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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.

(54) Title: TUMOR SPECIFIC OLIGOSACCHARIDE EPITOPES AND USE THEREOF

(57) Abstract: The present invention describes oligosaccharide sequences, which are specifically expressed by human tumors. The present invention is related to a method of determining an oligosaccharide sequence, which comprises a tumor specific terminal N-acetylglucosamine residue, in a biological sample, the presence of said sequence in said sample being an indication of the presence of cancer. The present invention provides antigenic substances comprising said oligosaccharide sequences in a polyvalent form and it further provides diagnostic agents, pharmaceutical compositions and cancer vaccines comprising said oligosaccharide sequences or substances binding to said oligosaccharide sequences. The present invention is also related to methods for the treatment of cancer. Further the present invention relates to a method of treatment or diagnosis of cancer by transferring a modified monosaccharide to cancer cells by glycosyl transferase. It also concerns an enzyme substrate composition capable of being transferred to a surface of pathogenic entity for use as medecine.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2003/000615

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 39/00, A61K 31/70, A61P 35/00, A61P 31/00, G01N 33/574, C07H 5/06
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)

IPC7: A61K, G01N, C07H, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, BIOSIS, MEDLINE, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	WO 03016915 A1 (CARBION OY), 27 February 2003 (27.02.2003)	1-45, 46-86 (PARTIALLY)
X	British Journal of Cancer, Volume 83, No. 10, 2000, PJ Johnson et al, "Structures of disease-specific serum alpha-fetoprotein isoforms", pages 1330-1337, see specially figure 1, G10 and G11	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
X	British Journal of Cancer, Volume 81, No. 7, 1999, PJ Johnson et al, "Glycan composition of serum alpha-fetoprotein in patients with hepatocellular carcinoma and non-seminomatous germ cell tumour", pages 1188-1195, se specially figure 3, G11 and G10	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)

[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 application or patent 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
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Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Micael Owald/BS Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 2003/000615

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0255342 A1 (UNIVERSITY COLLEGE LONDON), 3 February 1988 (03.02.1988), see specially page 1, column 2, lines 32-61	1-45, 46-86 (PARTIALLY)
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X	Eur. J. Biochem., Volume 161, 1986, James W. Dennis et al, "Asn-linked oligosaccharides in lectin-resistant tumor-cell mutants with varying metastatic potential", pages 359-373, the whole document	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
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X	DE 3807594 A1 (REUTTER, WERNER), 21 Sept 1989 (21.09.1989)	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
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X	Cancer Research, Volume 43, November 1983, Katsuko Yamashita et al, "Comparative Study of the Sugar Chains of gamma-Glutamyltranspeptidases Purified from Rat Liver and Rat AH-66 Hepatoma Cells", pages 5059-5063, see specially charts. 4-5	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
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X	J. Biochem., Volume 90, 1981, Katsuko Yamashita et al, "Structural Study of the Sugar Chains of alpha-Amylases Produced Ectopically in Tumors", pages 1281-1289, see specially figures 4-5	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
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X	Histochemical Journal, Volume 24, 1992, Boris E. Chechik et al, "Increased expression of highly branched N-linked oligosaccharides terminating in N-acetylglucosamine residues in neoplastic and sclerodermal chicken fibroblasts", pages 15-20, the whole document	1-5 (PARTIALLY),6-8, 13-86 (PARTIALLY)
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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	Molecular Immunology, Volume 24, No. 8, 1989, Gail Nixon Volman et al, "Analysis of Asparagine-linked oligosaccharide structures of chronic lymphocytic leukemia cells", pages 871-888 see specially table 5	1-5 (PARTIAL-LY),6-8, 13-86 (PARTI-ALLY)
X	Eur. J. Biochem., Volume 236, 1996, Tamao Endo et al, "Comparative study of the sugar chains of alkaline phosphatases purified from rat liver and rat AH-130 hepatoma cells Occurrence of fucosylated high-mannose-type and hybrid-type sugar chains", pages 579-590, see specially table 2	1-5 (PARTIAL-LY),6-8, 13-86 (PARTI-ALLY)
X	Clinical Cancer Research, Volume 5, 1999, Abdelhadi Rebbaa et al, "Expression of Bisecting GlcNac in Pediatric Brain Tumors and Its Association with Tumor Cell Response to Vinblastine", pages 3661-3668	1-5 (PARTIAL-LY),6-8, 13-86 (PARTI-ALLY)
P,X	Jpn J. Electroph, Volume 46: 163, 2002, Nobuhisa Ohtani et al, "Abnormality of the oligosaccharide moiety of human immunoglobulin G in sera of patients with either rheumatoid arthritis or cancer", pages 2-6, the whole document	1-5 (PARTIAL-LY),6-8, 13-86 (PARTI-ALLY)
X	Cancer Research, Volume 60, 1 October 2000, Marc Meichenin et al: "Tk, a New Colon Tumor-associated Antigen Resulting from Altered O-Glycosylation 1", page 5499 - page 5507	1-5,9,11-12, 13-45 AND 46-86 (PARTIAL-LY)
X	Cancer Research, Volume 53, 15 October 1993, F-G. Hanisch et al: "Monoclonal Antibody 2B5 Defines a Truncated O-Glycan, GlcNAcBeta 1-3GalBeta 1 4GlcNAcBeta 1-6 (GalNAc), on Mucins from Deep Gastric and Duodenal Glands as Well as Metaplasia and Neoplasia of Gastric Differentiation", page 4791 - page 4796	1-5,9,11-12, 13-45 AND 46-86 (PARTIAL-LY)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Jpn. J. Cancer Res., Volume 81, April 1990, Jun Nakayama et al: "Griffonia simplicifolia Agglutinin-2-binding Glycoprotein as a Novel Carbohydrate Antigen of Human Colonic Carcinoma", page 388 - page 395 --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)
X	DATABASE WPI Week 199049 Derwent Publications Ltd., London, GB; Class B04, AN 1990-365935 & JP 2264864 A (SHINETSU CHEM IND CO LTD), 29 October 1990 (1990-10-29) --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)
X	Glycobiology, Volume 4, no. 3, 1994, Jie Hu et al: "Structural characterization of intermediates in the biosynthetic pathway of neolacto glycosphingolipids: differential expression in human leukaemia cells", page 251 - page 257 --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)
X	Archives of biochemistry and biophysics, Volume 288, no. 1, July 1991, Eric H. Holmes et al: "Isolation and Fine-Structure Characterization of Four Monoclonal Antibodies Reactive with Glycoconjugates Containing Terminal GlcNAc Residues: Application to Aspects of Lacto-Series Tumor Antigen Biosynthesis 1", page 87 - page 96 --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)
X	WO 0021552 A1 (UNIVERSITY TECHNOLOGY CORPORATION), 20 April 2000 (20.04.2000), --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 10, 17 November 2000, (2000-11-17) & JP 20 00191685 A (NIPPON KOUTAI KENKYUSHO:KK), 11 July 2000 (2000-07-11) abstract --	1-5,9,11-12, 13-45 AND 46 -86 (PARTIAL-LY)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chembiochem, Volume 2, 2001, Thomas Bülter et al: "Chemoenzymatic Synthesis of Biotinylated Nucleotide Sugars as Substrates for Glycosyltransferases", page 884 - page 894 --	46-86 (PARTIALLY)
X	Glycobiology, Volume 11, no. 7, 2001, Zhao Chun Chen et al: "Synthesis of alpha-gal epitopes (Galalpha 1-3GalBeta 1-4GlcNAc-R) on human tumor cells by recombinant alpha 1,3galactosyltransferase produced in Pichia pastoris", page 577 - page 586 --	46-86 (PARTIALLY)
X	Vaccine, Volume 15, no. 11, 1997, Timothy R. Henion et al: "Synthesis of a-gal epitopes on influenza virus vaccines, by recombinant alpha 1,3galactosyltransferase, enables the formation of immune complexes with the natural anti-Gal antibody", page 1174 - page 1182 --	46-86 (PARTIALLY)
X	Methods in enzymology, Volume 362, 2003, Reiko Sadamoto et al: "Cell Wall Engineering of Living Bacteria through Biosynthesis", page 273 - page 286 --	46-86 (PARTIALLY)
X	Chemistry & Biology, Volume 8, 2001, George A. Lemieux et al: "Modulating cell surface immunoreactivity by metabolic induction of unnatural carbohydrate antigens", page 265 - page 275 --	46-86 (PARTIALLY)
X	Annu. Rev. Cell Dev. Biol., Volume 17, 2001, Eliana Saxon et al: "Chemical and Biological Strategies for Engineering Cell Surface Glycosylation", page 1 - page 23 --	46-86 (PARTIALLY)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6075134 A (CAROLYN BERTOZZI ET AL), 13 June 2000 (13.06.2000)	46-86 (PARTIALLY)
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X	WO 9114697 A1 (BROSSMER, REINHARD), 3 October 1991 (03.10.1991)	46-86 (PARTIALLY)
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X	WO 0187321 A2 (EUROPEAN MOLECULAR BIOLOGY LABORATORY), 22 November 2001 (22.11.2001)	46-86 (PARTIALLY)
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X	EP 0334962 A1 (ORIENTAL YEAST CO., LTD.), 4 October 1989 (04.10.1989)	46-86 (PARTIALLY)
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INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: **46-53**
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☒ Claims Nos.: **57-59, 69-70, 73-76, 83-84**
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:

see extra sheet

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 No. III *Observations where unity of invention is lacking (Continuation of item 3 of first sheet)*

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

see extra 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.: **1-45,46-86 (partially)**

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.

Box II.1

Claims 46-53 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims.

Box II.2

Present claims 57-59, 69-70, 73-76 and 83-84 relate to compositions defined by reference to desirable characteristics or properties, namely *inter alia* the capability of the enzyme substrate of claim 57 of being transferred to a surface of a pathogenic entity. The claims cover all enzyme substrates having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of compounds. Additionally, previously known compounds may be included in the scope of the present claims. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Box III

This International Searching Authority found multiple inventions.

The separate inventions are:

Invention 1.1, (claims 1-5 (partially), 6-8, 13-45 (partially) and 46-86 (partially)) concerns a pharmaceutical composition comprising a substance binding to a terminal N-glycan oligosaccharide sequence according to Formula I or Formula II and a method for diagnosing cancer in a biological sample comprising determining the presence of the above described terminal oligosaccharide. It also concerns: other pharmaceutical compositions, a diagnostic agent, an antigenic substance and use thereof, a cancer vaccine, a binding substance, a method for identifying therapeutics or diagnostic agents, a functional food, a method of transferring a modified monosaccharide derivative to a terminal β-N-acetylglucosamine (GlcNAc) structure and an enzyme substrate composition.

.../...

Invention 1.2, (claims 1-5 (partially), 9, 11-12, 13-45 (partially) and 46-86 (partially)) concerns a pharmaceutical composition comprising a substance binding to a terminal O-glycan oligosaccharide sequence according to Formula III or according to claim 12 and a method for diagnosing cancer in a biological sample comprising determining the presence of the above described terminal oligosaccharide. It also concerns: other pharmaceutical compositions, a diagnostic agent, an antigenic substance and use thereof, a cancer vaccine, a binding substance, a method for identifying therapeutics or diagnostic agents, a functional food, a method of transferring a modified monosaccharide derivative to a terminal β-GlcNAc structure and an enzyme substrate composition.

Invention 1.3, (claims 1-5 (partially), 10, 13-45 (partially) and 46-86 (partially)) concerns a pharmaceutical composition comprising a substance binding to a terminal GlcNac linked to a protein and a method for diagnosing cancer in a biological sample comprising determining the presence of the above described terminal oligosaccharide. It also concerns: other pharmaceutical compositions, a diagnostic agent, an antigenic substance and use thereof, a cancer vaccine, a binding substance, a method for identifying therapeutics or diagnostic agents, a functional food, a method of transferring a modified monosaccharide derivative to a terminal β-GlcNAc structure and an enzyme substrate composition.

Invention 2.1, (claims 46-86 (partially)) concerns a method of treatment or diagnosis of cancer by transferring a modified monosaccharide derivative to cancer cells by a glycosyl transferase or a transglycosylate enzyme.

Invention 2.2, (claims 46-86 (partially)) concerns a composition comprising an enzyme substrate, capable of being transferred specifically to a surface of a pathogenic entity by a transferring enzyme.

Invention 3, (claims 51-56 (partially) and 86 (partially)) concerns a substance according to Formula P1, a substance according to formula CT2 and a method to synthesise these substances. The pegylated peptides of formula P1 could generally be used for improving the quality of therapeutic proteins. The modification of cells and tissues according to Formula CT2 could generally be used for therapy such as transplantation or treatment of wounds or tissue damage.

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