



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

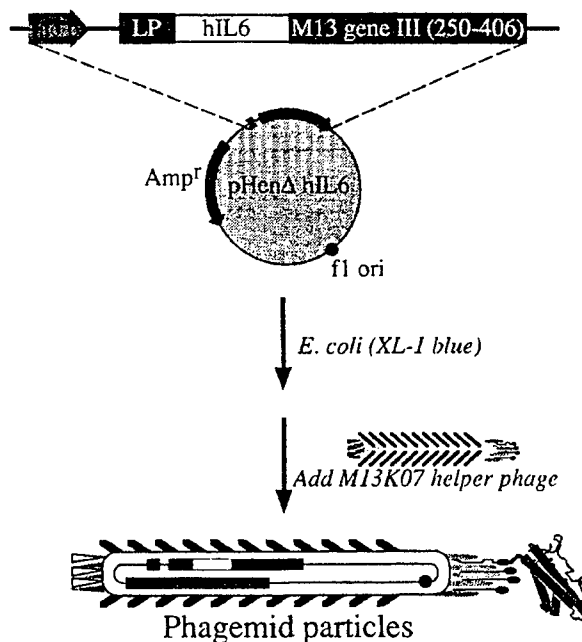
<p>(51) International Patent Classification <sup>5</sup> : G01N 33/68, 33/74, C12N 15/12, 15/18, C07K 7/26</p>	A3	<p>(11) International Publication Number: <b>WO 95/00852</b></p> <p>(43) International Publication Date: 5 January 1995 (05.01.95)</p>
<p>(21) International Application Number: PCT/IT94/00095</p> <p>(22) International Filing Date: 23 June 1994 (23.06.94)</p> <p>(30) Priority Data: RM93A000409 23 June 1993 (23.06.93) IT</p> <p>(71) Applicant (for all designated States except US): ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI S.P.A. [IT/IT]; Via Pontina Km 30.600, I-00040 Pomezia (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SAVINO, Rocco [IT/IT]; Via della Tecnica, 76, I-00040 Pomezia (IT). LAHM, Armin [IT/IT]; Piazza S. Maria Ausiliatrice, 18, I-00153 Roma (IT). CILIBERTO, Gennaro [IT/IT]; Viale Gorgia di Leontini, 330/19, I-00124 Casalpalocco (IT).</p> <p>(74) Agents: DI CERBO, Mario et al.; Società Italiana Brevetti S.p.A., Piazza di Pietra, 39, I-00186 Roma (IT).</p>		<p>(81) Designated States: AU, CA, CN, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 30 March 1995 (30.03.95)</p>

(54) Title: A METHODOLOGY FOR SELECTING SUPERAGONISTS, ANTAGONISTS AND SUPERANTAGONISTS OF HORMONES WHOSE RECEPTOR COMPLEX INCLUDES GP 130

## (57) Abstract

It has been found that the ligands of the group of cytokins similar to Interleukin 6 (IL-6), that is Oncostatin M (OSM), Leukemia Inhibitory Factor (LIF), Ciliary Neurotrophic Factor (CNTF) and Interleukin 11 (IL-11), induce formation of a receptor complex of which the membrane molecule gp 130 is a part. It is thus possible to formulate the hypothesis that two different surfaces of the protein (in this class of hormones), known as site 1 and site 2, bind to two different molecules: site 1 to the specific receptor and site 2 to gp 130. The invention allows the identification of these sites and the isolation of variants having, with respect to the wild hormone, a greater affinity for the specific receptor (superagonists and superantagonists) or affinity for gp 130 reduced or abolished (antagonists and superantagonists). The figure shows the construct pHenΔ hIL-6 and the production of phasmidic particles that can be used to select agonists of Interleukin 6.

## pHenΔ hIL6 AND PRODUCTION OF PHAGEMID PARTICLES



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IT 94/00095

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 5 G01N33/68 G01N33/74 C12N15/12 C12N15/18 C07K7/26

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 5 G01N C07K A01K C12P C12N

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.
A	WO,A,92 21029 (GENENTECH INCORPORATED) 26 November 1992 cited in the application see the whole document ---	1-8
A	WO,A,90 04788 (GENENTECH INCORPORATED) 3 May 1990 see the whole document ---	1-8
A	EP,A,0 411 946 (T. KISHIMOTO) 6 February 1991 see the whole document ---	1-8
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

20 February 1995

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**INTERNATIONAL SEARCH REPORT**

Internat. Application No PCT/IT 94/00095
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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.
T	<p>EMBO JOURNAL, vol.13, no.6, 1994, HEIDELBERG FRG pages 1357 - 1367 'Generation of interleukin-6 receptor antagonists by molecular-modeling guided mutagenesis of residues important for gp 130 activation' see the whole document -----</p>	1-8

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/IT 94/00095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9221029	26-11-92	EP-A- 0586549	16-03-94
		JP-T- 6507715	01-09-94
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WO-A-9004788	03-05-90	CA-A- 2001774	28-04-90
		EP-A- 0397834	22-11-90
		JP-T- 4502454	07-05-92
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EP-A-0411946	06-02-91	JP-A- 4029997	31-01-92
		AU-B- 635296	18-03-93
		AU-A- 6003990	07-02-91
		CA-A- 2022610	04-02-91
		US-A- 5132403	21-07-92
		US-A- 5223611	29-06-93
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