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15 June 2000 (15.06.00)

(54) Title: METHODS OF ALTERING CARDIAC CELL PHENOTYPE

(57) Abstract

Methods for improving or maintaining cardiac function in patients are disclosed. The methods include the stimulation of heart muscle regeneration, the treatment of patients with congestive heart failure and the prevention of organ transplant rejection. Methods are also disclosed for the treatment of patients after myocardial infarction and/or patients with congestive heart failure by adenovirus–mediated delivery of peptides, including, but not limited to, NKX–2.5, MEF2, GATA4, BCL–2, HGH, and Fas ligand, that alter the phenotype of cells in the heart.

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INTERNATIONAL SEARCH REPORT

Interi. ɔnal Application No
PCT/US 99/11961

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K48/00

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 95 12979 A (UNIV SOUTHERN CALIFORNIA) 18 May 1995 (1995-05-18) cited in the application	1,3, 14-21, 23,24, 37,39,40
Y	page 2, line 10 -page 3, line 3 page 9, line 26 -page 10, line 4 page 11, line 28 -page 12, line 6 page 14, line 3 - line 9 page 14, line 24 -page 15, line 4 ---	2,4,22, 25-36
Y	HARVEY ET AL: "TARGETED MUTAGENESIS OF THE HEART-EXPRESSED HOMEOBOX GENE NKX-2-5 RESULTS IN ABNORMAL HEART DEVELOPMENT AND EMBRYONIC LETHALITY" JOURNAL OF CELLULAR BIOCHEMISTRY, SUPPLEMENT 18D,1994, page 477 XP000857694 abstract W113 --- -/--	2,4,22, 25-36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1999	12 04 2000

Name and mailing address of the ISA	Authorized officer
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	SITCH, D

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	SCHOTT ET AL: "CONGENITAL HEART DISEASE CAUSED BY MUTATIONS IN THE TRANSCRIPTION FACTOR NKX2-5" SCIENCE, vol. 281, 3 July 1998 (1998-07-03), pages 108-111, XP002125587 page 108 abstract	2,4,22, 25-36

X	WO 94 05776 A (CHILDRENS MEDICAL CENTER) 17 March 1994 (1994-03-17)	38,41,42
Y	page 2, line 15 - line 25 page 9, line 15 - line 33 page 18, line 7 - line 19 page 52, line 13 -page 53, line 21 page 54, line 10 - line 18	2,4,22, 25-36

Y	MOLKENTIN ET AL: "MYOCYTE-SPECIFIC ENHANCER-BINDING FACTOR (MEF-2) REGULATES ALPHA-CARDIAC MYOSIN HEAVY CHAIN GENE EXPRESSION IN VITRO AND IN VIVO" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, 1993, pages 19512-19520, XP002125588 page 19512 abstract	2,4,22, 25-36

X	ORNATSKY O I ET AL: "A dominant-negative form of transcription factor MEF2 inhibits myogenesis." JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 DEC 26) 272 (52) 33271-8., XP002125589	38,42
Y	page 33271 abstract page 33273, paragraph 5	2,4,22, 25-36

Y	GREPIN C ET AL: "Enhanced cardiogenesis in embryonic stem cells overexpressing the GATA - 4 transcription factor." DEVELOPMENT, (1997 JUN) 124 (12) 2387-95., XP002125590 page 2387 abstract	2,4,22, 25-36

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INTERNATIONAL SEARCH REPORT

Intern. ...nal Application No
PCT/US 99/11961

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOLKENTIN J D ET AL: "TRANSCRIPTION FACTOR GATA-4 REGULATES CARDIAC MUSCLE-SPECIFIC EXPRESSION OF THE ALPHA-MYOSIN HEAVY-CHAIN GENE" MOLECULAR AND CELLULAR BIOLOGY, (JUL 1994) VOL. 14, NO. 7, PP. 4947-4957. ISSN: 0270-7306., XP002125591 MED COLL WISCONSIN, DEPT PHYSIOL, 8701 WATERTOWN PLANK RD, MILWAUKEE, WI, 53226 (Reprint);MED COLL WISCONSIN, DEPT PHYSIOL, MILWAUKEE, WI, 53226; MED COLL WISCONSIN, DEPT MICROBIOL, MILWAUKEE, WI, 53226; MED COLL WISCONSIN, CARDIOVASC RES CTR, MILWAUKEE, WI, 53226; MED COLL WISCONSIN, CTR CANC, MILW	38,42
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A	WO 98 10085 A (COLLATERAL THERAPEUTICS ;PING PEIPEI (US); POST STEVEN R (US); GAO) 12 March 1998 (1998-03-12) cited in the application page 8, line 2 -page 12, line 21	14-21, 23,24
A	WO 96 26742 A (HAMMOND H KIRK ;UNIV CALIFORNIA (US); DILLMAN WOLFGANG H (US); GIO) 6 September 1996 (1996-09-06) cited in the application page 5, line 17 -page 8, line 19	14-21, 23,24
P,A	WO 98 50079 A (HAMMOND H KIRK ;KELLY TAMSIN L (US); UNIV CALIFORNIA (US)) 12 November 1998 (1998-11-12) cited in the application page 6, line 6 -page 8, line 10	14-21, 23,24

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 11961

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-4 and 14-36 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:

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. [X] 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.:

1-4,37(complete); 14-36,38-42(partially)

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

1. Claims: 1-4, 37 completely; 14-36, 38-42 partially

A method for improving or maintaining cardiac function in a patient comprising delivering a vector to the heart of said patient, said vector comprising a transgene coding for a cardiomyocyte-differentiating peptide;

a method for improving or maintaining cardiac function in a patient comprising delivering a vector to the heart of said patient, said vector comprising a transgene coding for a peptide selected from the group consisting of NKX-2.5, MEF2, and GATA4;

a method for stimulating heart muscle regeneration in a patient comprising delivering a vector comprising a transgene to the heart of said patient, wherein said transgene encodes a cardiomyocyte-differentiating peptide;

a kit for intracoronary injection comprising at least a nucleic acid encoding a cardiomyocyte-differentiating peptide in a vector;

a kit for intracoronary injection comprising at least a nucleic acid encoding NKX-2.5, MEF2, or GATA4 in a vector;

an adenovirus vector preparation comprising at least a recombinant adenoviral vector comprising a transgene coding for NKX-2.5, MEF2, or GATA4;

a kit for coronary sinus retroprofusion comprising at least a nucleic acid encoding NKX-2.5, MEF2, or GATA4 in a vector.

2. Claims: 5-10 completely; 15, 17-36, 38-42 partially

A method for improving or maintaining cardiac function in a patient comprising delivering a vector to the heart of said patient, said vector comprising a transgene coding for an anti-apoptotic protein;

a method for improving or maintaining cardiac function in a patient comprising delivering a vector to the heart of said patient, said vector comprising a transgene coding for BCL-2;

a method for treating congestive heart failure in a patient comprising delivering a vector comprising a transgene coding for BCL-2 to the heart of said patient;

a kit for intracoronary injection comprising at least a nucleic acid encoding BCL-2 in a vector;

an adenovirus vector preparation comprising at least a recombinant adenoviral vector comprising a transgene coding for BCL-2;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a kit for coronary sinus retroprofusion comprising at least a nucleic acid encoding BCL-2 in a vector.

3. Claims: 11-13 completely; 14-36, 38-42 partially

A method for improving or maintaining cardiac function in a patient comprising delivering a vector comprising a transgene coding for HGH to the heart of said patient;

a method for treating congestive heart failure in a patient comprising delivering a vecotor comprising a transgene coding for HGH to the heart of said patient;

a kit for intracoronary injection comprising at least a nucleic acid encoding HGH in a vector;

an adenovirus vector preparation comprising at least a recombinant adenoviral vector comprising a transgene coding for HGH;

a kit for coronary sinus retroperfusion comprising at least a nucleic acid encoding HGH in a vector.

4. Claims: 38, 39, 41, 42 partially; 43-65 completely

a kit for intracoronary injection comprising at least a nucleic acid encoding Fas ligand in a vector;

an adenovirus vector preparation comprising at least a recombinant adenoviral vector comprising a transgene coding for Fas ligand;

a kit for coronary sinus retroperfusion comprising at least a nucleic acid encoding Fas Ligand in a vector;

a method of reducing the likelihood of rejection of a transplanted organ in a patient comprising delivering a vector to the transplanted organ, said vector comprising a transgene coding for a Fas ligand.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/US 99/11961

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