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(54) Title: METHODS AND SYSTEMS FOR GENERATING CELL LINEAGE TREE OF MULTIPLE CELL SAMPLES

(57) Abstract: A method of generating a cell lineage tree of a plurality of cells of an individual is provided. The method comprising: (a) determining at least one genotypic marker for each cell of the plurality of cells; and (b) computationally clustering data representing the at least one genotypic marker to thereby generate the cell lineage tree of the plurality of cells of the individual.



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**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/IL06/00385

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC: G01N 33/48( 2006.01);G06G 7/48( 2006.01)  
 G01N 33/48( 2006.01);G06G 7/48( 2006.01)  
 USPC: 702/19;703/12  
 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)  
 U.S. : 702/19; 703/12

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 practicable, search terms used)  
 EAST, STN

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KLUGER et al. Lineage specificity of gene expression patterns. PNAS. 27 April 2004, Vol. 101, No.17, p.6508-6513, entire document.	1-2, 7-13, and 17-20
X	BRAUN et al. ALES: cell lineage analysis and mapping of developmental events. Bioinformatics. 2003, Vol. 19, No. 7, pages 851-858, entire document.	1-3, and 7-8
Y	RIENZO et al. Heterogeneity of Microsatellite Mutations Within and Between Loci, and Implications for Human Demographic Histories. Genetics. 1998, Vol. 148, pages 1269-1284, entire document.	6
Y	MEHR et al. Analysis of Mutational Lineage Trees from Sites of Primary and Secondary Ig Gene Diversification in Rabbits and Chickens. Journal of Immunology. 2004, Vol. 172, pages. 4790-4796, entire document.	1-5, 12, and 14-16

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL06/00385

## 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.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
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.:  
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:  
Please See Continuation Sheet

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 additional fees, this Authority did not invite payment of any additional fees.
  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.: 1-21
  
  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 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.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IL06/00385

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LU et al. Expression of bcl-2 in bladder neoplasms is a cell lineage associated and p53-independent event. J. Clinical pathology: Mol. Pathol. 1997, Vol. 50, pages.28-33, entire document.	21

**BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-11, drawn to a method of generating a cell lineage tree of a plurality of cells.

Group II, claim(s) 12-21, drawn to a method for assessing clonality of a neoplasm in an individual.

Group III, claim(s) 22-28, drawn to a method for identifying the presence of tumor stem cells.

Group IV, claim(s) 29-39, drawn to a system for generating a cell lineage tree of a plurality of cells.

Group V, claim(s) 40-44, drawn to a method of assessing growth dynamics of a population of cells.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of groups I-V share the technical features of determining at least one genotypic marker for each cell of the plurality of cells, computationally clustering data to generate a cell lineage tree and determining the cell-depth distribution. This technical feature is not special under Rule 13.2 because it has been disclosed in the art. Kluger et al (Lineage specificity of gene expression patterns, PNAS, Vol. 101, No. 17, p.6508-6513, 24 April 2004) teach a method of generating cell lineage tree from genotypic data from cells of the hematopoietic system. The genotypic data collected by Kluger et al is analyzed by a clustering algorithm, Principal component analysis and a distance matrix algorithm, i.e. neighbor-joining algorithm. The cell lineage tree then constructed based on the distribution cell depths determined from the distance between genetic profiles. Thus the inventions of group I-V do not share a special technical feature and lack unity.