



(11)

EP 3 572 530 A3

(12) **EUROPEAN PATENT APPLICATION**

(88) Date of publication A3:
26.02.2020 Bulletin 2020/09

(51) Int Cl.:
C12Q 1/68^(2018.01) G01N 33/53^(2006.01)

(43) Date of publication A2:
27.11.2019 Bulletin 2019/48

(21) Application number: **19180822.9**

(22) Date of filing: **22.10.2009**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
PT RO SE SI SK SM TR**

(30) Priority: **31.10.2008 US 110501 P**
15.07.2009 US 503318

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
16158591.4 / 3 093 350
14161006.3 / 2 770 066
09824031.0 / 2 340 315

(71) Applicant: **Quest Diagnostics Investments
Incorporated**
Wilmington, DE 19899 (US)

(72) Inventors:
• **Albitar, Maher**
San Juan Capistrano, CA California 92675 (US)
• **MA, Wanlong**
Aliso Viejo, CA California 92656 (US)

(74) Representative: **Hoffmann Eitle**
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

(54) **COMPOSITIONS AND METHODS FOR DETECTING MUTATIONS IN JAK2 NUCLEIC ACID**

(57) The invention disclosed herein is based on the identification of novel mutations in the JAK2 gene and JAK2 protein. The invention provides compositions and methods useful for diagnosing hematopoietic diseases

including, for example, myeloproliferative diseases. The invention also provides compositions and methods useful for determining a prognosis of an individual diagnosed as having a hematopoietic disease.

EP 3 572 530 A3



EUROPEAN SEARCH REPORT

Application Number
EP 19 18 0822

5

10

15

20

25

30

35

40

45

50

55

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	TEFFERI A: "JAK and MPL mutations in myeloid malignancies", LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 49, no. 3, 1 March 2008 (2008-03-01), pages 388-397, XP009157130, ISSN: 1042-8194, DOI: 10.1080/10428190801895360 * abstract * * page 390 - page 391 *	1-14	INV. C12Q1/68 G01N33/53
A	BESSES CARLOS ET AL: "JAK2 mutations at exon 12 and 14 in polycythemia vera and idiopathic erythrocytosis: Incidence and correlation with clinical characteristics", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 110, no. 11, part 1, 1 November 2007 (2007-11-01), page 746A, XP009157146, ISSN: 0006-4971 * the whole document *	1-14	TECHNICAL FIELDS SEARCHED (IPC) C12Q
A	LI SAI ET AL: "Clonal heterogeneity in polycythemia vera patients with JAK2 exon12 and JAK2-V617F mutations", BLOOD, vol. 111, no. 7, April 2008 (2008-04), pages 3863-3866, XP002670896, ISSN: 0006-4971 * abstract; figure 1 *	1-14	
----- -/--			
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 20 January 2020	Examiner Costa Roldán, Nuria
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

6 EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 19 18 0822

5

10

15

20

25

30

35

40

45

50

55

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	SCOTT L M ET AL: "JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis", NEW ENGLAND JOURNAL OF MEDICINE 20070201 US LNKD- DOI:10.1056/NEJM0A065202, vol. 356, no. 5, 1 February 2007 (2007-02-01), pages 459-468, XP002670897, ISSN: 0028-4793 * abstract; table 1 *	1-14	TECHNICAL FIELDS SEARCHED (IPC)
A	SMITH C A ET AL: "The saga of JAK2 mutations and translocations in hematologic disorders: pathogenesis, diagnostic and therapeutic prospects, and revised World Health Organization diagnostic criteria for myeloproliferative neoplasms", HUMAN PATHOLOGY, SAUNDERS, PHILADELPHIA, PA, US, vol. 39, no. 6, 1 June 2008 (2008-06-01), pages 795-810, XP022693901, ISSN: 0046-8177, DOI: 10.1016/J.HUMPATH.2008.02.004 [retrieved on 2008-06-03] * abstract * * page 800 - page 801 *	1-14	
A	US 2007/248961 A1 (ALBITAR MAHER [US] ET AL) 25 October 2007 (2007-10-25) * abstract; claims 1,2,35,36 *	1-14	
----- -/--			
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 20 January 2020	Examiner Costa Roldán, Nuria
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

6 EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 19 18 0822

5

10

15

20

25

30

35

40

45

50

55

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
T	LEE TAI-SUNG ET AL: "Structural effects of clinically observed mutations in JAK2 exons 13-15: comparison with V617F and exon 12 mutations", BMC STRUCTURAL BIOLOGY, BIOMED CENTRAL LTD., LONDON, GB, vol. 9, no. 1, 10 September 2009 (2009-09-10), page 58, XP021058180, ISSN: 1472-6807, DOI: 10.1186/1472-6807-9-58		
T	MA WANLONG ET AL: "Mutation Profile of JAK2 Transcripts in Patients with Chronic Myeloproliferative Neoplasias", JOURNAL OF MOLECULAR DIAGNOSTICS, AMERICAN SOCIETY FOR INVESTIGATIVE PATHOLOGY, BETHESDA, MD, US, vol. 11, no. 1, 1 January 2009 (2009-01-01), pages 49-53, XP009115055, ISSN: 1525-1578, DOI: 10.2353/JMOLDX.2009.080114 * abstract *		TECHNICAL FIELDS SEARCHED (IPC)
A	CONSTANTINESCU ET AL: "Mining for JAK-STAT mutations in cancer", TRENDS IN BIOCHEMICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 33, no. 3, 4 March 2008 (2008-03-04), pages 122-131, XP022510481, ISSN: 0968-0004 * the whole document *	1-14	

-/--			

The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 20 January 2020	Examiner Costa Roldán, Nuria
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 03.02 (P04C01)



EUROPEAN SEARCH REPORT

Application Number
EP 19 18 0822

5

10

15

20

25

30

35

40

45

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	KOPPIKAR PRIYA ET AL: "JAK2 and MPL mutations in myeloproliferative neoplasms", ACTA HAEMATOLOGICA, S. KARGER, BASEL, CH, vol. 119, no. 4, 1 January 2008 (2008-01-01), pages 218-225, XP009157128, ISSN: 0001-5792, DOI: 10.1159/000140634 * the whole document *	1-14	
A	R KRALOVICS: "Genetic complexity of myeloproliferative neoplasms", LEUKEMIA, vol. 22, no. 10, 1 October 2008 (2008-10-01), pages 1841-1848, XP055020868, ISSN: 0887-6924, DOI: 10.1038/leu.2008.233 * the whole document *	1-14	
A	ELISA RUMI: "Familial chronic myeloproliferative disorders: the state of the art", HEMATOLOGICAL ONCOLOGY, vol. 26, no. 3, 1 September 2008 (2008-09-01), pages 131-138, XP55148140, ISSN: 0278-0232, DOI: 10.1002/hon.863 * the whole document *	1-14	
A	A. V. JONES ET AL: "Rapid identification of JAK2 exon 12 mutations using high resolution melting analysis", HAEMATOLOGICA, vol. 93, no. 10, 1 October 2008 (2008-10-01), pages 1560-1564, XP55006957, ISSN: 0390-6078, DOI: 10.3324/haematol.12883 * the whole document *	1-14	
----- The present search report has been drawn up for all claims -----			
Place of search Munich		Date of completion of the search 20 January 2020	Examiner Costa Roldán, Nuria
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

6
EPO FORM 1503 03.02 (P04C01)

50

55



5

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing claims for which payment was due.

10

Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due and for those claims for which claims fees have been paid, namely claim(s):

15

No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for those claims for which no payment was due.

20

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:

25

see sheet B

30

All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

35

As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

40

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:

1-14

45

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:

50

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).

55



**LACK OF UNITY OF INVENTION
SHEET B**

Application Number

EP 19 18 0822

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: 1-14(partially)

An isolated nucleic acid comprising at least 17 contiguous nucleotides corresponding to SEQ ID NO: 1, wherein said nucleic acid comprises the mutation at exon 12 of JAK2 C2035T, and wherein said nucleic acid is less than 5000 nucleotides in length.

A polypeptide comprising at least 10 contiguous amino acids corresponding to SEQ ID NO: 2, wherein said isolated polypeptide comprises an amino acid substitution T514M in JAK2 protein, and wherein said polypeptide is less than 1100 amino acids.

Methods for detecting a hematopoietic disease comprising detecting the presence or absence of a JAK2 mutation using a biological sample obtained from an individual, comprising: a) evaluating a sample from the individual for the presence or absence of a mutation in JAK2 nucleic acid or JAK2 polypeptide, wherein said mutation in the JAK2 nucleic acid is c2035t and the mutation in the JAK2 polypeptide is an amino acid substitution T514M; and b) identifying said individual as having a hematopoietic disease when said JAK2 nucleic acid or JAK2 polypeptide, respectively, comprises said mutation.

2-8. claims: 1-14(partially)

For invention 2, the isolated nucleic acid comprises at least 17 contiguous nucleotides corresponding to SEQ ID NO: 1, wherein said nucleic acid comprises the next mutation listed in claim 11, i.e. mutation a2091t, and wherein said nucleic acid is less than 5000 nucleotides in length. The polypeptide comprises at least 10 contiguous amino acids corresponding to SEQ ID NO: 2, wherein said isolated polypeptide comprises an amino acid substitution N533Y in JAK2 protein, and wherein said polypeptide is less than 1100 amino acids. Methods for detecting a hematopoietic disease comprising detecting the presence or absence of a JAK2 mutation using a biological sample obtained from an individual, comprising: a) evaluating a sample from the individual for the presence or absence of a mutation in JAK2 nucleic acid or JAK2 polypeptide, wherein said mutation in the JAK2 nucleic acid is a2091t and the mutation in the JAK2 polypeptide is an amino acid substitution N533Y in JAK2 protein; and b) identifying said individual as having a hematopoietic disease when said JAK2 nucleic acid or JAK2 polypeptide, respectively, comprises said mutation.

For inventions 3 to 8 as for invention 2, wherein it is analysed the next mutation listed in claim 11, i.e. for invention 3, mutation T2127C which corresponds to amino acid substitution L545V; for invention 4 mutation T2133C which



LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 19 18 0822

5

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:

10

corresponds to amino acid substitution F547L, and so on until invention 8, mutation A2427G which corresponds to amino acid substitution I645V.

15

20

25

30

35

40

45

50

55

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

EP 19 18 0822

5 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.

20-01-2020

10	Patent document cited in search report	Publication date	Patent family member(s)	Publication date
	US 2007248961 A1	25-10-2007	AU 2007240430 A1	01-11-2007
			CA 2649732 A1	01-11-2007
15			CN 101466722 A	24-06-2009
			EP 2007785 A2	31-12-2008
			JP 2009534038 A	24-09-2009
			US 2007248961 A1	25-10-2007
			WO 2007124309 A2	01-11-2007
20	-----			
25				
30				
35				
40				
45				
50				
55				

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

专利名称(译)	检测JAK2-核酸中突变的组合物和方法		
公开(公告)号	EP3572530A3	公开(公告)日	2020-02-26
申请号	EP2019180822	申请日	2009-10-22
[标]申请(专利权)人(译)	奎斯特诊断投资公司		
申请(专利权)人(译)	Quest Diagnostics公司投资INCORPORATED		
当前申请(专利权)人(译)	Quest Diagnostics公司投资INCORPORATED		
[标]发明人	ALBITAR MAHER MA WANLONG		
发明人	ALBITAR, MAHER MA, WANLONG		
IPC分类号	C12Q1/68 G01N33/53		
CPC分类号	C12N9/1205 C12Q1/6883 C12Q2600/118 C12Q2600/156 C12Y207/10001 G01N33/573 G01N2333/91205 G01N2800/22 G01N2800/56		
优先权	61/110501 2008-10-31 US 12/503318 2009-07-15 US PCT/US2009/061691 2009-10-22 WO		
其他公开文献	EP3572530A2		
外部链接	Espacenet		

摘要(译)

本文公开的发明基于JAK2基因和JAK2蛋白中新突变的鉴定。本发明提供了可用于诊断包括例如骨髓增生性疾病的造血系统疾病的组合物和方法。本发明还提供了用于确定被诊断患有造血疾病的个体的预后的组合物和方法。

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant No.	CLASSIFICATION OF THE APPLICABLE IPC
Category	Citation of document with indication, where appropriate, of relevant passages		
A	TEFFERI A: "JAK and MPL mutations in myeloid malignancies", LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 49, no. 3, 1 March 2008 (2008-03-01), pages 386-397, XP009157130, ISSN: 1042-8194, DOI: 10.1080/10428190801895360 * abstract *	1-14	INV. C12Q1/68 G01N33/53
A	BESSES CARLOS ET AL: "JAK2 mutations at exon 12 and 14 in polycythemia vera and idiopathic erythrocytosis: incidence and correlation with clinical characteristics", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 110, no. 11, part 1, 1 November 2007 (2007-11-01), page 746A, XP009157146, ISSN: 0006-4971 * the whole document *	1-14	TECHNICAL FIELD SEARCHED: C12Q
A	LI SAI ET AL: "Clonal heterogeneity in polycythemia vera patients with JAK2 exon12 and JAK2-V617F mutations", BLOOD, vol. 111, no. 7, April 2008 (2008-04), pages 3863-3866, XP002670896, ISSN: 0006-4971 * abstract; figure 1 *	1-14	
-The present search report has been drawn up for all claims			
Munich		20 January 2020	Costa Roldán, Nuria
CATEGORY OF CITED DOCUMENTS A: prior art document B: non-patent literature C: patent literature D: non-written document E: other document			
I: priority or patentable invention II: scientific or technical document, not patentable, or other document III: document cited in the application IV: document cited for other reasons A: number of the same patent family, corresponding document			