

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 October 2000 (12.10.2000)

PCT

(10) International Publication Number  
**WO 00/59525 A3**

- (51) International Patent Classification<sup>7</sup>: A61K 38/18, 39/395, A61P 3/10
- (21) International Application Number: PCT/US00/09240
- (22) International Filing Date: 5 April 2000 (05.04.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/128,017 6 April 1999 (06.04.1999) US
- (71) Applicant: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (72) Inventors: HUANG, Xiaojian; 1058 Colorado Avenue, Palo Alto, CA 94303 (US). STEWART, Timothy, Andrew; 465 Douglas Street, San Francisco, CA 94114 (US).
- (74) Agents: MARSCHANG, Diane, L. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): 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).
- Published:  
— With international search report.
- (88) Date of publication of the international search report:  
8 February 2001
- 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.



WO 00/59525 A3

(54) Title: USE OF ErbB RECEPTOR LIGANDS IN TREATING DIABETES

(57) Abstract: The invention provides methods for treating pancreatic dysfunction, particularly diabetes, in mammals using ErbB receptor ligands, such as heregulin, betacellulin, and EGF. Methods of treating such conditions using anti-ErbB receptor agonist antibodies are further provided. The methods of the invention may be performed by direct administration of such therapeutically useful agents to mammals, or alternatively, by exposing certain pancreatic cell types to such agents *in vitro* and subsequently transplanting the treated cells to a mammal.

# INTERNATIONAL SEARCH REPORT

International Application No  
PC./US 00/09240

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K38/18 A61K39/395 A61P3/10

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 A61P

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 Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 17086 A (TAKEDA CHEMICAL INDUSTRIES LTD ;KOJIMA ITARU (JP)) 15 May 1997 (1997-05-15) cited in the application *see in particular claims 1,8-10,12,13,15,16; test examples 1-4; page 17, lines 2-25;	1,3,4,7, 14,15, 18,19, 22,24
Y	---  -/--	1,3-8, 10-16, 18-20

Further documents are listed in the continuation of box C.       Patent family members are listed in annex.

° Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document 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>"&amp;" document member of the same patent family</p>
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2000	23. 11. 00

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  ISERT B.
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------

INTERNATIONAL SEARCH REPORT

International Application No  
PC, /US 00/09240

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>WO 95 19785 A (RES TRIANGLE PHARM LTD) 27 July 1995 (1995-07-27) cited in the application</p> <p>* see in particular claims 1,5,6,11; page 10 (2nd paragraph); page 15 (3rd paragraph); Example 1 *</p>	<p>1,3,7, 10,11, 14,18, 22,24</p>
Y		<p>1,3-8, 10-16, 18-20</p>
X	<p>--- WO 96 30403 A (CAMBRIDGE NEUROSCIENCE INC ;REH THOMAS A (US); MARCHIONNI MARK A ()) 3 October 1996 (1996-10-03) * see page 7, lines 5-16; page 8, lines 1-11, 30-35;page 14, lines 31-33;claims 29,47,64 *</p>	<p>3,5,22, 24</p>
X	<p>--- GONUL B ET AL: "Effect of EGF on the corneal wound healing of alloxan diabetic mice." EXPERIMENTAL EYE RESEARCH, (1992 APR) 54 (4) 519-24., XP000917539 * see in particular the abstract*</p>	<p>3,22,24</p>
X	<p>--- HUOTARI M A ET AL: "Growth factor-mediated proliferation and differentiation of insulin -producing INS-1 and RINm5F cells: identification of betacellulin as a novel beta - cell mitogen." ENDOCRINOLOGY, (1998 APR) 139 (4) 1494-9., XP000917303 *see in particular the abstract; discussion *</p>	<p>14,15, 18,19, 22,24</p>
Y		<p>1,3-8, 10-16, 18-20</p>
	<p>--- -/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No  
 PC./US 00/09240

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>                             DATABASE BIOSIS [Online]                              BIOSCIENCES INFORMATION SERVICE,                              PHILADELPHIA, PA, US;                              MIETTINEN, P. J. (1) ET AL: "Proliferation                              and migration of pancreatic beta -cells is                              disturbed after inactivation of the EGF -R                              function."                              retrieved from STN                              XP002144679                              abstract                              &amp; HORMONE RESEARCH (BASEL), (1997) VOL.                              48, NO. SUPPL. 2, PP. 159. MEETING INFO.:                              5TH JOINT MEETING OF THE EUROPEAN SOCIETY                              FOR PAEDIATRIC ENDOCRINOLOGY AND THE                              LAWSON WILKINS SOCIETY FOR PEDIATRIC                              ENDOCRINOLOGY, IN COLLABORATION WITH THE                              AUSTRALIAN PA,                                -----                         </p>	<p>                             1,3-8,                              10-16,                              18-20                         </p>

# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/US 00/09240

## 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:
  
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:

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.:

1; 3-8; 10-13 in part; 14-16; 18-20; 22; 24 in part

### 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; 3-8; 10-13 in part; 14-16; 18-20; 22; 24 in part

Use of ErbB receptor ligands

2. Claims: 2; 9; 10-13 in part; 17; 21; 23; 24 in part

Use of ErbB receptor agonist antibody

**INTERNATIONAL SEARCH REPORT**  
 information on patent family members

International Application No  
 PC., US 00/09240

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717086 A	15-05-1997	AU 7506396 A	29-05-1997
		CA 2233009 A	15-05-1997
		CN 1202112 A	16-12-1998
		EP 0862451 A	09-09-1998
		JP 9188630 A	22-07-1997
-----			
WO 9519785 A	27-07-1995	AU 7628794 A	08-08-1995
		EP 0752882 A	15-01-1997
		JP 9511384 T	18-11-1997
-----			
WO 9630403 A	03-10-1996	AU 713384 B	02-12-1999
		AU 5376696 A	16-10-1996
		CA 2215330 A	03-10-1996
		EP 0820467 A	28-01-1998
		JP 11509831 T	31-08-1999
-----			