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09/635,368 9 August 2000 (09.08.2000) US
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see PCT Gazette No. 41/2002 of 10 October 2002, Section II
- 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 02/012336 A3**

(54) Title: TGF- $\beta$  THERAPEUTICS, COMPOSITIONS AND METHODS OF USE

(57) Abstract: The present invention relates to TGF $\beta$  therapeutics, TGF $\beta$  proteins or a combination of TGF $\beta$  proteins which are capable of stimulating growth and/or differentiation of pancreatic tissue. The invention also relates to pharmaceutical compositions comprising such proteins and/or therapeutics, methods for using such proteins and/or therapeutics in culturing pancreatic tissue and cells and methods for administering such proteins and/or therapeutics to a subject.

## INTERNATIONAL SEARCH REPORT

 Internat      pplication No  
 PCT/US 01/04192

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7    A61K38/18    C12N5/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) IPC 7    A61K    C12N    C07K		
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, MEDLINE, BIOSIS, CHEM ABS Data, SEQUENCE SEARCH		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 604 204 A (AMMANN ARTHUR J ET AL) 18 February 1997 (1997-02-18)	10,11
A	column 5, line 59 - column 6, line 26; claims 1,2,7; figures 1A,1B column 7, line 33 - line 54 ---	1-4
X	US 5 409 896 A (AMMANN ARTHUR J ET AL) 25 April 1995 (1995-04-25)	10
A	column 6, line 3 - line 39; claim 1; figures 1A,1B ---	1-4
X	US 5 705 477 A (ROBERTS ANITA B ET AL) 6 January 1998 (1998-01-06)	10
A	column 2, line 12 - line 25; claim 1 ---	14-16
X	US 5 656 587 A (ROBERTS ANITA B ET AL) 12 August 1997 (1997-08-12)	10
A	column 2, line 10 - line 24; claim 1 ---	14-16
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> 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  12 February 2003		Date of mailing of the international search report  19/02/2003
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  Charles, D

## INTERNATIONAL SEARCH REPORT

Internati plication No  
PCT/US 01/04192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIRALLES FRANCISCO ET AL: "TGF-beta plays a key role in morphogenesis of the pancreatic islets of Langerhans by controlling the activity of the matrix metalloproteinase MMP-2" JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, NEW YORK, US, US, vol. 143, no. 3, 2 November 1998 (1998-11-02), pages 827-836, XP002148144 ISSN: 0021-9525 page 828, left-hand column, paragraph 1 page 830, right-hand column, paragraph 4 -page 832, left-hand column, paragraph 2 page 834, left-hand column, paragraph 1 -page 835, left-hand column, paragraph 1 ----	14-17
X	SANVITO F ET AL: "TGF-beta-1 influences the relative development of the exocrine and endocrine pancreas in vitro" DEVELOPMENT, COMPANY OF BIOLOGISTS, CAMBRIDGE,, GB, vol. 120, no. 12, 1994, pages 3451-3462, XP002148143 ISSN: 0950-1991 page 3451, right-hand column, paragraph 1 page 3457, left-hand column, paragraph 3 -page 3458, left-hand column, paragraph 1 page 3459, right-hand column, paragraph 2 -page 3460, right-hand column, paragraph 3 ----	14-17
X	ALVAREZ A ET AL: "Regulation of pancreatic duct cell growth by transforming growth factor beta (TGFbeta) in vitro" GASTROENTEROLOGY, SAUNDERS, PHILADELPHIA, PA,, US, vol. 114, no. 4 PART 2, 15 April 1998 (1998-04-15), page A1375 XP000925857 ISSN: 0016-5085 the whole document ----	14-17
X,P	WO 00 47243 A (WANG MONICA ;GUICHERIT OIVEN (US); ONTOGENY INC (US); PANG KEVIN ()) 17 August 2000 (2000-08-17) the whole document ----	2-4,10, 14-16
E	WO 01 39784 A (ZULEWSKI HENDRIK ;VALLEJO MARIO (ES); ABRAHAM ELIZABETH J (US); GE) 7 June 2001 (2001-06-07) page 1, line 10 - line 15; claims 1,6,44,46,47 page 29, line 31 - line 34 ----	14-16
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## INTERNATIONAL SEARCH REPORT

Internati      plication No  
PCT/US 01/04192

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 542 679 A (CIBA GEIGY AG) 19 May 1993 (1993-05-19) page 3, line 17 - line 20; claims 1,15 page 4, line 44 - line 46 page 7, line 17 - line 19 page 7, line 49 - line 54 -----	1-3,5, 14,15,17

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/04192

**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 2-6 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.: 1, 7-9, 13, 19-21  
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:

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

Continuation of Box I.2

Claims Nos.: 1,7-9,13,19-21

Present claims 1, 7-9, 13, 19-21 relate to compounds defined by reference to a desirable characteristic or property, namely "TGF-beta therapeutic" (Claims 1, 7-9, 13, 19-21) and "TGF-beta agonist" (Claims 7, 19).

The claims cover all compounds 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 compounds. 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 compounds 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. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds TGF-beta protein (thus a protein with TGF-beta activity). Since no example of agonists has been given neither in the Claims nor in the Description, no search has been performed regarding this agent.

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.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal application No

PCT/US 01/04192

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US 5409896	A	25-04-1995	US 5158934 A	27-10-1992
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