



US006465241B2

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

(10) **Patent No.:** **US 6,465,241 B2**
 (45) **Date of Patent:** **Oct. 15, 2002**

(54) **METHOD, CHIP, DEVICE AND SYSTEM FOR EFFECTING AND MONITORING NUCLEIC ACID ACCUMULATION**

(75) Inventors: **Dan Haronian**, Efrat; **Menachem Nathan**, Tel Aviv; **Jonathan M. Gershoni**; **Arieh Yaron**, both of Rehovot, all of (IL)

(73) Assignee: **Ramot University Authority for Applied Research and Industrial Development Ltd.**, Tel Aviv (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/735,799**

(22) Filed: **Dec. 14, 2000**

(65) **Prior Publication Data**

US 2002/0061519 A1 May 23, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/157,531, filed on Sep. 21, 1998, now abandoned.

(51) **Int. Cl.**⁷ **C12M 1/34**; C12Q 1/68; C12P 19/34; G01N 21/29; G01N 21/64

(52) **U.S. Cl.** **435/287.2**; 435/6; 435/91.1; 435/287.1; 422/82.05; 422/82.11

(58) **Field of Search** 435/6, 91.1, 183, 435/283.1, 287.1, 287.2; 436/94; 536/23.1, 24.3, 24.33, 25.3, 25.32; 422/50, 55, 68.1, 82.05, 82.09, 82.11

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,485,277 A 1/1996 Foster
 5,498,392 A 3/1996 Wilding et al.
 5,599,668 A 2/1997 Stimpson et al.
 5,641,658 A 6/1997 Adams et al.

5,737,457 A 4/1998 Saini et al.

FOREIGN PATENT DOCUMENTS

EP 0517516 A1 * 9/1992
 WO WO 97/27328 * 7/1907

OTHER PUBLICATIONS

Schneider et al., Hartman interferometer: versatile integrated optic sensor for label-free, real-time quantification of nucleic acids, proteins, and pathogens. *Clin. Chem.*, 43, 1757-1763, 1997.*

Karymov et al., Fixation of DNA directly on optical waveguide surfaces for molecular probe biosensor development. *Sensors and Actuators B*, 29, 324-327, 1995.*

Kruchinin et al., Surface plasma resonance monitoring by means of polarization state measurement in reflected light as the basis of a DNA-probe biosensor. *Sensors and Actuators B*, 30, 77-80, 1996.*

Lee et al., "Allelic Discrimination by Nick-Translation PCR with Fluorogenic Probes", *Nucleic Acid Research*, 21(16):3761-3766, 1993.

(List continued on next page.)

Primary Examiner—Ethan C. Whisenant

Assistant Examiner—Frank W Lu

(74) *Attorney, Agent, or Firm*—Mark M. Friedman

(57)

ABSTRACT

A nucleic acid accumulation analyzing chip comprising an optical waveguide having a radiation input port and a radiation output port, the optical waveguide being formed with at least one optical microcavity along its optical path, at least one oligonucleotide being immobilized to the optical waveguide in the microcavity, such that when the at least one oligonucleotide is contacted with reaction reagents under conditions allowing a nucleic acid accumulation reaction to take place, accumulated nucleic acid is detectable by providing radiation at the radiation input port of the optical waveguide and monitoring radiation signal modulation at the radiation output port of the optical waveguide.

12 Claims, 4 Drawing Sheets



