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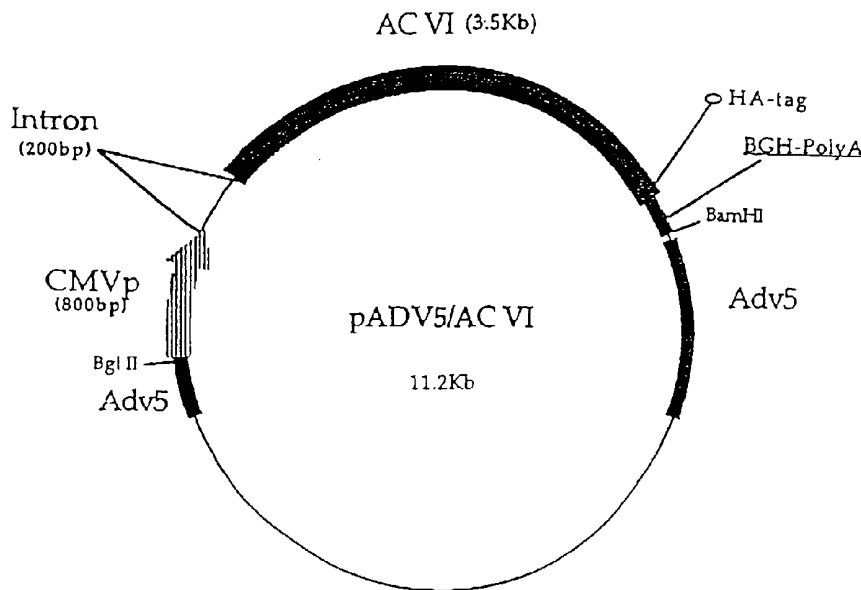
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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[Continued on next page]

(54) Title: MODIFIED ADENYLYLCYCLASE TYPE VI USEFUL IN GENE THERAPY FOR CONGESTIVE HEART FAILURE



(57) Abstract: The present invention relates to methods and compositions for enhancing cardiac function in mammalian hearts by inserting transgenes that increase beta-adrenergic responsiveness within the myocardium. The present invention can thus be used in the treatment of heart disease, especially congestive heart failure.

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IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/35411

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/88

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 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)
BIOSIS, EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAO M ET AL: "Increased expression of adenylylcyclase type VI proportionately increases beta-adrenergic receptor-stimulated production of cAMP in neonatal rat cardiac myocytes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, US, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 95, February 1998 (1998-02), pages 1038-1043, XP002128900 ISSN: 0027-8424	1, 2, 7-12, 17-24, 28-30
Y	abstract; figures 1, 5, 6 --- -/--	3, 4, 13, 14, 25, 26

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	*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
E earlier document but published on or after the international filing date	*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
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)	*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.
O document referring to an oral disclosure, use, exhibition or other means	* & * document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 26 March 2002	Date of mailing of the international search report 13.05.02
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 Novak, S

INTERNATIONAL SEARCH REPORT

Int Application No

PCT/US 00/35411

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LAI HSING-LIN ET AL: "The N terminus domain of type VI adenylyl cyclase mediates its inhibition by protein kinase C." MOLECULAR PHARMACOLOGY, vol. 56, no. 3, 1999, pages 644-650, XP002173130 ISSN: 0026-895X	1,2,7,8
Y	abstract; figures 1,2; table I	3,4, 9-14, 17-26, 28-30
X	----- WICKER R ET AL: "CLONING AND EXPRESSION OF HUMAN ADENYLYL CYCLASE TYPE VI IN NORMAL THYROID TISSUES" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, vol. 1493, no. 1/2, 7 September 2000 (2000-09-07), pages 279-283, XP001012908 ISSN: 0006-3002 abstract; figures 1,2	1-30
X	----- DATABASE EBI 'Online! EMBL; Ac:043306, 15 July 1999 (1999-07-15) "Adenylate Cyclase, Type VI" XP002173133 the whole document	1-30
X	----- RAIMUNDO SEBASTIAN ET AL: "Cloning and sequence of partial cDNAs encoding the human type V and VI adenylyl cyclases and subsequent RNA-quantification in various tissues." CLINICA CHIMICA ACTA, vol. 285, no. 1-2, July 1999 (1999-07), pages 155-161, XP001057232 ISSN: 0009-8981 the whole document	5,6
Y		1-4,7-30
X	----- KATSUSHIKA S ET AL: "CLONING AND CHARACTERIZATION OF A SIXTH ADENYLYL CYCLASE ISOFORM TYPES V AND VI CONSTITUTE A SUBGROUP WITHIN THE MAMMALIAN ADENYLYL CYCLASE FAMILY" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 89, no. 18, 1992, pages 8774-8778, XP002173131 1992 ISSN: 0027-8424 abstract; figures 1-4	1-30
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INTERNATIONAL SEARCH REPORT

International Application No

PCI/US 00/35411

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EBI 'Online! EMBL; Ac: M94968, 13 October 1992 (1992-10-13) "Canis familiaris adenylyl cyclase type VI mRNA sequence" XP002191734	5,6
Y	the whole document	1-4,7-30
Y	--- ESPINASSE ISABELLE ET AL: "Decreased type VI adenylyl cyclase mRNA concentration and Mg ²⁺ -dependent adenylyl cyclase activities and unchanged type V adenylyl cyclase mRNA concentration and Mn ²⁺ -dependent adenylyl cyclase activities in the left ventricle of rats with myocardial infarction and longstanding heart failure." CARDIOVASCULAR RESEARCH, vol. 42, no. 1, April 1999 (1999-04), pages 87-98, XP001055428 ISSN: 0008-6363 the whole document	1-30
Y	--- ROTH DAVID M ET AL: "Cardiac-directed adenylyl cyclase expression improves heart function in murine cardiomyopathy." CIRCULATION, vol. 99, no. 24, 22 June 1999 (1999-06-22), pages 3099-3102, XP002173132 ISSN: 0009-7322 the whole document	1-30
Y	--- US 5 578 481 A (ISHIKAWA YOSHIHIRO) 26 November 1996 (1996-11-26) the whole document	1-4, 7-14, 17-26, 28-30
A	--- HABER N ET AL: "Chromosomal mapping of human adenylyl cyclase genes type III, type V and type VI" HUMAN GENETICS, BERLIN, DE, vol. 94, no. 1, 1 July 1994 (1994-07-01), pages 69-73, XP002084073	
P,X	--- US 6 107 076 A (GILMAN ALFRED G ET AL) 22 August 2000 (2000-08-22) the whole document	1-30
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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 00/35411

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	DATABASE EBI 'Online! EMBL; Ac:AF250226, 12 July 2000 (2000-07-12) "Homo sapiens adenylyl cyclase type VI mRNA, complete cds" XP002191735 the whole document -----	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/35411

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.:

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: 1-4, 7-14 (partially), 17-26 (partially),
28-30 (partially)

Polynucleotides encoding a modified adenylylcyclase (AC) isoform VI, and vectors and cells comprising such polynucleotides.

2. Claims: 5,6, 7-14 (partially), 15,16, 17-26 (partially),
27, 28-30 (partially)

Isolated polynucleotides encoding a (wildtype) human adenylylcyclase VI, and vectors and cells harbouring such polynucleotides.

INTERNATIONAL SEARCH REPORT

Int: Application No
PCT/US 00/35411

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
US 5578481	A	26-11-1996	US 5334521 A	02-08-1994
			AU 666146 B2	01-02-1996
			AU 2844992 A	20-05-1993
			CA 2082986 A1	19-05-1993
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			ZA 9208877 A	12-05-1993

US 6107076	A	22-08-2000	NONE	
