



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>7</sup> : G01N 33/50, A61K 38/22, 38/19, A61P 37/00 // C12Q 1/68, (A61K 38/22, 31:35), (A61K 38/19, 31:35)</p>	A3	<p>(11) International Publication Number: <b>WO 00/07014</b></p> <p>(43) International Publication Date: 10 February 2000 (10.02.00)</p>
<p>(21) International Application Number: PCT/EP99/05489</p> <p>(22) International Filing Date: 27 July 1999 (27.07.99)</p> <p>(30) Priority Data: 98202524.9 28 July 1998 (28.07.98) EP</p> <p>(71) Applicant (for all designated States except US): VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECH- NOLOGIE VZW [BE/BE]; Rijvisschestraat 120, B-9052 Zwijnaarde (BE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BROEKAERT, Daniël [BE/BE]; Hovigen 5, B-9950 Waarschoot (BE). VANDEK- ERCKHOVE, Joël, Stefaan [BE/BE]; Rode Beukendreef 27, B-8210 Loppem (BE). VERHEE, Annick [BE/BE]; Pas- toor Denyslaan 60, B-8810 Lichtervelde (BE). WAELPUT, Wim [BE/BE]; Nieuwerkerkenstraat 111, B-9100 Nieuw- erkerken-Waas (BE). TAVERNIER, Jan [BE/BE]; Bottel- weg 2, B-9860 Balegem (BE).</p> <p>(74) Common Representative: VLAAMS INTERUNIVERSITAIR INSTITUUT VOOR BIOTECHNOLOGIE VZW; Rijviss- chestraat 120, B-9052 Zwijnaarde (BE).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> <p>(88) Date of publication of the international search report: 27 April 2000 (27.04.00)</p>	
<p>(54) Title: LEPTIN-MEDIATED GENE-INDUCTION</p>		
<p>(57) Abstract</p> <p>Using the PC12 cell line as a model system a series of transcripts induced through activation of the leptin receptor or gp130 was identified. Based on kinetic studies on undifferentiated PC12 cells, two distinct gene-sets could be discerned: STAT-3, SOCS-3, Metallothionein-II, the serine/threonine kinase Fnk and the rat homologue of MRF-1 which are immediate early response genes, and Pancreatitis Associated Protein I, Squalene Epoxidase, Uridinediphosphate Glucuronyl Transferase and Annexin VIII, which are late induced target genes. In the latter case only, a strong co-stimulation with the adenylate cyclase activator forskolin was observed. Two additional transcripts encoding Leptin Induced Protein I (LIP-I) and Leptin Induced Protein II (LIP-II) were also identified. LIP-II is a rat orthologue of the human Down Syndrome Cell Adhesion Molecule (DS-CAM). In both cases, no forskolin co-stimulatory effect was observed. On PC12 cells differentiated to a neural phenotype by combined <math>\beta</math>-NGF and forskolin treatment, Pancreatitis Associated Protein III, Peripherin and Mx2 protein were further identified as being regulated by leptin. Finally, from an RDA experiment using mRNA from either hyper-IL-6- or leptin-induced PC12 cells, the Reg gene, another member of the Pancreatitis Associated Protein family, and HIP-1 were identified as selectively up-regulated by H-IL-6. STAT-3 and SOCS-3 have been recognized in leptin signalling <i>in vivo</i> before. In this invention it is also demonstrated that leptin modulates the <i>in vivo</i> expression of the MT-II, Fnk and Pancreatitis Associated Protein I genes.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/05489

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 G01N33/50 A61K38/22 A61K38/19 A61P37/00 //C12Q1/68,  
(A61K38/22, 31:35), (A61K38/19, 31:35)

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 G01N A61K C07K

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	<p>C. VAISSE ET AL.: "LEPTIN ACTIVATION OF STAT3 IN THE HYPOTHALAMUS OF WILD-TYPE AND ob/ob MICE BUT NOT db/db MICE." NATURE GENETICS, vol. 14, September 1996 (1996-09), pages 95-97, XP002099319 NEW YORK, N.Y., US cited in the application page 95, left-hand column, paragraph 1</p>	1, 2, 4, 5
X	<p>C. BJÖRBAEK ET AL.: "IDENTIFICATION OF SOCS-3 AS A POTENTIAL MEDIATOR OF CENTRAL LEPTIN RESISTANCE." MOLECULAR CELL, vol. 1, no. 4, March 1998 (1998-03), pages 619-625, XP002099320 page 619, right-hand column, paragraph 3 page 622, right-hand column, paragraph 2</p>	1, 2, 4, 5

Further documents are listed in the continuation of box C.

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)
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- "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.
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Date of the actual completion of the international search

17 January 2000

Date of mailing of the international search report

02/02/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/05489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 20158 A (SMITHKLINE BEECHAM PLC)                      14 May 1998 (1998-05-14)                      claims 1,3; example 2</p> <p style="text-align: center;">---</p>	6
A	<p>J.H. BEATTIE ET AL.: "OBESITY AND                      HYPERLEPTINEMIA IN METALLOTHIONEIN (-I AND                      -II) NULL MICE."                      PROCEEDINGS OF THE NATIONAL ACADEMY OF                      SCIENCES OF USA,                      vol. 95, January 1998 (1998-01), pages                      358-363, XP002099321                      WASHINGTON, DC, US                      cited in the application                      page 362, left-hand column, line 41 - line                      51                      page 362, right-hand column, paragraph 2</p> <p style="text-align: center;">---</p>	1-5
P,X	<p>W. WAELPUT ET AL.: "ANALYSIS OF SIGNAL                      TRANSDUCTION VIA THE LEPTIN RECEPTOR."                      INTERNATIONAL JOURNAL OF OBESITY,                      vol. 22, no. SUPPL. 3,                      August 1998 (1998-08), page S99                      XP000867244                      LONDON, GB                      abstract nr. P13</p> <p style="text-align: center;">-----</p>	1-5

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/05489

## 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:  
Remark: Although claims 1-5 (all partially, as being related to an in vivo use) are being 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.: 7, 8  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7,8

Present claims 7 and 8 respectively relate to molecules obtainable by the screening method of claim 6 and a pharmaceutical composition comprising a molecule according to claim 7, defined by reference to a desirable characteristic or property, namely: molecules which interfere directly or indirectly with the induction of immediate early response genes and/or late target genes or with the activity of the products of said genes of claim 1. The claims cover all molecules and pharmaceutical compositions having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such molecules and pharmaceutical compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the molecules and pharmaceutical compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of leptin and/or a cytokine to activate a signaling cascade as defined in claims 1-5 and a method of screening molecules as defined in claim 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/05489

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820158 A	14-05-1998	AU 4789297 A	29-05-1998
		CZ 9901499 A	13-10-1999
		EP 0951564 A	27-10-1999
		NO 992107 A	30-06-1999

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