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(54) Title: SINGLE-MOLECULE PLATFORM FOR DRUG DISCOVERY: METHODS AND APPARATUSES FOR DRUG DISCOVERY, INCLUDING DISCOVERY OF ANTICANCER AND ANTIVIRAL AGENTS

(57) Abstract: The present application discloses methods and apparatuses for single molecule drug screening, discovery and validation. These methods and apparatuses allow a user to detect rapidly, using observation of single molecules, whether and how a drug candidate interferes with a target enzyme involved in a particular disease pathway. The methods and apparatuses described herein utilize single molecule manipulation and detection technologies (e.g., optical or magnetic tweezers) to directly detect whether the characteristic dynamics, or "mechanical signature," of the target enzyme-substrate interaction are substantially altered or modulated by a drug candidate. Furthermore, the methods and apparatuses are useful for analyzing the modulation of the mechanical signature in order to identify potential interference mechanisms of a drug candidate. In one aspect of the invention, the methods and apparatuses disclosed herein relate to monitoring the real-time dynamic mechanical signatures of individual polymerase molecules (e.g. DNA polymerases, RNA polymerases, and reverse transcriptases) along a polynucleotide substrate in the presence of drug candidates that either inhibit or otherwise modulate the polymerization process. Identification and analysis of such drug candidates is critical for anti-viral, anti-cancer, and antibiotic drug development.



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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US07/09747

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC: **G01N 33/567( 2006.01),C12M 1/34**  
**C12N 9/22( 2006.01)**

USPC: **436/501,435/287.3,435/287.2,435/199**  
 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. : 436/501,435/287.3,435/287.2,435/199

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 east, scirus, google scholar

Electronic data base consulted during the international search (name of data base and, where practicable, 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	US 7,291,504 ( Seul et al) 06 November 2007, see entire document.	1-6, 11-13
A	H. Gai. Visualizing chemical interactions in life sciences with wide-field fluorescence microscopy towards the single-molecule level Trends in Anal. chem 2007, Vol 26, 980-991.	1-6, 11-13

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	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"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/US07/09747

## 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.: 1-6 and 11-13
  
  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.

**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, claims 1-5, 6, 11-13, drawn to method of screening drug using Human DNA polymerase.

Group II, claims 1-5,7, 11-13, drawn to method of screening drug using viral DNA polymerase.

Group III, claims 1-5, 10-13, drawn to method of screening drug using bacterial DNA polymerase.

Group IV, claims 1-5, 8-9, 11-13, drawn to method of screening drug using viral reverse transcriptase.

The inventions listed as Groups I-IV 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 technical feature linking group I-IV appears to be that they all related to screening drug using DNA polymerase and its inhibitor. The screening drug using DNA polymerase and its inhibitor does not constitute a "special technical feature" as defined by PCT Rule 13.2, because it does not claim a feature which defines a contribution over the prior art as screening drug using DNA polymerase and its inhibitor is taught by Asuka et al. ( EP1486785, December 15, 2004).