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Lane, Arlington, MA 02474 (US). **ROSSOMANDO, Anthony** [US/US]; 50 Asti Avenue, Revere, MA 02151 (US).

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(74) Agent: **ELRIFI, Ivor, R.**; Mintz, Levin, Cohn, Ferris, Glosky and Popeo PC, One Financial Center, Boston, MA 02111 (US).

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(71) Applicant (*for all designated States except US*): **BIO-GEN, INC.** [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US).

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(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **SAH, Dinah, W., Y.** [US/US]; Apt. 2608, 4 Longfellow Place, Boston, MA 02114 (US). **PEPINSKY, R., Blake** [US/US]; 30 Falmouth Road, Arlington, MA 02474 (US). **BORJACK-SJODIN, Paula, Ann** [US/US]; 46 Florence Road, Waltham, MA 02453 (US). **MILLER, Stephan, S.** [US/US]; 6 Woodside

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(54) Title: POLYMER CONJUGATES OF NEUBLASTIN AND METHODS OF USING SAME

(57) Abstract: A variant neublustin polypeptide suitable for formation of a conjugate comprising the variant neublustin polypeptide coupled to a polymer containing a polyalkylene glycol moiety is disclosed. The present conjugate has prolonged bioavailability and, in preferred embodiments, prolonged biological activity relative to non-modified or wild-type forms of neublustin. The conjugates of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications.

INTERNATIONAL SEARCH REPORT

In national Application No

PCT/US 02/02319

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 C07K14/475 C12N15/12 A61K47/48 A61K38/18		
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 C07K C12N 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)		
CHEM ABS Data, EPO-Internal, BIOSIS, SEQUENCE SEARCH, PAJ, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 01815 A (BLOM NIKOLAJ ;HANSEN CLAUS (DK); JOHANSEN TEIT E (DK); NEUROSEARCH) 13 January 2000 (2000-01-13) cited in the application the whole document	1-84
Y	BALOH R H ET AL: "ARTEMIN, A NOVEL MEMBER OF THE GDNF LIGAND FAMILY, SUPPORTS PERIPHERAL AND CENTRAL NEURONS AND SIGNALS THROUGH THE GFRALPHA3- RET RECEPTOR COMPLEX" NEURON, CAMBRIDGE, MA, US, vol. 21, no. 6, December 1998 (1998-12), pages 1291-1302, XP000857438 cited in the application abstract; figure 1	1-84
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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	Date of mailing of the international search report	
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Name and mailing address of the ISA	Authorized officer	
European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ury, A	

INTERNATIONAL SEARCH REPORT

 Int. Patent Application No
 PCT/US 02/02319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BALOH ROBERT H ET AL: "Functional mapping of receptor specificity domains of glial cell line-derived neurotrophic factor (GDNF) family ligands and production of GFR α 1 RET-specific agonists." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 5, 4 February 2000 (2000-02-04), pages 3412-3420, XP002216531 ISSN: 0021-9258 cited in the application the whole document ---	1-84
Y	WO 99 43813 A (FANDL JAMES P ;STAHL NEIL (US); REGENERON PHARMA (US)) 2 September 1999 (1999-09-02) examples 8,15 ---	1-84
Y	US 5 770 577 A (KINSTLER OLAF BORIS ET AL) 23 June 1998 (1998-06-23) column 14, line 12-20 column 16, line 17-23 ---	1-84
Y	DELGADO C ET AL: "THE USES AND PROPERTIES OF PEG-LINKED PROTEINS" CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, XX, XX, vol. 9, no. 3/4, 1992, pages 249-304, XP002930070 ISSN: 0743-4863 Whole document and in particular abstract, paragraphs C.1 and IV. ---	1-84
Y	FRANCIS G E ET AL: "PEGYLATION OF CYTOKINES AND OTHER THERAPEUTIC PROTEINS AND PEPTIDES: THE IMPORTANCE OF BIOLOGICAL OPTIMISATION OF COUPLING TECHNIQUES" INTERNATIONAL JOURNAL OF HEMATOLOGY, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 68, no. 1, July 1998 (1998-07), pages 1-18, XP000791226 ISSN: 0925-5710 page 2 "1.PEGylation of protein and peptides". ---	1-84
Y	REDDY K R: "CONTROLLED-RELEASE, PEGYLATION, LIPOSOMAL FORMULATIONS: NEW MECHANISMS IN THE DELIVERY OF INJECTABLE DRUGS" ANNALS OF PHARMACOTHERAPY, XX, XX, vol. 34, no. 7/8, July 2000 (2000-07), pages 915-923, XP001010043 ISSN: 1060-0280 Whole document and in particular figure 3; table 1 -----	1-84

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 78-84 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:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/02319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001815	A	13-01-2000	AU 4769399 A 24-01-2000
			BR 9911908 A 27-03-2001
			CA 2336218 A1 13-01-2000
			CN 1311818 T 05-09-2001
			WO 0001815 A2 13-01-2000
			EE 200100008 A 17-06-2002
			EP 1095140 A2 02-05-2001
			HU 0103758 A2 28-01-2002
			JP 2002519061 T 02-07-2002
			NO 20010088 A 06-03-2001
			PL 345950 A1 14-01-2002
			TR 200100056 T2 21-11-2001
			US 2002055467 A1 09-05-2002
WO 9943813	A	02-09-1999	AT 212375 T 15-02-2002
			AU 749660 B2 04-07-2002
			AU 2976399 A 15-09-1999
			CA 2320402 A1 02-09-1999
			DE 69900816 D1 14-03-2002
			DE 69900816 T2 29-08-2002
			DK 1056856 T3 06-05-2002
			EP 1056856 A1 06-12-2000
			ES 2168006 T3 16-05-2002
			JP 2002504370 T 12-02-2002
			PT 1056856 T 31-07-2002
			WO 9943813 A1 02-09-1999
			US 2002123462 A1 05-09-2002
US 5770577	A	23-06-1998	AT 175973 T 15-02-1999
			AU 694589 B2 23-07-1998
			AU 4107196 A 06-06-1996
			CA 2204640 A1 23-05-1996
			CN 1173183 A 11-02-1998
			CZ 9701375 A3 14-10-1998
			DE 69507507 D1 04-03-1999
			DE 69507507 T2 27-05-1999
			DK 792288 T3 13-09-1999
			EP 0792288 A1 03-09-1997
			ES 2126331 T3 16-03-1999
			GR 3029790 T3 30-06-1999
			HU 77747 A2 28-07-1998
			IL 115965 A 28-01-2001
			JP 10508853 T 02-09-1998
			KR 253762 B1 01-05-2000
			NO 972176 A 14-07-1997
			NZ 296452 A 28-01-1999
			RU 2136694 C1 10-09-1999
			SK 57197 A3 11-02-1999
WO 9615146 A1 23-05-1996			
ZA 9509653 A 26-08-1997			