

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number  
**WO 2004/078140 A3**

- (51) International Patent Classification<sup>7</sup>: **C12P 21/06**, C12N 9/00, 9/24, 1/20, 15/00, C07H 21/04
- (21) International Application Number: PCT/US2004/006656
- (22) International Filing Date: 5 March 2004 (05.03.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/452,360 5 March 2003 (05.03.2003) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:  
US 60/452,360 (CON)  
Filed on 5 March 2003 (05.03.2003)
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (88) Date of publication of the international search report: 17 November 2005
- 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.

(54) Title: SOLUBLE HYALURONIDASE GLYCOPROTEIN (sHASEGP), PROCESS FOR PREPARING THE SAME, USES AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEREOF

(57) Abstract: The invention relates to the discovery of novel soluble neutral active Hyaluronidase Glycoproteins (sHASEGP's), methods of manufacture, and their use to facilitate administration of other molecules or to alleviate glycosaminoglycan associated pathologies. Minimally active polypeptide domains of the soluble, neutral active sHASEGP domains are described that include asparagine-linked sugar moieties required for a functional neutral active hyaluronidase domain. Included are modified aminoterminal leader peptides that enhance secretion of sHASEGP. The invention further comprises sialated and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics over naturally occurring slaughterhouse enzymes. Further described are suitable formulations of a substantially purified recombinant sHASEGP glycoprotein derived from a eukaryotic cell that generate the proper glycosylation required for its optimal activity.



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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/066564

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C12P 21/06; C12N 9/00, 9/24, 1/20, 15/00; C07H 21/04  
 US CL : 424/94.1; 435/4, 6, 69.1, 183, 200, 252.3, 320.1, 325; 536/23.2, 23.5

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)  
 U.S. : 424/94.1; 435/4, 6, 69.1, 183, 200, 252.3, 320.1, 325; 536/23.2, 23.5

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 practicable, search terms used)  
 Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHER GN et al. The dual functions of GPI anchored PH-20: hyaluronidase and intracellular signalling, Matrix Biol. December 2001, Vol.20, No.8, pages 515-525.	1-37, 67-68, 78-79, 89-91, 144-153
X	CHER GN et al. The PH-20 protein in cynomolgus macaque spermatozoa: identification of two different forms exhibiting hyaluronidase activity, Dev. Biol. 1996, Vol.175, No.1, pages 142-153.	1-37, 67-68, 78-79, 89-91, 144-153
X --- Y	US 5,721,348 (PRIMAKOFF et al.) 24 February 1998 (24.02.1998) (sequence 1, 3, 4, 5, 6 have 100% match with sequence 6 of the patent)	1-10, 13-17, 20-24, 29-34, 37-51, 54-59  11-12, 18-19, 35-36, 67-161
X --- Y	US 5,854,046 (AU-YOUNG et al.) 29 December 1998 (29.12.1998) (see entire document, sequence 3 in the reference has 99.7% match with sequences 1,3,4,5,6)	1-10, 13-17, 20-24, 29-34, 37-51, 54-59  11-12, 18-19, 35-36, 67-161

Further documents are listed in the continuation of Box C.  See patent family 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 application or patent 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	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search 27 May 2005 (27.05.2005)	Date of mailing of the international search report 26 AUG 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Manjunath N. Rao, Ph.D. Telephone No. 571-272-1600

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US04/06656

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,958,750 (AU-YOUNG et al.) 28 September 1999 (28.09.1999) (see entire document, sequence 3 in the reference has 99.7% match with sequences 1,3,4,5,6)	1-10, 13-17, 20-24, 29-34, 37-51, 54-59 ----- 11-12, 18-19, 35-36, 67-161
X -- Y	US 6,057,110 (AU-YOUNG et al.) 2 May 2000 (02.05.2000) (see entire document, sequence 3 in the reference has 99.7% match with sequences 1,3,4,5,6)	1-10, 13-17, 20-24, 29-34, 37-51, 54-59 ----- 11-12, 18-19, 35-36, 67-161

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US04/06634

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation 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.: 1-51,54-59 and 67-161
- Remark on Protest  The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US04/06656

### BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-51, 54-59, 67-161, drawn to a substantially purified glycoprotein comprising a soluble hyaluronidase, a pharmaceutical composition comprising the same, polynucleotide encoding the polypeptide, vectors, host cells comprising the same, and several methods of use of the polypeptide and the pharmaceutical compositions.

Group II, claim 52, drawn to an antibody.

Group III, claim 53, drawn to a non-human transgenic animal.

Group IV, claims 60-66, drawn to a method of *ex vivo* gene therapy.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I is drawn to polynucleotide encoding a polypeptide having the special technical feature of hyaluronidase activity which groups II-IV do not have.

Group II is drawn to an antibody having the special technical feature of antibodies which groups I and III-IV do not have.

Group III is drawn to a non-human transgenic animal having the special technical feature of transgenics which groups I-II and IV do not have.

Group IV is drawn to method having the special technical feature of gene therapy which groups I-III do not have.

Furthermore, The ISA considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first-recited product, a polynucleotide encoding hyaluronidase, a vector, a host cell, a method for producing and several methods of using the polypeptide. Furthermore the ISA considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.