



(11) **EP 1 914 554 A3**

(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
06.08.2008 Bulletin 2008/32

(43) Date of publication A2:
23.04.2008 Bulletin 2008/17

(21) Application number: **07023699.7**

(22) Date of filing: **20.04.2001**

(51) Int Cl.:
G01N 33/68 (2006.01) **G01N 33/574** (2006.01)
C07K 16/24 (2006.01) **C12N 15/19** (2006.01)
C12Q 1/68 (2006.01) **A61K 48/00** (2006.01)
A61K 38/19 (2006.01) **A61P 15/06** (2006.01)
A61P 29/00 (2006.01) **A61P 35/00** (2006.01)

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **20.04.2000 AU PQ703700**
11.05.2000 AU PQ746500

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
01923411.1 / 1 279 039

(71) Applicant: **ST VINCENT'S HOSPITAL SYDNEY
LIMITED**
Darlinghurst, NSW 2010 (AU)

(72) Inventors:
• **Breit, Samuel Norbert**
Gordon, NSW 2072 (AU)
• **Brown, David Alexander**
Bondi Beach, NSW 2026 (AU)

(74) Representative: **Harding, Charles Thomas**
D Young & Co
120 Holborn
London EC1N 2DY (GB)

(54) **Diagnostic assay and method of treatment involving macrophage inhibitory cytokine-1 (MIC-1)**

(57) Methods for diagnosing risk of miscarriage and/or premature birth, foetal abnormalities, cancer (e.g. prostate cancer) and inflammatory disease (e.g. rheumatoid arthritis) are disclosed which involve determining abnormal levels of macrophage inhibitory cytokine-1 (MIC-1) in a body sample or, otherwise, determining the

presence of a MIC-1 variant protein. Also disclosed are methods for reducing the risk of miscarriage and/or premature birth in pregnant subjects, and methods for treatment of inflammatory disease and/or cancer.

EP 1 914 554 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 02 3699

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 99/06445 A (HUYNH THANH V ; HSIAO EDWARD (US); LEE SE JIN (US); SEBALD SUZANNE (US) 11 February 1999 (1999-02-11) * page 5, line 24 - page 6, line 2 * * page 16, line 8 - line 20 * * page 18, line 22 - page 19, line 2 * * claims 15-41 *	1-6	INV. G01N33/68 G01N33/574 C07K16/24 C12N15/19 C12Q1/68 A61K48/00 A61K38/19 A61P15/06 A61P29/00 A61P35/00
A	FAIRLIE W D ET AL: "MIC-1 IS A NOVEL TFG-BETA SUPERFAMILY CYTOKINE ASSOCIATED WITH MACROPHAGE ACTIVATION" JOURNAL OF LEUKOCYTE BIOLOGY, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL, US, vol. 65, no. 1, January 1999 (1999-01), pages 2-5, XP000937688 ISSN: 0741-5400 * abstract * * figure 2 * * page 5, column 1, paragraph 4 - column 2, paragraph 1 *	1-6	
			TECHNICAL FIELDS SEARCHED (IPC)
D,Y	WO 97/00958 A (ST VINCENTS HOSP SYDNEY [AU]; BREIT SAMUEL NORBERT [AU]; BOOTCOV MICHE) 9 January 1997 (1997-01-09) * page 2, line 21 - line 24 * * page 5, line 14 - line 19 * * page 6, line 14 - line 17 * * claim 37 * * figure 1 *	1,2,5,6	G01N A61K A61P
Y	WO 99/21011 A (FIBROGEN INC [US]; CHUNLIN YANG [US]) 29 April 1999 (1999-04-29) * claims 1-7 *	1,2,5,6	
<div style="border: 1px solid black; padding: 5px;"> <p>The present search report has been drawn up for all claims</p> </div>			
Place of search		Date of completion of the search	Examiner
The Hague		13 March 2008	van der Kooij, M
<div style="display: flex; justify-content: space-between;"> <div> <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p> </div> <div> <p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p> </div> </div>			

 6
EPO FORM 1503 (03.02 (P04C01))

**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:
- 1-6
- ☐ The present supplementary European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims (Rule 164 (1) EPC).



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-6

A method of diagnosis of rheumatoid arthritis comprising measuring the amount of MIC-1 present in a body sample from a test subject and comparing said measured amount of MIC-1 against an amount measured in a normal subject.

2. claims: 7-11

A method of diagnosis or assessment of cancer characterized by an abnormal expression level of MIC-1 comprising measuring the amount of MIC-1 in the test sample and compare said amount with that of a normal subject.

3. claim: 12

A method of treating inflammation by administering an effective amount of MIC-1 to a subject.

4. claim: 13

A method of genotyping a human subject in relation to MIC-1 comprising determining whether said subject is homozygous or heterozygous for a MIC-1 protein having either an aspartic acid or histidine at position 202 or a position corresponding to position 202 of immature human wild type MIC-1.

5. claims: 14-16 and 18-20

Composition comprising MIC-1 for use in treating a pregnant subject to reduce the risk of miscarriage and/or premature birth.

6. claim: 17 and 21

A recombinant adenoviral or adenoviral-associated vector including an expressible MIC-1-encoding nucleotide sequence or liposomes containing a linear MIC-1-encoding DNA operably linked to an appropriate promoter sequence for use in treating a pregnant subject to reduce the risk of miscarriage and/or premature birth.

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 02 3699

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

13-03-2008

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9906445	A	11-02-1999	AU	8591198 A	22-02-1999


WO 9700958	A	09-01-1997	CA	2225377 A1	09-01-1997
			EP	0833912 A1	08-04-1998
			NZ	310370 A	27-04-2001

WO 9921011	A	29-04-1999	AU	1276899 A	10-05-1999

专利名称(译)	涉及巨噬细胞抑制性细胞因子-1 (MIC-1) 的诊断测定和治疗方法		
公开(公告)号	EP1914554A3	公开(公告)日	2008-08-06
申请号	EP2007023699	申请日	2001-04-20
申请(专利权)人(译)	圣文森特医院SYDNEY LIMITED		
当前申请(专利权)人(译)	圣文森特医院SYDNEY LIMITED		
[标]发明人	BREIT SAMUEL NORBERT BROWN DAVID ALEXANDER		
发明人	BREIT, SAMUEL NORBERT BROWN, DAVID ALEXANDER		
IPC分类号	G01N33/68 G01N33/574 C07K16/24 C12N15/19 C12Q1/68 A61K48/00 A61K38/19 A61P15/06 A61P29/00 A61P35/00 G01N33/53 A61K38/00 A61P43/00 C12N15/09		
CPC分类号	A61K38/195 A61P15/06 A61P29/00 C07K16/24 C07K2317/34 C12Q1/6883 C12Q1/6886 C12Q2600/156 C12Q2600/158 G01N33/6893 G01N2800/102		
代理机构(译)	HARDING , CHARLES THOMAS		
优先权	2000PQ7037 2000-04-20 AU 2000PQ7465 2000-05-11 AU		
其他公开文献	EP1914554B1 EP1914554A2		
外部链接	Espacenet		

摘要(译)

公开了用于诊断流产和/或早产，胎儿异常，癌症（例如前列腺癌）和炎性疾病（例如类风湿性关节炎）的风险的方法，其涉及确定体内巨噬细胞抑制性细胞因子-1 (MIC-1) 的异常水平。样品或，否则，确定MIC-1 变体蛋白的存在。还公开了降低妊娠受试者中流产和/或早产风险的方法，以及治疗炎性疾病和/或癌症的方法。

		EUROPEAN SEARCH REPORT		Application Number EP 07 02 3699
DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of documents with indication, where appropriate, of relevant passages	Relevance to claims	CLASSIFICATION OF THIS APPLICATION (IPC)	
A	WO 99/06445 A (HUYNH THANH V.; HSIAO EDWARD (US); LEE SE JIN (US); SEBALD SUZANNE (US)) 11 February 1999 (1999-02-11) * page 5, line 24 - page 5, line 2 * * page 16, line 8 - line 20 * * page 18, line 22 - page 19, line 2 * * claims 15-41 *	1-6	INV. G01N33/68 G01N33/574 C07K16/24 C12N15/19 C12Q1/68 A61K48/00 A61K38/19 A61P15/06 A61P29/00 A61P35/00	
A	FAILLIE W D ET AL: "MIC-1 IS A NOVEL TFG-BETA SUPERFAMILY CYTOKINE ASSOCIATED WITH MACROPHAGE ACTIVATION" JOURNAL OF LEUKOCYTE BIOLOGY, FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL, US, vol. 65, no. 1, January 1999 (1999-01), pages 2-5, XP000937688 ISSN: 0741-5400 * abstract * * figure 2 * * page 5, column 1, paragraph 4 - column 2, paragraph 1 *	1-6		
D, Y	WO 97/00958 A (ST VINCENTS HOSP SYDNEY [AU]; BREIT SAMUEL NORBERT [AU]; BOOTCOV MICHE) 9 January 1997 (1997-01-09) * page 2, line 21 - line 24 * * page 5, line 14 - line 19 * * page 6, line 14 - line 17 * * claim 37 * * figure 1 *	1,2,5,6	G01N A61K A61P	
Y	WO 99/21011 A (FIBROGEN INC [US]; CHUNLIN YANG [US]) 29 April 1999 (1999-04-29) * claims 1-7 *	1,2,5,6		
6. This present search report has been drawn up for all claims				
Name of applicant The Hague		Date of invention or first publication 13 March 2008		Inventor van der Kooij, M
CATEGORY OF CITED DOCUMENTS				
1. prior art 2. state of the art 3. prior art 4. state of the art 5. prior art 6. state of the art 7. prior art 8. state of the art 9. prior art 10. state of the art 11. prior art 12. state of the art 13. prior art 14. state of the art 15. prior art 16. state of the art 17. prior art 18. state of the art 19. prior art 20. state of the art 21. prior art 22. state of the art 23. prior art 24. state of the art 25. prior art 26. state of the art 27. prior art 28. state of the art 29. prior art 30. state of the art 31. prior art 32. state of the art 33. prior art 34. state of the art 35. prior art 36. state of the art 37. prior art 38. state of the art 39. prior art 40. state of the art 41. prior art 42. state of the art 43. prior art 44. state of the art 45. prior art 46. state of the art 47. prior art 48. state of the art 49. prior art 50. state of the art 51. prior art 52. state of the art 53. prior art 54. state of the art 55. prior art 56. state of the art 57. prior art 58. state of the art 59. prior art 60. state of the art 61. prior art 62. state of the art 63. prior art 64. state of the art 65. prior art 66. state of the art 67. prior art 68. state of the art 69. prior art 70. state of the art 71. prior art 72. state of the art 73. prior art 74. state of the art 75. prior art 76. state of the art 77. prior art 78. state of the art 79. prior art 80. state of the art 81. prior art 82. state of the art 83. prior art 84. state of the art 85. prior art 86. state of the art 87. prior art 88. state of the art 89. prior art 90. state of the art 91. prior art 92. state of the art 93. prior art 94. state of the art 95. prior art 96. state of the art 97. prior art 98. state of the art 99. prior art 100. state of the art				