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Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

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15 October 2009

(54) Title: COMPOSITIONS AND METHODS FOR IDENTIFICATION OF SUBSPECIES CHARACTERISTICS OF *MYCOBACTERIUM TUBERCULOSIS*

(57) Abstract: The present invention provides compositions, kits and methods for rapid genotyping of strains of *Mycobacterium tuberculosis* by molecular mass and base composition analysis. Drug-resistant strains of *Mycobacterium tuberculosis* may be identified in human clinical samples and as such, provide for methods of treatment of humans infected with drug resistant strains of *Mycobacterium tuberculosis*.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/067911**A. CLASSIFICATION OF SUBJECT MATTER***C12N 15/31(2006.01)i*

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: C12N 15/31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Utility models and applications for Utility models since 1975

Japanese Utility models and application for Utility models since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS (KIPO internal), Google, NCBI PubMed, Delphion (detect*, Mycobacteri*, genotyp*, drug resistant* and similar terms.)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP1098003 A2(MARINE BIOTECHNOLOGY INSTITUTE CO., LTD.) 09 May 2001. See the whole document, especially abstract, sequence ID. NOS. 23, 29, 21, 9, claims.	17-23
X	US 6,892,139 B2 (D. EISENBERG, et al.) 10 May 2005. See the whole document, especially abstract, sequence ID. NO. 3, claims 6-13.	17-23
X	H. KASAI, et al. 'Differentiation of phylogenetically related slowly growing Mycobacteria by their gyrB sequences.' In Journal of Clinical Microbiology Vol.38(1):301-308 (January 2000). See the whole document, especially abstract, Materials and Methods, Tables 1-2.	17-23
X	H. E. TAKIFF, et al. 'Cloning and nucleotide sequence of Mycobacterium tuberculosis gyrA and gyrB genes and detection of quinolone resistance mutations.' In Antimicrobial Agents and Chemotherapy Vol.38(4):773-780 (1994). See the whole document, especially abstract, Materials and Methods, figures 1-3.	17-23

☒ Further documents are listed in the continuation of Box C.☒ See patent family 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 application or patent 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 citation or other special reason (as specified)

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2008/067911

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. IWAMOTO AND H. SAITO, 'Comparative study of two typing methods, hsp65 PRA and ITS sequencing, revealed a possible evolutionary link between Mycobacterium kansasii type I and II isolates.' In FEMS Microbiol Lett. Vol.254:129-133 (2006). See the whole document, especially abstract, Materials and Methods, Table 2.	17-23
X	S. NIEMANN, et al. 'The species Mycobacterium africanum in the light of new molecular markers.' In Journal of Clinical Microbiology Vol.42(9):3958-3962 (September 2004). See the whole document, especially abstract, Materials and Methods.	17-23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2008/067911**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 37-44, 46, 47
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 37-44, 46, 47 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☐ Claims Nos.:
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:
3. ☒ Claims Nos.: 5, 6, 9-13,
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See the Supplemental Box.

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.: 17-23

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box III

This ISA found multiple inventions as follows:

Invention 1.

The subject matter of claims 17–23 is directed to an oligonucleotide primer pair characterized by the SEQ ID NO: 1515 and SEQ ID 1538.

Inventions 2–35

Claims 1–4, 7, 8 and 14–16 consist of 34 inventions which are directed to a method of identifying a *Mycobacterium tuberculosis* genotype in a sample. Each invention is characterized by one of primer pairs 3546–3548, 3550–3561, 3581–3584, 3586, 3587, 3599, 3601, 3908, 3633, 3697, 3828, 4234, 4235, 4236, 4237, 4362, 4364, 4366, which are written in claim 7, respectively.

Inventions 36–69

Claims 24–25 consist of 34 inventions which are directed to a kit for identifying a *Mycobacterium tuberculosis* genotype in a sample. Each invention is characterized by a primer pair of the SEQ ID NO: 1515 and SEQ ID 1538 and one of primer pairs 3546–3548, 3550–3561, 3581–3584, 3586, 3587, 3599, 3601, 3908, 3633, 3697, 3828, 4234, 4235, 4236, 4237, 4362, 4364, 4366, respectively.

Inventions 70–341

Claim 26 consists of 272 inventions which are directed to a kit for identifying a *Mycobacterium tuberculosis* genotype in a sample. Each invention is characterized by one of primer pairs 3551–3556, 3908, 3633, 3697, 3828, 4234–4237, 4364, 4366 and a primer pair hybridizing one of genes *rpoB*, *embB*, *fabG*, *inhA*, *katG*, *gyrA*, *pncA*, *prcA*, *rv2348c*, *rv3815c*, *rv0147*, *erg3*, *rv0083*, *rv1047*, *rv1814*, *rv0041*, and *rv0260c*, respectively.

Inventions 342–375

Claims 27–36 consists of 34 inventions which are directed to a method of identifying a drug-resistant strain of *Mycobacterium tuberculosis*. Each invention is characterized by one of primer pairs 3546–3548, 3550–3561, 3581–3584, 3586, 3587, 3599, 3601, 3908, 3633, 3697, 3828, 4234, 4235, 4236, 4237, 4362, 4364, 4366, respectively.

Inventions 376

Claims 45 is directed to a method for determining the identity and quantity of *Mycobacterium tuberculosis* in a sample, characterized by the step of comparison of *Mycobacterium tuberculosis* amplicon data to with the calibration amplicon data.

The only common technical feature of the above 376 inventions is sequences of genes of *Mycobacterium tuberculosis*. However, this feature is a common knowledge to the skilled person in the art (for example EP 1098003 A2 (09.05.2001)).

Since a "special technical feature", which links groups of inventions, means those technical feature that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art, the inventions 1–376 are not so linked as to form a single inventive concept (PCT Rule 13.1 and 13.2).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2008/067911

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1098003 A2	09.05.2001	EP 1098003 A3 JP 3565752 B2 JP 03-565752 B2 JP 2001-128679 A	26.05.2004 15.09.2004 18.06.2004 15.05.2001
US 06892139 B2	10.05.2005	AU 2000-27442 A1 CA 2359898 A1 EP 1155379 A1 JP 2002-535972 A US 2002-164588 A1 WO 2000-045322 A1	28.01.2000 03.08.2000 21.11.2001 29.10.2002 07.11.2002 03.08.2000