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- (71) Applicant (for all designated States except US): **NOBEX CORPORATION** [US/US]; P.O. Box 13940, Research Triangle Park, NC 27709-3940 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KOSUTIC, Gordana** [—/US]; 6425 Secret Drive, Raleigh, NC 27612 (US). **EKWURIBE, Nnochiri, N.** [NG/US]; 216 Colts-gate Drive, Cary, NC 27511 (US). **PRICE, Christopher, H.** [US/US]; 200 Commons Way, Chapel Hill, NC 27516 (US). **ANSARI, Aslam, M.** [—/US]; 19651 Club Lake Road, Montgomery Village, MD 20886 (US). **ODEN-BAUGH, Amy, L.** [US/US]; 4023 Quail High Boulevard, Morrisville, NC 27560 (US).
- (74) Agent: **MYERS BIGEL SIBLEY & SAJOVEC, P.A.**; P.O. Box 37428, Raleigh, NC 27627 (US).
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- (88) Date of publication of the international search report: 1 September 2005
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(54) Title: MIXTURES OF CALCITONIN DRUG-OLIGOMER CONJUGATES AND METHODS OF USE IN PAIN TREATMENT

(57) Abstract: A mixture of conjugates in which each conjugate in the mixture comprises a calcitonin drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may lower serum calcium levels in a subject by 10, 15 or even 20 percent or more. Moreover, the mixture may be more effective at surviving an *in vitro* model of intestinal digestion than non-conjugated calcitonin. Furthermore, the mixture may exhibit a higher bioavailability than non-conjugated calcitonin. The compositions of this invention are useful in the treatment of various bone disorders and pain.

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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US04/16784

<p>A. CLASSIFICATION OF SUBJECT MATTER                  IPC(7) : C07K 1/113, 14/535, 7/00; A61K 38/00                  US CL : 530/, 307, 351, 313, 345; 514/2, 3, 8, 12, 13                  According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols)                  U.S. : 530/, 307, 351, 313, 345; 514/2, 3, 8, 12, 13</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)                  Please See Continuation Sheet</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td>US 2003/0060606 A1 (EKWURIBE et al.) 27 March 2003 (27.03.2003), abstract, claims 1-172 and [0011]-[0052].</td> <td>1-13</td> </tr> <tr> <td>Y</td> <td>US 6,506,730 B1 (LEE et al.) 14 January 2003 (14.01.2003), abstract, columns 5-11 and claims 1-18.</td> <td>1-2</td> </tr> <tr> <td>Y</td> <td>US 5,773,581 A (CAMBLE et al.) 30 June 1998 (30.06.1998), columns 3-5 and 11-14, Examples 27-28.</td> <td>1-2</td> </tr> <tr> <td>Y</td> <td>LEE et al. Isolation, Characterization, and Stability of Positional Isomers of Mono-PEGylated Salmon Calcitonins. Pharmaceutical Research, 1999, Vol. 15, No. 6, pages 813-818. Entire document.</td> <td>1-2</td> </tr> <tr> <td>Y</td> <td>LEE et al. Preparation and Characterization of Mono-PEGylated Epidermal Growth Factor: Evaluation of in Vitro Biologic Activity. Pharmaceutical Research. June 2002, Vol. 19, No. 6, pages 845-851. Entire document.</td> <td>1-2</td> </tr> <tr> <td>Y</td> <td>LUCKE et al. Biodegradable poly(D,L-lactic acid)-poly(ethylene glycol)-monomethyl ether diblock copolymers: structures and surface properties relevant to their use as biomaterials. Biomaterials. December 200, Vol. 21, pages 2361-2370. Entire document.</td> <td>1-2 and 13</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	US 2003/0060606 A1 (EKWURIBE et al.) 27 March 2003 (27.03.2003), abstract, claims 1-172 and [0011]-[0052].	1-13	Y	US 6,506,730 B1 (LEE et al.) 14 January 2003 (14.01.2003), abstract, columns 5-11 and claims 1-18.	1-2	Y	US 5,773,581 A (CAMBLE et al.) 30 June 1998 (30.06.1998), columns 3-5 and 11-14, Examples 27-28.	1-2	Y	LEE et al. Isolation, Characterization, and Stability of Positional Isomers of Mono-PEGylated Salmon Calcitonins. Pharmaceutical Research, 1999, Vol. 15, No. 6, pages 813-818. Entire document.	1-2	Y	LEE et al. Preparation and Characterization of Mono-PEGylated Epidermal Growth Factor: Evaluation of in Vitro Biologic Activity. Pharmaceutical Research. June 2002, Vol. 19, No. 6, pages 845-851. Entire document.	1-2	Y	LUCKE et al. Biodegradable poly(D,L-lactic acid)-poly(ethylene glycol)-monomethyl ether diblock copolymers: structures and surface properties relevant to their use as biomaterials. Biomaterials. December 200, Vol. 21, pages 2361-2370. Entire document.	1-2 and 13
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<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.      <input type="checkbox"/> See patent family annex.</p> <table border="1"> <tr> <td>* Special categories of cited documents:</td> <td>"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</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			* Special categories of cited documents:	"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	"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent published on or after the international filing date	"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	"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)	"&" document member of the same patent family	"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										
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<p>Date of the actual completion of the international search                  17 July 2005 (17.07.2005)</p>		<p>Date of mailing of the international search report                  25 JUL 2005</p>																					
<p>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</p>		<p>Authorized officer                  Samuel W Liu                  Telephone No. (571) 272-1600</p>																					

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	LEE et al. Polymeric nanoparticle composed of fatty acids and poly(ethylene glycol) as a drug carrier. International Journal of Pharmaceutics. January 2003, Vol. 251, pages 23-32. Entire document.	4-12
Y,P	US 2003/0153488 A1 (MAY et al.) 14 August 2003 (14.08.2003), paragraph [0054].	1-13 -

# INTERNATIONAL SEARCH REPORT

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Continuation of B. FIELDS SEARCHED Item 3:

Databases: Medline, US Pre-Grant publication Full-Text database, US Patent Full-Text database, EPO Abstracts database, JPO Abstracts database, Derwent World Patent Index, and, issued patents AA, pending patents AA and Genbank (for sequence search).  
Search terms: calcitonin, conjugate, polyethylene glycol (PEG), polymer, lysine and polyalkylen glycol.