

(12) **United States Patent**
Griffiths et al.

(10) **Patent No.:** **US 9,029,083 B2**
(45) **Date of Patent:** ***May 12, 2015**

(54) **VITRO EVOLUTION IN MICROFLUIDIC SYSTEMS**

(75) Inventors: **Andrew David Griffiths**, Strasburg (FR); **David Weitz**, Cambridge, MA (US); **Darren Link**, Lexington, MA (US); **Keunho Ahn**, San Diego, CA (US); **Jerome Bibette**, Paris (FR)

(73) Assignees: **Medical Research Council**, London (GB); **President and Fellows of Harvard College**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1500 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/665,030**

(22) PCT Filed: **Oct. 10, 2005**

(86) PCT No.: **PCT/GB2005/003889**
§ 371 (c)(1),
(2), (4) Date: **Apr. 14, 2009**

(87) PCT Pub. No.: **WO2006/038035**

PCT Pub. Date: **Apr. 13, 2006**

(65) **Prior Publication Data**

US 2009/0197248 A1 Aug. 6, 2009

Related U.S. Application Data

(63) Continuation of application No. 10/961,695, filed on Oct. 8, 2004, now Pat. No. 7,968,287.

(51) **Int. Cl.**
C12Q 1/68 (2006.01)
G01N 33/53 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC **B01J 19/0046** (2013.01); **B01F 3/0807** (2013.01); **B01F 5/0646** (2013.01);
(Continued)

(58) **Field of Classification Search**

USPC 435/6.1, 7.1, 91.2, 283.1; 422/68.1; 536/23.1, 24.33
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,097,692 A 11/1937 Fiegel
2,164,172 A 6/1939 Dalton

(Continued)

FOREIGN PATENT DOCUMENTS

AU 2004225691 B2 6/2010
CA 2520548 A1 10/2004

(Continued)

OTHER PUBLICATIONS

Adang et al., "The Contribution of Combinatorial Chemistry to Lead Generation: An Interim Analysis", *Curr. Med. Chem.*, 8: 985-998 (2001).

(Continued)

Primary Examiner — Narayan Bhat

(74) *Attorney, Agent, or Firm* — Brown Rudnick LLP; Thomas C. Meyers

(57) **ABSTRACT**

The invention describes a method for isolating one or more genetic elements encoding a gene product having a desired activity, comprising the steps of: (a) compartmentalising genetic elements into microcapsules; and (b) sorting the genetic elements which express the gene product having the desired activity; wherein at least one step is under microfluidic control. The invention enables the in vitro evolution of nucleic acids and proteins by repeated mutagenesis and iterative applications of the method of the invention.

11 Claims, 25 Drawing Sheets

