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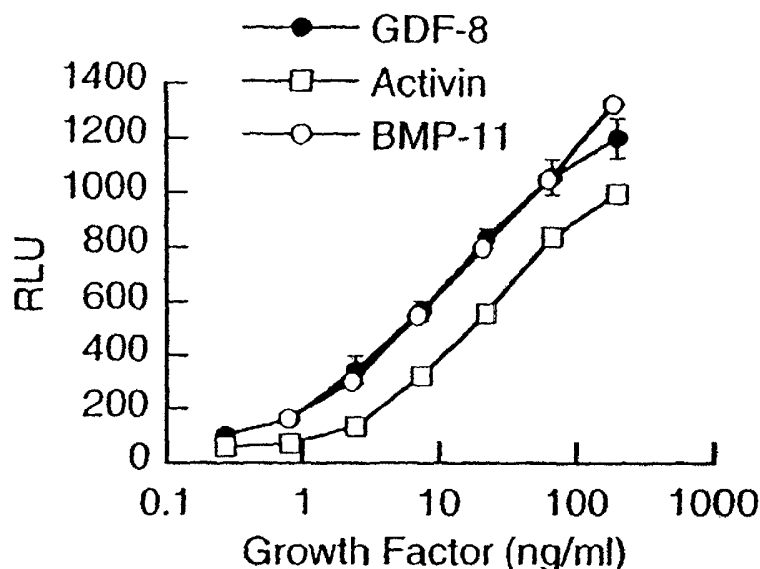
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[Continued on next page]

(54) Title: MODIFIED AND STABILIZED GDF PROPEPTIDES AND USES THEREOF



(57) Abstract: Modified and stabilized propeptides of Growth Differentiation Factor proteins, such as GDF-8 and Bone Morphogenetic Protein-11, are disclosed. Also disclosed are methods for making and using the modified propeptides to prevent or treat human or animal disorders in which an increase in muscle tissue would be therapeutically beneficial. Such disorders include muscle or neuromuscular disorders (such as amyotrophic lateral sclerosis, muscular dystrophy, muscle atrophy, congestive obstructive pulmonary disease, muscle wasting syndrome, sarcopenia, or cachexia), metabolic diseases or disorders (such as type 2 diabetes, noninsulin-dependent diabetes mellitus, hyperglycemia, or obesity), adipose tissue disorders (such as obesity) and bone degenerative diseases (such as osteoporosis).



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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C07K14/475 C07K14/51 C12N15/62 A61K38/18 A61P21/00 A61P3/00 A61P19/10		
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 C12N C07K 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 43781 A (METAMORPHIX INC (US) TOPOUZIS WRIGHT RATOVITSKI LIANG BRADY SINHA ET A) 27 July 2000 (2000-07-27) cited in the application page 4, line 9-11 page 6; figure 17 page 21, paragraph 1 page 22, line 26 -page 23, line 14; figure 13 page 32 -page 41 -/--	1-6, 15, 16, 18-26, 29-32, 36-41, 50, 52-65, 74, 75, 77-85, 88-91, 95-100, 108, 109, 111-118
<input checked="" type="checkbox"/>	Further documents are listed in the continuation of box C.	<input checked="" type="checkbox"/>
° 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 17 February 2003		Date of mailing of the international search report 25. 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 Macchia, G

INTERNATIONAL SEARCH REPORT

International Application No

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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	page 43 -page 44 page 66 -page 69; example 10 page 80 -page 85; claims --- ZHU X. ET AL.: "Dominant negative myostatin produces hypertrophy without hyperplasia in muscle" FEBS LETTERS, vol. 474, no. 1, 26 May 2000 (2000-05-26), pages 71-75, XP004337183 ISSN: 0014-5793 the whole document	1-6, 16, 19-26, 31, 32, 36-41, 50, 53-57
X	WO 99 24058 A (GENETICS INSTITUTE, INC. (US); CELESTE A.J.; WOZNEY J.M.; THIES S.R.) 20 May 1999 (1999-05-20) page 14	60-62, 74, 80-84, 88-91, 95-99, 108, 112-118
P, X	WO 02 09641 A (THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE (US); LEE; MCPHERRON) 7 February 2002 (2002-02-07) the whole document	1-6, 16, 19, 20, 22-26, 31, 32, 36-41, 50, 53-57
A	WO 99 45949 A (GENETICS INSTITUTE, INC. (US); WOOD CLIVE R.; FITZ LORI JO) 16 September 1999 (1999-09-16)	
A	WO 99 56768 A (METAMORPHIX INC (US) STRASSMANN GIDEON; LIANG LI-FANG; TOPOUZIS STAVRO) 11 November 1999 (1999-11-11) the whole document	55, 58, 114, 117
A	WO 00 11163 A (REGENERON PHARMACEUTICALS, INC. (US); ECONOMIDES ARIS N.; STAHL NEIL) 2 March 2000 (2000-03-02) the whole document	7, 66

INTERNATIONAL SEARCH REPORT

International application No.
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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:

Although claims 38-59 and 97-118 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. 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: 4, 5, 19, 33-35, 41 all totally; 1-3, 6-14, 16-18, 20-28, 31, 32, 36-40, 42-48, 50-59 all partially

A modified GDF-8 propeptide having an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide. Said modified GDF-8 propeptide containing an inactivated proteolytic cleavage site. Related products compositions and methods.

2. Claims: 15, 29, 30, 49 all totally; 1-3, 6-14, 16-18, 20-28, 31, 32, 36-40, 42-48, 50-59 all partially

A modified GDF-8 propeptide having an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide. Said modified GDF-8 propeptide having an altered glycosylation site. Related products, compositions and methods.

3. Claims: 63, 64, 78, 92-94, 100 all totally; 60-62, 65-73, 75-77, 79-87, 90, 91, 95-99, 101-107, 110-118 all partially

A modified BMP-11 propeptide having an increased in vivo or in vitro half-life relative to a corresponding unmodified BMP-11 propeptide. Said modified BMP-11 propeptide containing an inactivated proteolytic cleavage site. Related products, compositions and methods.

4. Claims: 74, 88, 89, 108, 109 all totally; 60-62, 65-73, 75-77, 79-87, 90, 91, 95-99, 101-107, 110-118 all partially

A modified BMP-11 propeptide having an increased in vivo or in vitro half-life relative to a corresponding unmodified BMP-11 propeptide. Said modified BMP-11 propeptide having an altered glycosylation site. Related products, compositions and methods.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/03467

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