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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 June 2007 (28.06.2007)

PCT

(10) International Publication Number
WO 2007/071985 A1

(51) International Patent Classification:
G01N 1/28 (2006.01) *H05K 3/04* (2006.01)

(21) International Application Number: PCT/GB2006/004790

(22) International Filing Date: 19 December 2006 (19.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0525847.0 20 December 2005 (20.12.2005) GB

(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF BRISTOL** [GB/GB]; Senate House, Tyndall Avenue, Bristol BS8 1TH (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **CLAEYSSENS, Frederik** [BE/GB]; School of Chemistry, University of Bristol, Bristol BS8 1TS (GB).

(74) Agents: **BECK, Simon** et al.; Withers & Rogers LLP, Goldings House, 2 Hays Lane, London SE1 2HW (GB).

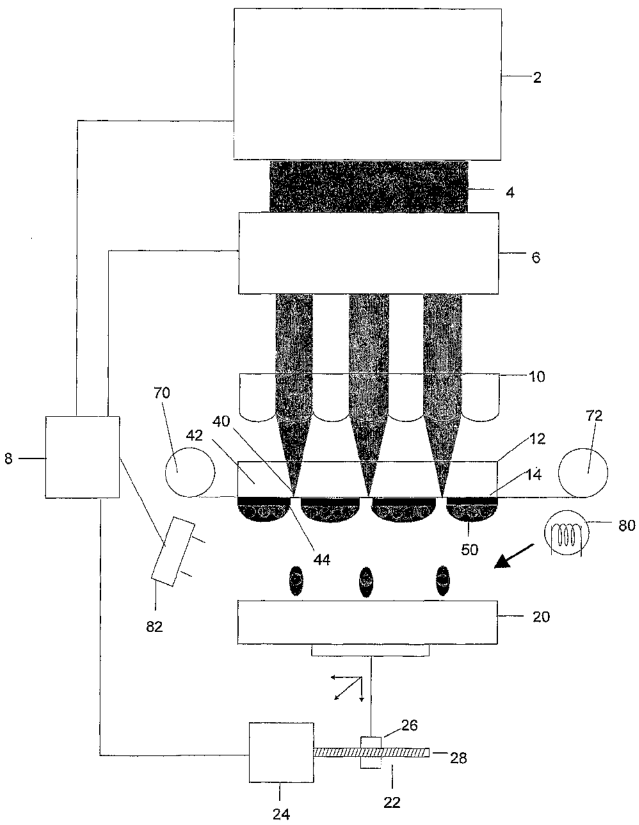
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: METHOD OF AND APPARATUS FOR TRANSFERRING MATERIAL FROM A CARRIER TO A SUBSTRATE BY LASER IRRADIATION



(57) Abstract: An apparatus for transferring material (50) from a carrier (12) to a substrate (20) , the apparatus comprising: a source of electromagnetic energy (2) a spatial modulator (6) wherein energy from the source of electromagnetic energy (2) is spatially modulated by the spatial modulator (6) so as to allow transfer of energy to the carrier (12) to be controlled, and whereby irradiation of the carrier (12) causes the material (50) to be transferred to the substrate (20) .

WO 2007/071985 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD OF AND APPARATUS FOR TRANSFERRING MATERIAL FROM A CARRIER TO A SUBSTRATE BY LASER IRRADIATION

Field of the Invention

The present invention relates to the transfer of material from a carrier to a substrate via radiation induced transfer.

Background of the Invention

There is a desire to design and fabricate bio-compatible structures, for example micro arrays for use in sensors and biomedical testing. Prior art techniques for placing biological material on a substrate include photolithography, spotting and ink jet printing.

Summary of the Invention

According to a first aspect of the present invention there is provided an apparatus for transferring material from a carrier to a substrate, the apparatus comprising:

a source of electromagnetic energy; and

a spatial modulator;

wherein energy from the source of electromagnetic energy is spatially modulated by the spatial modulator so as to allow transfer of energy to the carrier to be controlled, and whereby irradiation of the carrier causes the material to be transferred to the substrate.

It is thus possible to use electromagnetic energy, for example light, to allow parallel writing of a variety of materials onto a substrate where the materials are transferred by laser induced forward transfer (LIFT).

Preferably, the spatial modulator is a spatial light modulator. A number of competing technologies may be used as a spatial light modulator. Digital micro mirror devices are particularly useful as such commercially available devices having a transmission wave length from the ultraviolet to the infrared thereby enabling light more freedom of choice in the selection of a laser light source.

According to a second aspect for present invention there is provided an apparatus for removing organic or polymer materials from a substrate, comprising a source of infra-red, visible or ultra-violet light, a spatial light modulator and an array of focussing elements for directing the light that has been spatially modulated by the spatial light modulator onto the substrate so as to cause light induced transfer of material from the substrate.

According to a third aspect of the present invention there is provided a method of forming a structure on a substrate using a light induced transfer apparatus comprising a laser, a spatial light modulator, and a carrier medium, where the spatial light modulator is interposed in an optical path between the laser and the carrier medium, and the substrate is adjacent the carrier medium, the method comprising;

a) defining a write pattern for a deposition step and;
b) controlling the spatial light modulator such that light irradiates the carrier medium in accordance with the write pattern.

Brief Description of the Figures

The present invention will now be described by way of example only, with reference to the accompanying figures, in which:

Figure 1 schematically illustrates an apparatus constituting an embodiment of the present invention;

Figure 2 schematically illustrates use of the arrangement shown in Figure 1 to perform micro-stereo lithography; and

Figure 3 schematically illustrates an apparatus which combines an embodiment of the present invention with the micro-stereolithography apparatus to form an integrated system.

Description of Example Embodiments of the Present Invention

Figure 1 schematically illustrates an apparatus constituting an embodiment of the present invention for parallel writing of materials onto a substrate. As schematically shown in Figure 1 the apparatus comprises a laser 2 for producing a beam of light 4 which impinges on a spatial light modulator 6. The spatial light modulator may be selected from any appropriate technology such as LCD array or digital micro mirror array. The spatial light modulator 6 is responsive to signals from the controller 8 such that individual pixels within the spatial light modulator 6 can be used to selectively pass or inhibit, as appropriate, passage of light from the laser towards a micro lens array 10 and ultimately towards a carrier 12. The lenses within the micro lens array act to focus the laser light towards a surface 14 of the carrier 12. In use a substrate 20 is positioned adjacent the surface 14 of the carrier 12 and advantageously is moveable with respect to the lens array 10. The substrate may be carried on a single, two or three axis moveable table which are commercially available. However, for completeness, the table may be connected to a worm drive 22 such that actuation of a motor, such as the stepper motor 24, causes a carriage 26 to translate along a helically threaded rod 28. Thus, the position of the substrate 20 can be accurately controlled in one or more directions.

The laser 2 may be selected to be a continuous light source, or a pulsed laser. Light from the laser is spatially modulated by the spatial light modulator 6 and then delivered to the micro lens array 10. The micro lenses are readily available components already used in printing technology, imaging technology and the like. Suitable micro lenses may have focal lengths of up to 1cm and can focus to a 10 micrometer spot size, and can be transparent from the deep ultra violet to the near infrared (200 nanometres - 2000 nanometres). In use, the lens size and laser power have to be matched such that energy in the order of 50 to 100 micro joules can be brought to a focus for each individual spot 40 at the surface 14 of the carrier 12. Given that energy densities of 100 joules per centimetre squared can be employed, a $1cm^2$ device with 100 to 1000 spots can be envisaged (with lens dimensions being in the order of 1000 to 200-300 micrometres) and consequently dense deposition patterns of the order of ten thousand spots per square centimetre can be built up with 10 to 100 write steps.

As shown in Figure 1 the carrier 12 comprises a transparent film 42 with an absorber layer 44 formed at the first surface 14. The function of the absorber there is to absorb the laser energy and to enhance ejection of the material 50 carried on the absorber layer 44.

The absorber layer may consist of a thin film of metal, for example having a thickness of between 10 and 100 nanometres. Where the material 50 to be transferred is a cell or other bio material bio-compatible metals such as silver, platinum and gold may be used. The metal absorber material transfers with the ejected material 50. The absorber layer may also consist of a thin film of a photo-decomposing polymer, again in the range of 10 to 100 nanometres thickness. Photo-decomposing polymers with a high absorption coefficient for the chosen laser wavelength can be used as an absorber material. The examples of suitable polymers are triazene polymers. These polymers have a photoactive triazonium group within the main chain of the polymer which enables explosive decomposition of the polymer by radiation. The decomposition products of these polymers are gases and do not contaminate the transferred material 50. Finally, the carrier 12 carries the material 50 which is to be transferred. Suitable transfer materials are liquids, polymers, powders, complex biomaterials such as DNA and proteins, and even entire cells. Tests by the inventor have shown that cells can and do survive laser induced forward transfer using the technologies described herein. The carrier 12 loses material during the write process and therefore must be translated with respect to the micro-lenses to introduce fresh regions as the carrier for a subsequent write step. Given that the carrier is typically a thin film, then the film may be wound from one spool to another, such as from a supply spool 70 to a take up spool 72 (not to scale). Alternatively, the carrier may be held in a carousel such that translation or rotation of the carousel can cause different parts of a film to be exposed for writing or different films carrying different materials to be selected for subsequent write steps. Thus, multiple target materials can be deposited onto the substrate 20.

The laser 2 has been assumed to have a constant intensity profile over its beam width. However, many standard laser beams have a gaussian spatial intensity profile whereas the ideal intensity profile for use with a spatial light modulator would be a "top hat" beam profile. Therefore, beam shaping optics may be introduced between the laser and the spatial light modulator. Alternatively, the profile of the laser beam may be obtained (either by assumptions that it has a gaussian profile, or by using one or more photo detectors to measure the beam profile) and the control signals to the pixels within the spatial light modulator may be varied such that those pixels in the less intense regions of the laser beam transmit the beam for longer compared to those pixels in the more intense regions such that the product of transmit time by beam intensity during any writing step is substantially uniform. Electrical compensation of the beam intensity profile is only really appropriate with continuous light lasers.

The ejection path of particles from the carrier 12 to the substrate 20 is substantially normal to the carrier surface. The carrier and the substrate are separated by a distance generally of between 0.1 and 10 millimetres and hence small deviations in the ejection path can lead to the deposited material landing at a site which does not correspond to the intended position for that material. An optical imaging system comprising a light source 80 and a camera 82 may be used to monitor the surface of the substrate 20 in order to determine where the or each deposited item of material has landed and to compare the actual landing position with the desired landing position. An error estimate can be formed and this can either be used as a simple quality metric or where systematic offsets can be determined then the substrate 20 may be translated with respect to the lens array in order to correct for the error. If it is determined that, for example, one of the carrier films in the carousel is slightly bowed then the write step may be sub-divided into a variety of write steps and the substrate may be moved slightly between each one of these sub write steps in order that, overall, approximately the correct deposition pattern is achieved on the substrate.

Figure 2 schematically shows an alternative arrangement in which the spatial light modulator and lens array can be used within a micro-stereo lithography system for the fast prototyping of 3D objects through photo-polymerisation of photo curable polymers. The feature sizes produced in such a stereo lithographic process are dependent on the laser pulse length. With continuous or nanosecond lasers, features on a micrometer size can be produced whereas with femto second lasers sub wavelength features of the order of 100 nanometres can be written. Examples of bio-compatible photo-curable materials include biodegradable polymers such as poly (ε-caprolactone) or poly (L-lactide) based polymers and silicate based in organic-organic hybrid polymers, known as ORMOCERs (ORganically MOdified CERamics).

The biodegradable polymers are useful as candidates for scaffolding materials in tissue engineering to give initial rigidity to artificial tissues. They also have the advantage of degrading during formation of the extra-cellular matrix, yielding a scaffold-free engineered tissue. ORMOCERs, on the other hand, do not decompose under biological conditions, and can be used to produce permanent and rigid scaffolds or constructs for analysis platforms, such as micro-cantilevers. It has been shown that organic materials, and even cells, will survive suspension within the photo-curable polymers and hence parallel writing followed by vertical translation of the substrate with respect to the surface of a liquid polymer bath can be used to simultaneously write a scaffold or 3 dimensional structure which includes biomaterial such as living cells. The apparatus described can be used as a 'tissue synthesiser'; i.e. a single device by which complex tissues with multiple cell types can be generated *de novo* in a multistep process. Such an arrangement is illustrated in Figure 3. In the first step a pattern of living cells is written into a matrix of photo-polymerisable biocompatible material 100 as described hereinbefore with respect to Figure 1. In a second step the carrier is removed from the optical path and the relative separation between the lens array 10 and the surface of the photocurable polymer is altered such that the light is focussed onto the surface to cure the polymer. It may be desirable to form some alignment features in the polymer such that optical inspection can be performed to ensure that each step is in correct alignment prior to activating the write or cure steps. Thus a scaffold can be generated around the living cells by photopolymerisation of the matrix. Reiteration of these two steps yields a scaffold containing living cells that can be further grown into artificial tissue. Combining the two techniques also allows incorporation of vascularization 101 (or blood vessels) into the tissue, which is necessary for delivering nutrients and oxygen to and waste products from cells embedded within the tissue. This enables engineering of tissues larger than ~100-200 micrometer in thickness, which is the upper limit of tissues engineered without vascularization. This stepwise deposition also allows for incorporation of different cell types 102, 103 in a single engineered tissue.

Unexpectedly, the orientation of the apparatus can make a difference to the transfer process. It might be assumed that the process would work best if the carrier was placed above the substrate such that the material transferred in the same direction as the local gravitational field (whether this be due to a massive object or due to acceleration) but in fact the process can give better results when transferring against the direction of the local gravitational field.

Additionally, as the ejection and stopping of, for example, cells can be traumatic for the cell, transferring against the prevailing gravitational direction reduces the deceleration that the cell experiences.

In the case of the tissue synthesiser, as shown in figure 3, the apparatus will be used with the carrier placed above the substrate (along the direction of the gravitational field). Since the substrate consists in this case of a film of viscous medium 100 (ORMOCER or biodegradable polymers) the energy of the impact will be greatly reduced and dissipated throughout the viscous medium, hence enhancing cell survival on impact in this case.

The transfer apparatus may also have a pressure controlled chamber around the substrate and carrier such that changes in gas pressure (and hence density and viscosity) can be used to control object speed at the time of impact with the substrate.

CLAIMS

1. An apparatus for transferring material from a carrier to a substrate, the apparatus comprising:

    a source of electromagnetic energy; and

    a spatial modulator

    wherein energy from the source of electromagnetic energy is spatially modulated by the spatial modulator so as to allow transfer of energy to the carrier to be controlled, and whereby irradiation of the carrier causes the material to be transferred to the substrate.

2. An apparatus as claimed in claim 1, further including a beam profile compensator for compensating the spatial distribution of electromagnetic energy across the spatial modulator.

3. An apparatus as claimed in claim 1 or 2, further including a controller for controlling the times that individual ones or groups of pixels within the modulator direct electromagnetic energy towards the carrier such that a product of time and energy for each pixel reaches a target value.

4. An apparatus as claimed in any one of the preceding claims, in which a plurality of carriers are provided in a carousel, such that different carriers carry different materials for transfer to the substrate.

5. An apparatus as claimed in claim 4, in which the carousel can be moved in response to a controller.

6. An apparatus as claimed in any of the preceding claims, further comprising on imaging system for imaging the substrate to verify the suitability of the substrate to receive the materials and/or to verify that the material has been placed correctly.

7. An apparatus as claimed in claim 6, in which a controller monitors the placement of material from a deposition step and uses this information to modify the position of the substrate and/or the modulator pattern for a subsequent deposition step.

8. An apparatus as claimed in any one of the preceding claims, further comprising a holder for a stereo-lithographic material, and wherein the spatial modulator is used to control irradiation of the stereo-lithographic material.

9. An apparatus as claimed in any preceding claim, in which the material on the carrier is an organic material.

10. An apparatus as claimed in any one of the preceding claims, in which the source of electromagnetic energy is a laser and the energy is infra-red, visible or ultra-violet light.

11. An apparatus for removing organic or polymer materials from a substrate, comprising a source of infra-red, visible or ultra-violet light, a spatial light modulator and an array of focussing elements for directing the light that has been spatially modulated by the spatial light modulator onto the substrate so as to cause light induced transfer of material from the substrate.

12. A method of forming a structure on a substrate, using a light induced transfer apparatus comprising a laser, a spatial light modulator, and a carrier medium, where the spatial light modulator is interposed in an optical path between the laser and the carrier medium, and the substrate is adjacent the carrier medium, the method comprising;

a) defining a write pattern for a deposition step and;

b) controlling the spatial light modulator such that light irradiates the carrier medium in accordance with the write pattern.

13. A method as claimed in claim 12, further comprising at least one further deposition step.

14. A method as claimed in claim 12 or 13, further including the step of curing a photopolymer.

Fig 1

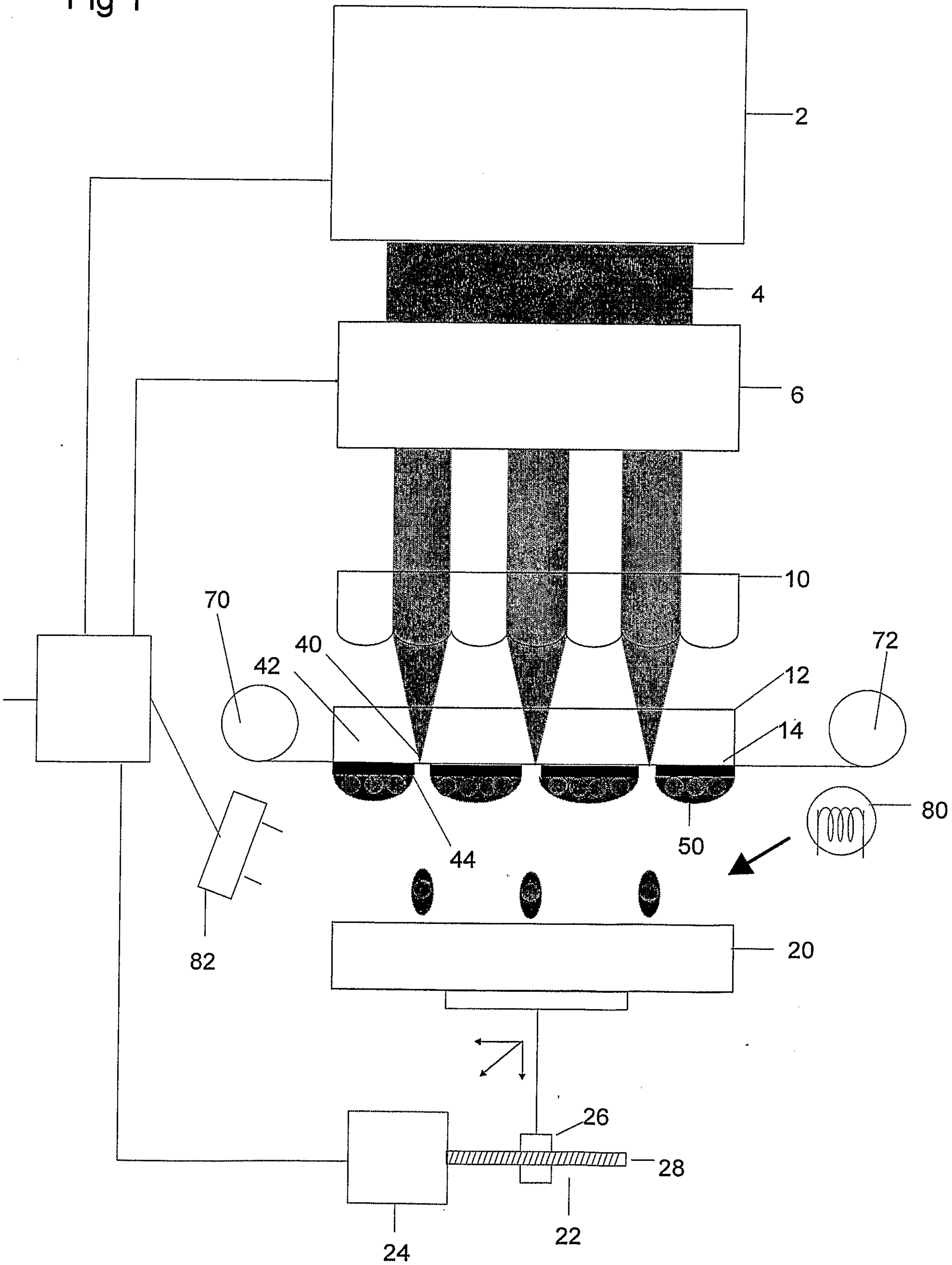


Fig 2

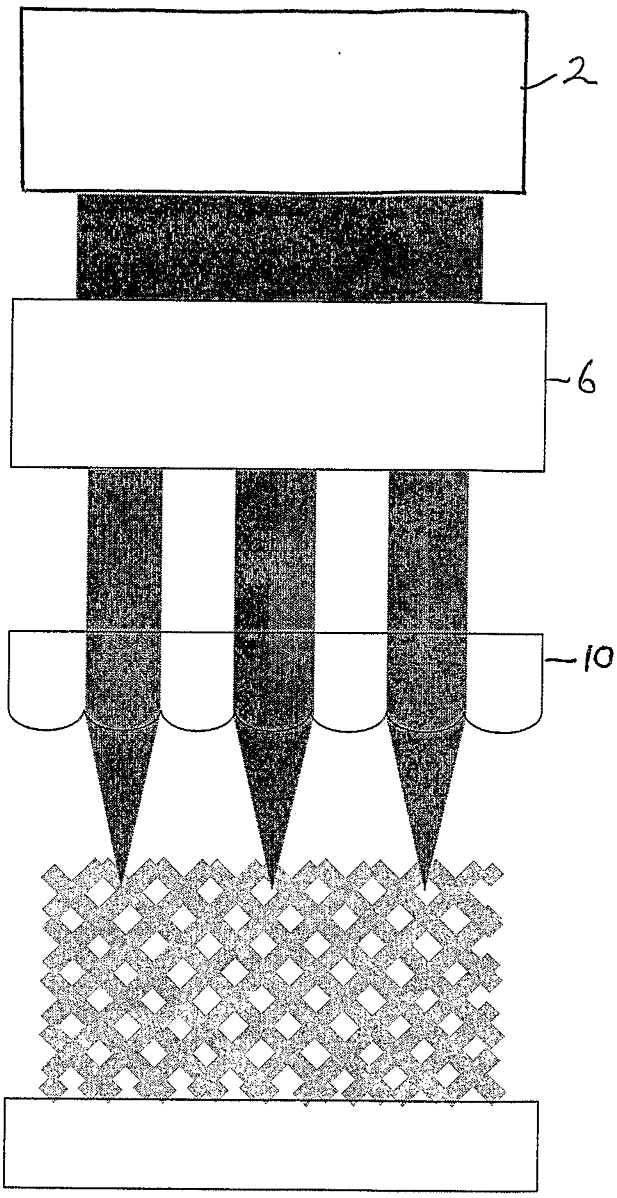
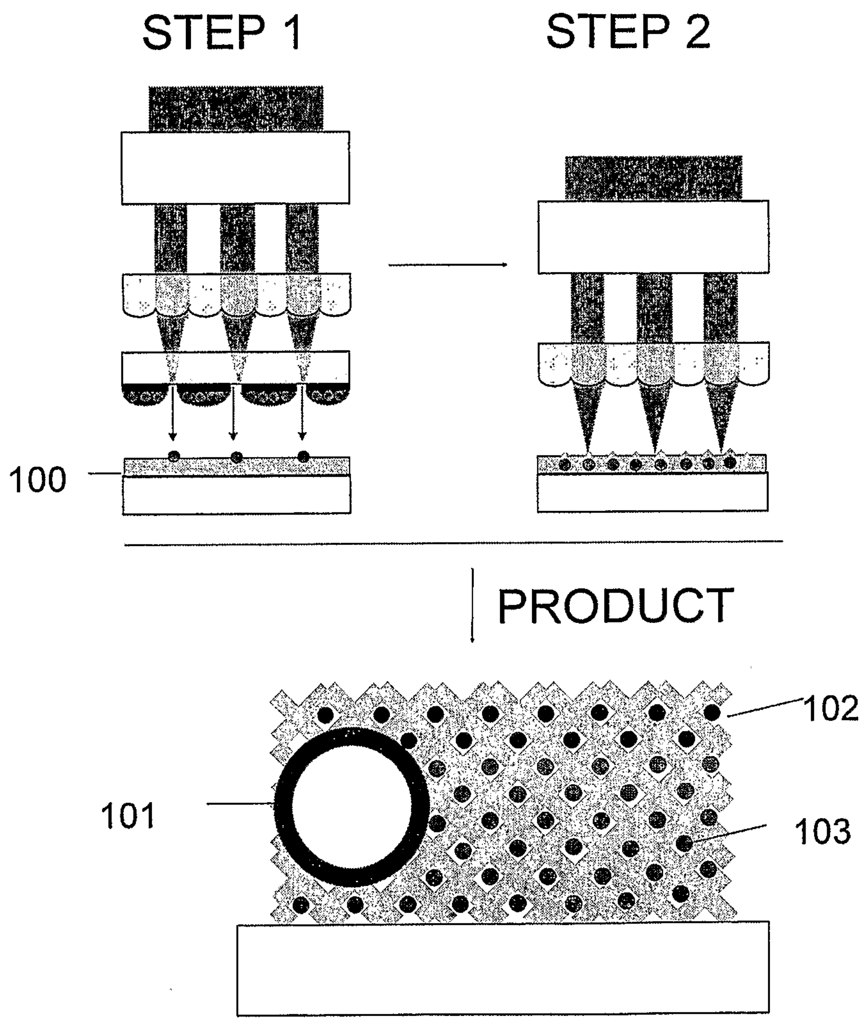


Fig 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/004790

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N1/28 H05K3/04

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)
B41J H05K G01N

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)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/101165 A (US NAVY) 4 December 2003 (2003-12-04) page 6, line 1 - page 14, line 11; figures	1,8,10, 12-14
X	US 2004/022947 A1 (DUIGNAN, MICHAEL T. ET AL) 5 February 2004 (2004-02-05) paragraphs [0030] - [0067]; figure 1	1,2,8, 10,12
X	WO 97/29355 A (P.A.L.M. GMBH) 14 August 1997 (1997-08-14) page 8, line 23 - page 16, line 9; figures 2-5	1,4,5,9, 10,12,13
X	WO 2005/107949 A (P.A.L.M. MICROLASER TECHNOLOGIES AG) 17 November 2005 (2005-11-17) page 17, line 26 - page 27, line 7; figures	1,4,5,9, 10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2007	21/03/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Innecken, Axel

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/004790

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/040427 A (INST DATA STORAGE [SG]; WU DONGJIANG [SG]; HONG MING HUI [SG]) 15 May 2003 (2003-05-15) page 5, line 21 - page 9, line 27; figures	1,10,12, 13
X	US 6 159 832 A1 (MAYER, FREDERICK J.) 12 December 2000 (2000-12-12) column 3, line 55 - column 9, line 25; figures 2-5	1,6,8, 10,12,13
X	US 5 508 065 A1 (WEINER, KURT H.) 16 April 1996 (1996-04-16) column 3, line 28 - column 6, line 21; figure	1,8,10, 12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/004790

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03101165	A	04-12-2003	AU 2000261986	A1	12-12-2003
US 2004022947	A1	05-02-2004	NONE		
WO 9729355	A	14-08-1997	AT 196360	T	15-09-2000
			CA 2245553	A1	14-08-1997
			DE 29723120	U1	14-05-1998
			WO 9729354	A1	14-08-1997
			EP 0879408	A1	25-11-1998
			ES 2150754	T3	01-12-2000
			JP 3311757	B2	05-08-2002
			JP 2000504824	T	18-04-2000
			US 5998129	A	07-12-1999
WO 2005107949	A	17-11-2005	DE 102004021904	A1	01-12-2005
WO 03040427	A	15-05-2003	NONE		
US 6159832	A1		NONE		
US 5508065	A1		NONE		