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A61K 35/76, 35/12, 35/74

(74) Agent: **SCHÜSSLER, Andrea**; Huber & Schüssler, Trud-
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(71) Applicant and

(72) Inventor: **SZALAY, Aladár, A.** [HU/DE]; Hessenstrasse
64, 97078 Würzburg (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **YU, Yong, A.**
[CN/US]; 8465 Regents Road #245, San Diego, CA
92122 (US). **SHABAHANG, Shahrokh** [US/US]; 550
Pepper Way, Redlands, CA 92373 (US). **TIMIRYASOVA,**
Tatyana [RU/US]; 7524 Charmant Drive #525, San Diego,
CA 92122 (US).

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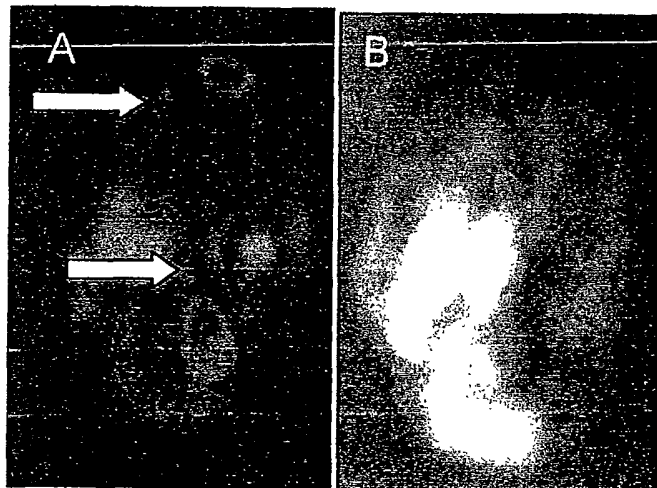
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MICROORGANISMS AND CELLS FOR DIAGNOSIS AND THERAPY OF TUMORS



(57) Abstract: Described are diagnostic and phar-
maceutical compositions comprising a microorgan-
ism or cell containing a DNA sequence encoding a
detectable protein or a protein capable of inducing a
detectable signal, e.g. a luminescent or fluorescent
protein, or a protein inducing a signal detectable by
magnetic resonance imaging (MRI) or a cell receptor
capable of binding a ligand and, particular embodi-
ment, furthermore (a) DNA sequence(s) encoding (a)
protein(s) suitable for tumor therapy and/or elimina-
tion of metastatic tumors, e.g. a cytotoxic or cyto-
static protein.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/66 C12Q1/02 A61K49/00 C12N15/03 G01N33/50
G01N33/574 A61K35/76 A61K35/12 A61K35/74

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 C12Q A61K C12N 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, BIOSIS, MEDLINE, CHEM ABS Data, COMPENDEX, INSPEC, PAJ, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 25399 A (SLOAN KETTERING INST CANCER ;VION PHARMACEUTICALS INC (US)) 12 April 2001 (2001-04-12) the whole document page 20, line 5 - line 13 page 24, line 5 - line 11 page 4, line 8 - line 24 page 9, line 35 - line 36 page 18, line 21 -page 19, line 7 page 42, line 24 -page 53, line 33 page 54, line 32 -page 56, line 1 page 62, line 32 -page 64, line 8 claims 1-5,7,16,34-37,55-58,60-67	1-3,11, 14,16, 18,22, 24,25
Y	--- -/--	1-25



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

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"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

26 September 2003

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31 OCT 2003

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,
Fax: (+31-70) 340-3016

Authorized officer

Tuynman, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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E	US 6 511 967 B1 (CHIOCCA ENNIO ANTONIO ET AL) 28 January 2003 (2003-01-28) the whole document ---	1-11,16, 18,19, 22,24,25
X	WO 01 05229 A (BRIGHAM & WOMENS HOSPITAL ;CHIOCCA E ANTONIO (US); GEN HOSPITAL CO) 25 January 2001 (2001-01-25) the whole document claims 1-16 page 16, line 7 -page 17, line 17 page 21, line 27 -page 22, line 6 page 22, line 19 - line 25	1-3,11, 15,16, 18,23-25
Y		1-5,11, 13-21, 23-25
X	MACLAREN D C ET AL: "RECEPTIVE, NON-INVASIVE IMAGING OF THE DOPAMINE D2 RECEPTOR AS A REPORTER GENE IN LIVING ANIMALS" GENE THERAPY, MACMILLAN PRESS LTD., BASINGSTOKE, GB, vol. 6, May 1999 (1999-05), pages 785-791, XP000920594 ISSN: 0969-7128 the whole document	1,4,5, 11,18, 24,25
Y		1-6,11, 13-15, 18,20, 23-25
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Y		1,3,11, 13-18, 20,21, 23-25
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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WEISSLEDER RALPH ET AL: "In vivo magnetic resonance imaging of transgene expression." NATURE MEDICINE, vol. 6, no. 3, March 2000 (2000-03), pages 351-354, XP002194183 ISSN: 1078-8956 the whole document page 351, left-hand column, line 31 -right-hand column, line 19 figure 1 --- -/--	1,4,10, 15,18,19

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	CLAIRMONT C ET AL: "Enhanced antitumor activity from tumor-targeting Salmonella expressing endostatin." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 732 XP008015903 91st Annual Meeting of the American Association for Cancer Research.; San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X the whole document	1-3,11, 13-18, 21,24,25
Y	--- DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2000 (2000-07) LI SHUN-QIANG ET AL: "An engineered and assembled fusion protein of antitumor antibiotic lidamycin and scFv antibody directed against type IV collagenase." Database accession no. PREV200100011314 XP002244308 abstract & YAOXUE XUEBAO, vol. 35, no. 7, July 2000 (2000-07), pages 488-491, ISSN: 0513-4870	1-5,11, 13-18, 20,23-25
Y	--- WO 91 07989 A (UNIV OTTAWA ;UNIV LAVAL (CA)) 13 June 1991 (1991-06-13) abstract --- -/--	1-17,20, 24,25

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I onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	GROVE J I ET AL: "VIRUS-DIRECTED ENZYME PRODRUG THERAPY USING CB1954" ANTI-CANCER DRUG DESIGN, BASINGSTOKE, GB, vol. 14, no. 6, December 1999 (1999-12), pages 461-472, XP009003925 ISSN: 0266-9536 the whole document ---	1,22
Y	NEWTON D L ET AL: "EXPRESSION AND CHARACTERIZATION OF RECOMBINANT HUMAN EOSINOPHIL- DERIVED NEROTOXIN AND EOSINOPHIL-DERIVED NEUROTOXIN-ANTI- TRANSFERRIN RECEPTOR SFV" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 269, no. 43, 28 October 1994 (1994-10-28), pages 26739-26745, XP000647481 ISSN: 0021-9258 abstract ---	1,2,4,7, 11
X	WEST ANNE E ET AL: "Identification of a somatodendritic targeting signal in the cytoplasmic domain of the transferrin receptor." JOURNAL OF NEUROSCIENCE, vol. 17, no. 16, 1997, pages 6038-6047, XP002255871 ISSN: 0270-6474 ---	1,4,10, 11,23
Y	the whole document ---	1,2,4,6, 18,19
Y	SUDIMACK J ET AL: "TARGETED DRUG DELIVERY VIA THE FOLATE RECEPTOR" ADVANCED DRUG DELIVERY REVIEWS, AMSTERDAM, NL, vol. 41, no. 2, 2000, pages 147-162, XP000990851 ISSN: 0169-409X the whole document ---	1,2, 4-15, 18-24
Y	REDDY J A ET AL: "FOLATE-MEDIATED TARGETING OF THERAPEUTIC AND IMAGING AGENTS TO CANCERS" CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, XX, XX, vol. 15, no. 6, 1998, pages 587-627, XP000901554 ISSN: 0743-4863 the whole document --- -/--	1-25

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2.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHMIDT W ET AL: "Generation of effective cancer vaccines genetically engineered to secrete cytokines using adenovirus-enhanced transferrin infection (AVET)" GENE: AN INTERNATIONAL JOURNAL ON GENES AND GENOMES, ELSEVIER SCIENCE PUBLISHERS, BARKING, GB, vol. 190, no. 1, 29 April 1997 (1997-04-29), pages 211-216, XP004064404 ISSN: 0378-1119 abstract ---	1,2,15, 18,24,25
P,X	MOUNTZ JAMES M ET AL: "Tc-99m NeoTect imaging in vivo of T cells from hCAR transgenic mice." FASEB JOURNAL, vol. 16, no. 5, 22 March 2002 (2002-03-22), page A1211 XP008022544 Annual Meeting of Professional Research Scientists on Experimental Biology; New Orleans, Louisiana, USA; April 20-24, 2002, March 22, 2002 ISSN: 0892-6638 ---	1-5,11, 16-18
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X	LARSON S M ET AL: "Triumph over mischance: a role for nuclear medicine in gene therapy." JOURNAL OF NUCLEAR MEDICINE: OFFICIAL PUBLICATION, SOCIETY OF NUCLEAR MEDICINE. UNITED STATES AUG 1997, vol. 38, no. 8, August 1997 (1997-08), pages 1230-1233, XP008022594 ISSN: 0161-5505 the whole document ---	1,2,4,5, 8,9,11, 18,22, 24,25
X	WARRINGTON KENNETH H ET AL: "Developing VDEPT for DT-diaphorase (NQ01) using an AAV vector plasmid." INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS, vol. 42, no. 4, 1 November 1998 (1998-11-01), pages 909-912, XP001165756 ISSN: 0360-3016 the whole document --- -/--	1-3,8, 11,16, 18,22, 24,25

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2. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUZUKI SATOSHI ET AL: "Coexpression of the partial androgen receptor enhances the efficacy of prostate-specific antigen promoter-driven suicide gene therapy for prostate cancer cells at low testosterone concentrations." CANCER RESEARCH, vol. 61, no. 4, 15 February 2001 (2001-02-15), pages 1276-1279, XP002255872 ISSN: 0008-5472 the whole document ---	1-4, 8, 11, 16-18, 22, 24, 25
X	ZINN KURT R ET AL: "Noninvasive monitoring of gene transfer using a reporter receptor imaged with a high-affinity peptide radiolabeled with ^{99m} Tc or ¹⁸⁸ Re." JOURNAL OF NUCLEAR MEDICINE, vol. 41, no. 5, May 2000 (2000-05), pages 887-895, XP002255873 ISSN: 0161-5505 ---	1, 2, 4, 5, 8, 11, 18, 19, 24, 25
Y	the whole document ---	20
Y	WELLING M M ET AL: "Technetium-99m labelled antimicrobial peptides discriminate between bacterial infections and sterile inflammations." EUROPEAN JOURNAL OF NUCLEAR MEDICINE. GERMANY MAR 2000, vol. 27, no. 3, March 2000 (2000-03), pages 292-301, XP000997947 ISSN: 0340-6997 cited in the application the whole document ---	20
P, Y	WELLING M M ET AL: "Radiochemical and biological characteristics of Tc-UBI 29-41 for imaging of bacterial infections" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 29, no. 4, May 2002 (2002-05), pages 413-422, XP004357344 ISSN: 0969-8051 cited in the application the whole document --- -/--	20

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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.
P, X	BERMUDES DAVID ET AL: "Live bacteria as anticancer agents and tumor-selective protein delivery vectors." CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT. ENGLAND MAR 2002, vol. 5, no. 2, March 2002 (2002-03), pages 194-199, XP008022593 ISSN: 1367-6733 the whole document ---	1-3, 11, 13-17
X	MOORE ANNA ET AL: "Measuring transferrin receptor gene expression by NMR imaging." BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1402, no. 3, 24 April 1998 (1998-04-24), pages 239-249, XP002255874 ISSN: 0006-3002 abstract ---	1, 2, 4, 6, 10, 11, 18, 19
X	BOUVIER CLAUDIA ET AL: "Functional characterization of the human dopamine D-4.2 receptor using vaccinia virus as an expression system." EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 290, no. 1, 1995, pages 11-17, XP008022548 ISSN: 0014-2999 the whole document ---	1, 2, 4, 11, 13
Y	THEUER C P ET AL: "A RECOMBINANT FORM OF PSEUDOMONAS EXOTOXIN DIRECTED AT THE EPIDERMAL GROWTH FACTOR RECEPTOR THAT IS CYTOTOXIC WITHOUT REQUIRING PROTEOLYTIC PROCESSING" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 24, 1992, pages 16872-16877, XP002255875 ISSN: 0021-9258 cited in the application the whole document ---	1-3, 10-17, 21
X	ZINN K R ET AL: "Simultaneous evaluation of dual gene transfer to adherent cells by gamma-ray imaging" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 28, no. 2, February 2001 (2001-02), pages 135-144, XP004233298 ISSN: 0969-8051 the whole document ---	1, 2, 4, 5, 8, 11, 18, 19, 22, 24, 25
Y	---	20
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I International 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.
X	WEISSLEDER R ET AL: "DRUG TARGETING IN MAGNETIC RESONANCE IMAGING" MAGNETIC RESONANCE QUARTERLY, NEW YORK, NY, US, vol. 8, no. 1, March 1992 (1992-03), pages 55-63, XP001006103 the whole document page 59, left-hand column, line 32 -right-hand column, line 10 ----	1,2,4,6, 10,15, 18,19
Y	NIBBERING P H ET AL: "Radiolabelled antimicrobial peptides for imaging of infections: A review." NUCLEAR MEDICINE COMMUNICATIONS, vol. 19, no. 12, December 1998 (1998-12), pages 1117-1119, XP008022643 ISSN: 0143-3636 the whole document -----	1-17,20

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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: 1-25 (partially)

Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal

1.1. Claims: 1-17,20,24,25 (partially)

I.1: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal, furthermore containing DNA sequence (s) encoding (a) protein (s) suitable for tumor therapy and/or elimination of metastatic tumors further comprising an antimicrobial compound fused to a protein suitable for tumor therapy and/or elimination of metastatic tumors

1.2. Claims: 1,2,3,10-17,21,24,25 (partially)

I.2: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal, furthermore containing DNA sequence (s) encoding (a) protein (s) suitable for tumor therapy and/or elimination of metastatic tumors wherein said protein suitable for tumor therapy and/or elimination of metastatic tumors is endostatin or recombinant chimeric toxin PE37/transforming growth factor alpha (TGF-alpha)

1.3. Claims: 1-9,11-25 (partially)

II: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein capable of inducing a detectable signal is a luminescent and/or fluorescent protein

1.4. Claims: 1-5,11-15,18-25 (partially)

III.1: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein is a cell receptor capable of binding a ligand wherein said composition further comprises a ligand which is a radionuclide-labelled ligand.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1.5. Claims: 1,10-25 (partially)

IV: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal, wherein said protein capable of inducing a detectable signal is a protein inducing a signal detectable by magnetic resonance imaging (MRI) or capable of binding a contrasting agent, chromophore or a ligand required for visualization of tissues

1.6. Claims: 1-14,18-25 (partially)

V: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said microorganism is a bacterium or a virus

1.7. Claims: 1-10,15,18-25 (partially)

VI: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said cell is a mammalian cell

2. Claims: 1,2,3,10-17,22,24,25 (partially)

I.3: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal, furthermore containing DNA sequence (s) encoding (a) protein (s) suitable for tumor therapy and/or elimination of metastatic tumors wherein said protein suitable for tumor therapy and/or elimination of metastatic tumors is a protein capable of converting a nontoxic prodrug into a toxic drug which is cytotoxic to a tumor.

3. Claims: 1-4,6,11-25 (partially)

III.2: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein is a cell receptor capable of binding a ligand wherein said composition further comprises a ligand which is a paramagnetic-or superparamagnetic-metal-labelled ligand.

4. Claims: 1-4,7,11-25 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

III.3: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein is a cell receptor capable of binding a ligand wherein said composition further comprises a ligand which is coupled to a toxin.

5. Claims: 1-4,8,11-25 (partially)

III.4 : Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein is a cell receptor capable of binding a ligand wherein said composition further comprises a ligand which is coupled to a therapeutic protein.

6. Claims: 1-9,11-25 (partially)

III.5 : Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal wherein said protein is a cell receptor capable of binding a ligand wherein said ligand is an antibody.

7. Claims: 1-25 (partially)

VII: Diagnostic and pharmaceutical compositions comprising a microorganism or cell containing a DNA sequence encoding a detectable protein or protein capable of inducing a detectable signal further comprising an antimicrobial compound fused to a detectable protein or a protein capable of inducing a detectable signal

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

INTERNATIONAL SEARCH REPORT

International Application No
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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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