



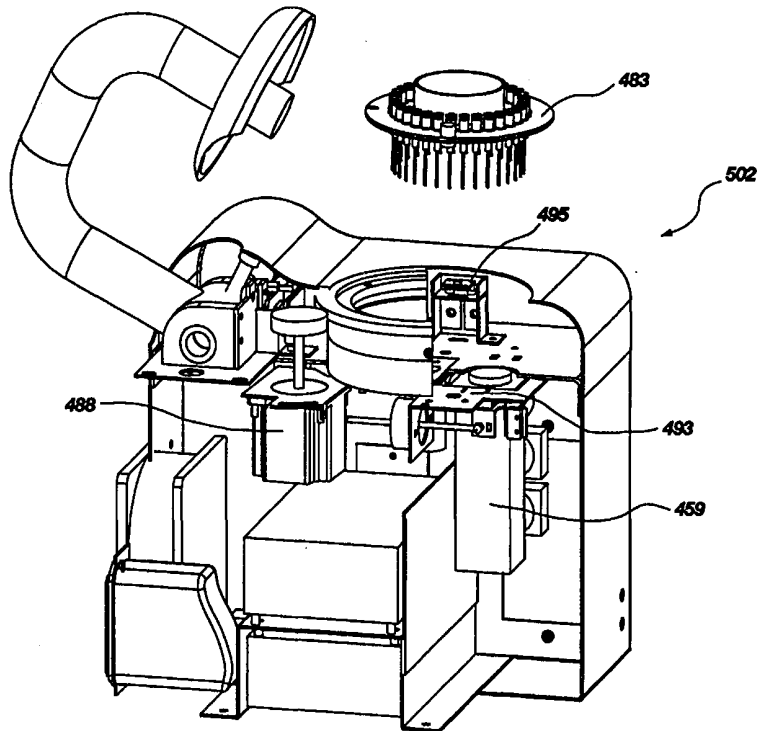
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(51) International Patent Classification</b> <sup>6</sup> :<br><b>C12Q 1/68, B01L 7/00, G01N 21/76, 21/07</b>   | <b>A3</b> | <b>(11) International Publication Number:</b> <b>WO 97/46712</b><br><b>(43) International Publication Date:</b> 11 December 1997 (11.12.97)  |
| <p><b>(21) International Application Number:</b>      PCT/US97/09856</p> <p><b>(22) International Filing Date:</b>              4 June 1997 (04.06.97)</p> <p><b>(30) Priority Data:</b><br/> 08/658,993              4 June 1996 (04.06.96)              US</p> <p><b>(71) Applicant (for all designated States except US):</b> UNIVERSITY OF UTAH RESEARCH FOUNDATION [US/US]; 210 Park Building, Salt Lake City, UT 84112 (US).</p> <p><b>(72) Inventors; and</b><br/> <b>(75) Inventors/Applicants (for US only):</b> WITTWER, Carl, T. [US/US]; 2568 East 1700 South, Salt Lake City, UT 84108 (US). RIRIE, Kirk, M. [US/US]; 149 Chestnut Street, Idaho Falls, ID 84302 (US). RASMUSSEN, Randy, P. [US/US]; 601 South 900 East, Salt Lake City, UT 84102-3418 (US). HILLYARD, David, R. [US/US]; 3545 Ceres, Salt Lake City, UT 84124 (US).</p> <p><b>(74) Agents:</b> CLAYTON, Grant, R. et al.; Thorpe, North &amp; Western, L.L.P., Suite 200, 9035 South 700 East, Sandy, UT 84070 (US).</p> |           | <p><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b><br/> <i>With international search report.</i></p> <p><b>(88) Date of publication of the international search report:</b><br/> 7 May 1998 (07.05.98)</p> |

**(54) Title:** SYSTEM AND METHOD FOR CARRYING OUT AND MONITORING BIOLOGICAL PROCESSES

**(57) Abstract**

A thermal cycling method and device is disclosed. The device comprises a sample chamber whose temperature can be rapidly and accurately modulated over a range of temperatures needed to carry out a number of biological procedures, such as the DNA polymerase chain reaction. Biological samples are placed in glass micro capillary tubes and then located inside the sample chamber. A programmable controller regulates the temperature of the sample inside the sample chamber. Monitoring of the DNA amplification is monitored by fluorescence once per cycle or many times per cycle. The present invention provides that fluorescence monitoring of PCR is a powerful tool for DNA quantification.



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# INTERNATIONAL SEARCH REPORT

International Application No  
**PCT/US 97/09856**

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C12Q1/68 B01L7/00 G01N21/76 G01N21/07

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 6 B01L G01N C12Q

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 practical, 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. |
|------------|--|-----------------------|
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Further documents are listed in the continuation of box C.

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- \*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
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Date of the actual completion of the international search

**20 February 1998**

Date of mailing of the international search report

**20 FEB 1998**

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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## INTERNATIONAL SEARCH REPORT

 Intern: al Application No  
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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
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| X  | EP 0 636 413 A (PERKIN ELMER CORP) 1<br>February 1995<br>see column 9, line 30 - line 42   | 1                     |
| X  | see column 13, line 27 - line 29<br>see column 14, line 48 - column 15, line 30; figures 3,4   | 21,22                 |
| X  | see column 16, line 10 - line 12   | 5-9,36,<br>37         |
| X  | see column 16, line 39 - line 52   | 10,36,37              |
| X  | see column 16, line 56 - column 17, line 7; figure 5   | 12                    |
| A  | see column 19, line 2 - line 23; figures 10,11   | 49                    |
| A  | see column 22, line 6 - column 23, line 14; figures 12-15  | 49                    |
|  | see column 34, line 3 - line 18; figure 30   |                       |
|  | see column 35, line 3 - column 36, line 12; claims 17,40-44  |                       |
| X  | see column 35, line 18 - line 23   | 13-17                 |
| A  | see column 35, line 57 - column 36, line 12  | 104                   |
| X  | see figure 30  | 24,25                 |
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| X  | MULLIS ET AL.: "the polymerase chain reaction"<br>1994 , BIRKHAUSER , BOSTON (US)<br>XP002042556<br>cited in the application<br>see page 175, column 1; figure 15.1<br>see page 176, column 2; figure 15.2   | 1                     |
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| A  | see column 9, line 42 - line 53<br>see column 11, line 2 - line 28<br>see column 13, line 41 - column 14, line 65; figure 9  | 49                    |
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| A  | WO 95 21382 A (FIELDS ROBERT E) 10 August 1995<br>see page 15, line 8 - line 24; figures 1,2<br>see page 16, line 2 - line 12; figures 2,5   | 49                    |
| A  | see page 30, line 24 - page 32, line 20  | 1                     |
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International Application No  
PCT/US 97/09856

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
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| Category *   | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| A  | EP 0 318 255 A (EASTMAN KODAK CO) 31 May 1989<br>see column 7, line 20 - line 45; figures 2-4<br>see column 8, line 32 - line 51<br>see column 9, line 8 - line 48; figures 6,7<br>see column 13, line 47 - column 14, line 34; figures 16-18,20<br>--- | 49                    |
| A  | WEAST: "handbook of chemistry and physics"<br>1972, CRC, CLEVELAND (USA) XP002042557<br>cited in the application<br>see page E6<br>---  | 49                    |
| A  | EP 0 674 009 A (BECTON DICKINSON CO) 27 September 1995<br>see column 4, line 46 - line 51<br>see column 5, line 26 - line 32<br>see column 6, line 37 - line 43<br>see column 11, line 22 - line 40<br>---  | 49                    |
| A  | WO 96 06354 A (BIOCIRCUITS CORP) 29 February 1996<br>see page 6, paragraph 2<br>see page 9, paragraph 2<br>see page 15, last paragraph<br>see page 23, paragraph 3<br>---   | 49                    |
| A  | WO 92 20778 A (KINDCONI PTY LIMITED) 26 November 1992<br>see page 6, line 20 - line 32; claims 13-17; figures<br>---  | 49                    |
| A  | US 3 219 416 A (NATELSON) 23 November 1965<br>see column 1, line 59 - line 70   | 49-51                 |
| X  | see column 2, line 29 - line 35; figure 1<br>---  | 83-86                 |
| A  | FR 2 122 187 A (DAMON CORPORATION) 25 August 1972<br>see page 9, line 4 - line 25; figures 4-6<br>see page 12, line 11 - line 30<br>---   | 49                    |
| A  | EP 0 404 258 A (BONINI CLAUDIO) 27 December 1990<br>see column 3, line 26 - line 43; figures 1-3<br>---   | 52,54                 |
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# INTERNATIONAL SEARCH REPORT

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|---|
| International Application No<br>PCT/US 97/09856 |
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| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
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| Category *   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| X  | EP 0 580 362 A (TOSOH CORP) 26 January 1994<br>see page 2, line 54 - page 3, line 12   | 13,26,<br>27,32       |
| Y<br>A   | see page 3, line 17 - line 45; figures<br>see page 7, line 45 - line 48<br>see page 7, line 53 - page 8, line 28;<br>figure 12   | 55<br>60,62           |
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| Y  | EP 0 171 140 A (UNIVERSITY OF TOKYO) 12 February 1986<br>see page 14, line 8 - page 17, line 3;<br>figure 1  | 55                    |
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| X  | TYAGI S ET AL: "MOLECULAR BEACONS: PROBES THAT FLUORESCCE UPON HYBRIDIZATION" BIO/TECHNOLOGY, vol. 14, 1 March 1996, pages 303-308, XP000196024<br>see page 305, column 1, last paragraph - page 307, column 1, paragraph 2; figures 5-7 | 39-41,<br>44-48,60    |
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| A  | WO 93 20240 A (ABBOTT) 14 October 1993<br>see page 20, line 9 - line 16  | 55                    |
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| X  | EP 0 640 828 A (HOFFMANN LA ROCHE) 1 March 1995<br>see page 25, line 23 - line 49  | 13                    |
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| A  | JP 07 031 500 A (HAMAMATSU) 3 February 1995<br>see figures 3-5   | 28,29,62              |
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| A  | EP 0 711 840 A (HITACHI) 15 May 1996<br>see page 3, line 10 - line 25<br>see page 8, line 1 - line 4<br>see page 8, line 39 - line 50  | 28,29,60              |
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| Y  | EP 0 211 334 A (US ENERGY) 25 February 1987<br>see page 4, line 28 - page 5, line 27<br>see page 6, line 8 - page 7, line 10;<br>figures   | 66                    |
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| Y  | AU 528 259 B (UNION CARBIDE CORP) 21 April 1983  | 66                    |
| X  | see page 4, line 19 - page 5, line 23;<br>figures 1,2,6  | 93-101                |
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Intern. Patent Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | US 3 999 868 A (SANZ MANUEL ET AL) 28<br>December 1976<br>see figures<br>---  | 66                    |
| X          | US 4 908 112 A (PACE SALVATORE J) 13 March<br>1990<br>see column 3, line 39 - line 51<br>see column 5, line 60 - line 66<br>see column 8, line 38 - line 57; figure 6<br>---                    | 79                    |
| Y          | US 3 556 659 A (HAWES ROLAND C) 19 January<br>1971<br>see column 1, line 27 - line 31<br>see column 3, line 12 - line 36<br>see column 7, line 20 - line 38; figure 5<br>---                    | 79                    |
| Y          | EP 0 519 623 A (CIBA CORNING DIAGNOSTICS<br>CORP) 23 December 1992<br>see page 9, line 18 - page 10, line 56;<br>claims 1,2,5,8,17; figures<br>---  | 79                    |
| X          | WO 95 21266 A (UNIV CALIFORNIA) 10 August<br>1995<br>see page 3, line 32 - page 5, line 1<br>see page 6, line 12 - line 29<br>---   | 104-107               |
| X          | see page 6, line 18<br>see page 7, line 5 - line 12<br>see page 10, line 16 - line 20; claims<br>17-21<br>---   | 106                   |
| E          | EP 0 805 190 A (PERKIN-ELMER) 5 November<br>1997<br>see paragraph D; figure 6; table 6<br>---   | 104-107               |
| A          | EP 0 229 943 A (MOLECULAR BIOSYSTEMS INC)<br>29 July 1987<br>see page 2, last paragraph - page 3,<br>paragraph 1<br>see page 8, last paragraph - page 9, line<br>10<br>---                      | 104-107               |
| A          | US 5 268 486 A (WAGGONER ALAN S ET AL) 7<br>December 1993<br>see column 6, line 9 - line 24<br>---  | 104,106               |
| A          | MUJUMDAR R B ET AL: "CYANINE DYE LABELING<br>REAGENTS CONTAINING ISOTHIOCYANATE GROUPS"<br>CYTOMETRY,<br>vol. 10, 1 January 1989,<br>pages 11-19, XP000575307<br>see figure 5; table 2<br>----- | 104,106               |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 09856

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

SEE ADDITIONAL 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 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.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

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1. Claims: 1-12,36-38,49-54

rapid thermal cycling with a temperature rate of 1 to 10°C / second, and container for nucleic acid amplification

2. Claims: 13-32,33-35,39-48,55-59,60-65

system for performing PCR, monitoring the reaction by detecting the fluorescence in real time, and controlling the reaction using the monitored signal.

3. Claims: 66-78,83-86,93-103

carousel for sample vessels and methods for adding samples to capillary vessels using the carousel

4. Claims: 79-81,82,87-92,108-117

Device for monitoring the fluorescence, wherein the illumination and detection along an axis substantially parallel to a wall along the second dimension of the vessel

5. Claims: 104-107

System for detecting the presence of a nucleic acid sequence using fluorescein as a donor fluorophore and CY5 as an acceptor fluorophore.

The International Searching Authority considers that the present application contains 5 inventions. This observation is based on the following reasons.

The prior art has been identified as EP-A-636413 (Perkin-Elmer Corporation). This document describes methods and apparatuses for rapid Polymerase Chain Reaction in capillary tubes, using fluorescence detection for monitoring the progress of the reaction.

1. From the comparison of claims 1-12, 36-38, and 49-54 with this prior art, the special technical features in the sense of Rule 13.2 PCT, making a contribution over this prior art would be the type of container used for the rapid thermal cycling (claim 49), its volume not greater than about 10 microliters (claim 3 and 49), the choice of its material according to thermal conductivity (claim 49). From these special technical features, the problem to be solved by the first invention would be the optimisation of the heat exchange for completion of polymerase chain reaction.

2. From the comparison of claims 13-32,33-35,39-48, 55-59, 60-65 with the same prior art EP636413 (see col. 35 lines 21-29), the special technical feature in the sense of Rule 13.2 PCT of this second set of claims would be the control of the means for heating and cooling in accordance with the detected fluorescence (claims 14-17,34). The problem to be solved by

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this second set of claims would be the control of the reaction using the monitored fluorescence.

3. From the comparison of claims 66-78, 83-86, 93-103 with the same prior art EP636413 (see fig. 10-18), the special technical feature in the sense of Rule 13.2 PCT of this third set of claims would be a carousel for sample vessels with sample receiving port and a method for adding a sample to the vessel using the carousel. The problem to be solved by this third set of claims would be the dispensing of samples in capillary vessels.

4. From the comparison of claims 79-81,82,87-92,108-117 with the same prior art EP636413 (see fig. 30), the special technical feature in the sense of Rule 13.2 PCT of this fourth set of claims would be the arrangement for illuminating and detecting the fluorescence of the sample along an axis parallel to a certain wall of the vessel. The problem to be solved by this fourth set of claims could be seen in maximising the detected fluorescence(see application, fig, 19h,19i and page 53, lines 5-20).

5. From the comparison of claims 104-107 with the same prior art EP636413 (see col.35 line 57 to col.36, line 12), the special technical feature in the sense of Rule 13.2 PCT of this fifth set of claims would be the use of fluorescein and CY5 as fluorophores for detecting the presence of a nucleic acid sequence. The problem to be solved by this fourth set of claims could be a more specific detection (see application, page 44, line 33 to page 46, line 31).

The above analysis shows that the special technical features and the problems solved by the inventions herein above named 2 to 5 are not the same or similar to those of invention 1, and that there is no technical correspondence between these problems or features, as required by Rules 13.1 and 13.2 PCT.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

|                              |
|------------------------------|
| International Application No |
| PCT/US 97/09856              |

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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