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- 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.*



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(54) Title: DIFFERENTIAL DELIVERY OF NITRIC OXIDE

(57) Abstract: This invention relates to devices and methods for the local, differential delivery of nitric oxide within the body. The devices include devices having at least two differing nitric oxide donor compounds, such as nitric oxide donor compounds having differing half-lives and nitric oxide donor compounds having different release mechanisms. The devices also include devices having at least two chemically distinct compositions to which nitric oxide donor compounds are adsorbed or attached or within which the donor compounds are disposed. The devices are typically used to increase local nitric oxide concentration in the body upon placement of the medical article at a delivery position on or within a patient. The methods of the present invention include a method of treating an atherosclerotic lesion which comprises: exposing the lesion to a first higher concentration of nitric oxide effective to reduce the number of cells within the lesion; and subsequently exposing the lesion to a second lower concentration of nitric oxide effective to inhibit restenosis. The methods of the present invention also include methods for preferentially providing differing nitric oxide donor compounds within different tissues to effect therapy.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/05220

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/22 A61K31/04 A61L27/54 A61L29/16 A61P9/10

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 7 A61K A61L A61P

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, BIOSIS, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 35416 A (NITROMED INC ;BRIGHAM & WOMENS HOSPITAL (US)) 14 November 1996 (1996-11-14) claims 25-30; examples 1,5 ---	1,2, 5-14, 16-26, 32-41, 57-59
X	US 6 103 275 A (BALABAN ALEXANDRU T ET AL) 15 August 2000 (2000-08-15) column 2, line 62 -column 3, line 2; claim 2; figure 7; example 3 --- -/--	1-5, 13-17, 19, 21-23, 25,32, 34-40, 57,58

 Further documents are listed in the continuation of box C. Patent family members are listed in 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
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- *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

29 January 2003

Date of mailing of the international search report

13.02.03

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/05220

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 994 444 A (ROHLY KEN ET AL) 30 November 1999 (1999-11-30)</p> <p>column 5, line 34 - line 51; figures 3,4; examples I-VI column 6, line 25 - line 35; claim 20 ---</p>	<p>1,2, 4-14, 16-19, 22-25, 32-40, 57,58</p>
X	<p>WO 99 30716 A (ALCON LAB INC ;MILLER STEVEN T (US); YANNI JOHN M (US); GAMACHE DA) 24 June 1999 (1999-06-24)</p> <p>page 6, line 19; examples 2,3 ---</p>	<p>1,2,5,9, 22,23, 25,27, 28,32, 34,35, 41,57,59</p>
X	<p>PULFER S K ET AL: "INCORPORATION OF NITRIC OXIDE-RELEASING CROSSLINKED POLYETHYLENIMINE MICROSPHERES INTO VASCULAR GRAFTS" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, WILEY, NEW YORK, NY, US, vol. 37, no. 2, November 1997 (1997-11), pages 182-189, XP000978327 ISSN: 0021-9304 * see abstract * * see material and methods * ---</p>	<p>1,2, 4-11,13, 14, 16-19, 21-25, 27-40, 57,58</p>
X	<p>MOWERY KELLY A ET AL: "Preparation and characterization of hydrophobic polymeric films that are thromboresistant via nitric oxide release." BIOMATERIALS, vol. 21, no. 1, January 2000 (2000-01), pages 9-21, XP002218425 ISSN: 0142-9612 cited in the application * see abstract * * see materials and methods * ---</p>	<p>1,2, 4-11,13, 14, 16-19, 21-25, 27-40, 57,58</p>
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/05220

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>GANAHA FUMIKIYO ET AL: "Efficient inhibition of in-stent restenosis by controlled hybrid stent-based local release of nitric oxide." CIRCULATION, vol. 104, no. 17 Supplement, 23 October 2001 (2001-10-23), page II.506 XP002218426 Scientific Sessions 2001 of the American Heart Association; Anaheim, California, USA; November 11-14, 2001, October 23, 2001 ISSN: 0009-7322 abstract</p>	1-44, 57-61
X	<p>WO 00 62614 A (NITROSYSTEMS INC) 26 October 2000 (2000-10-26) page 8, last paragraph -page 9, paragraph 1; claims 1-17; figure 8 page 16, last paragraph -page 17, paragraph 1 page 17, paragraph 3 page 29, paragraph 3</p>	45-56
X	<p>WO 98 06389 A (UNIV LELAND STANFORD JUNIOR) 19 February 1998 (1998-02-19) page 6, paragraph 3; claims 1-9 page 8, line 20 - line 21 page 12, last paragraph; figures 2A,,5-7</p>	45-56
X	<p>WO 97 16983 A (UNIV LELAND STANFORD JUNIOR) 15 May 1997 (1997-05-15) page 13, line 11 - line 17 page 17, line 28 - line 34 page 18, paragraph 2; examples 5,8,11,12,17</p>	45-56
X	<p>EP 0 546 796 A (AJINOMOTO KK) 16 June 1993 (1993-06-16) abstract page 2, line 23 - line 27; claims 1-7; example 1</p>	45-56
A	<p>JANERO D R ET AL: "Nitric oxide and postangioplasty restenosis: Pathological correlates and therapeutic potential" FREE RADICAL BIOLOGY AND MEDICINE, ELSEVIER SCIENCE, XX, vol. 29, no. 12, 15 December 2000 (2000-12-15), pages 1199-1221, XP002218451 ISSN: 0891-5849 page 1201, column 2 page 1210, column 2, paragraph 2 -page 1211, column 2, last paragraph; figure 7</p>	1-61

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/05220

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-44, 57-61

Invention 1 relates to a medical article comprising one or more nitric oxide donors and the medical use thereof.

2. Claims: 45-56

Invention 2 relates to a method of treating an atherosclerotic lesion by exposing said lesion to nitric oxide.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No

PCT/US 02/05220

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