLINICAL RHEUMATOLOGY, vol. 9, no. 4, November 1995, pages 689-710, XP002048554 ---	1-26

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/22733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 98 05357 A (THE KENNEDY INSTITUTE OF RHEUMATOLOGY) 12 February 1998 see the whole document -----	1-26

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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:
see FURTHER INFORMATION sheet PCT/ISA/210
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.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 1-9 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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