

- Anatomic and metabolic imaging of brain and spinal cord tumors for diagnostic and therapeutic purposes.

- Intravenous treatment of brain and spinal cord tumors.

- Imaging of intravenous drug delivery to brain and spinal cord tumors.

- Potential to be used for imaging and treatment of other neurological disorders in which the BBB becomes porous.

Market: In 2008, it is estimated that malignant tumors of the brain and spinal cord will account for about 1.5% of all cancers and 2.3% of all expected cancer-related deaths.

Development Status: Early stage development; Pre-clinical data available.

Inventor: Hemant Sarin (CC).

Patent Status: U.S. Provisional Application No. 61/055,328 filed 22 May 2008 (HHS Reference No. E-063-2008/0-US-01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: Surekha Vathyam, PhD; 301-435-4076; vathyams@mail.nih.gov.

Induced Internalization of Surface Receptors

Description of Technology: Cell-surface receptors are responsible for the biological activities of many molecules. Specific ligands bind to them, causing the cell-surface receptors to internalize or bring the receptor and ligand inside the cell. A number of diseases, including cancer, metabolic disorders, and viral infections are known to require the expression of cell-surface receptors for critical pathogenetic steps. This has prompted significant research efforts towards the development of pharmaceutical agents that block the signals from cell-surface receptors. While this current research shows great promise, there is a strong need for new therapeutic strategies that utilize the mechanistic properties of cell-surface receptors.

This technology describes a strategy for artificially inducing the internalization of surface receptors, and thereby blocking the effects of the ligands associated with that receptor. This method employs bifunctional ligands that bind to both a scavenger receptor and a target receptor. As proof of concept, the inventors Drs. Narazaki and Tosato have shown that a ligand capable of binding to the scavenger receptor SREC-1 and the neuropilin-1 receptor NRP1 induces the internalization of NRP1 and inhibits NRP1 signaling. The inventors propose that this strategy can be used to inhibit

signaling from any target receptor if an appropriate bifunctional ligand is used. For example, the concept could be expanded to other receptors, such as HDL and LDL receptors. Likewise the bifunctional ligand could include specific antibodies or modified ligands that recognize cell surface receptors of biological importance. Accordingly, this approach could be used to limit tumor angiogenesis, limit tumor growth, block metastasis formation, block inflammation, block viral infection, and treat just about any disease where we identify a cell surface receptor as the molecular basis for disease.

Applications:

- Method of inducing the internalization of target receptors.
- Inhibiting diseases or conditions associated with target receptors, such as HIV infection, cancer, or angiogenesis.
- Treating diseases or conditions associated with target receptors, such as cancer, viral infections, or HIV infections.

Market:

- Cancer is one of the leading causes of death in the United States and it is estimated that there will be more than half a million deaths caused by cancer in 2008.

- It is estimated that over one million people in the U.S. are living with HIV/AIDS and approximately 50,000 new infections occur each year.

Development Status: The technology is currently in the pre-clinical stage of development.

Inventors: Masashi Narazaki and Giovanna Tosato (NCI).

Patent Status: U.S. Provisional Application No. 61/023,397 filed 24 Jan 2008 (HHS Reference No. E-250-2007/0-US-01).

Licensing Status: Available for licensing.

Licensing Contact: Whitney A. Hastings; 301-451-7337; hastingsw@mail.nih.gov.

Collaborative Research Opportunity: The National Cancer Institute, Laboratory of Cellular Oncology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the technology aimed at promoting selective receptor internalization as a means to neutralize ligand function and receptor signaling. Please contact John D. Hewes, PhD at 301-435-3121 or hewesj@mail.nih.gov for more information.

Methods of Determining the Prognosis of an Adenocarcinoma

Description of Technology: Available for licensing and commercial

development is a novel method for determining the prognosis of a subject with adenocarcinoma in an organ, such as the lung, and to aid in the selection of a specific therapeutic regimen. Lung adenocarcinoma (AC) is the predominant histological subtype of lung cancer, which is the leading cause of cancer deaths worldwide. The risk of metastasis remains substantial in AC patients, even when a curative resection of early-stage AC is performed. The prognosis includes the determination of the likelihood of survival, the likelihood of metastasis, or both. The method includes quantization of the expression of a plurality of Th1 and Th2 cytokines of interest in the adenocarcinoma and in non-cancerous tissue in the organ. Altered expression of one or more of the Th1 and Th2 cytokines in the adenocarcinoma as compared to the non-cancerous tissue determines the prognosis for the subject. The method is capable of distinguishing patients with lymph node metastasis versus those with short term survival. Furthermore, methods are provided for evaluating the effectiveness of anti-cancer agents.

Applications: Prognosis of adenocarcinoma, aid in the selection of specific therapeutic regimens and evaluation of the effectiveness of anti-cancer agents.

Development Status: The technology is in early stage of development.

Inventors: Curtis C. Harris, Masahiro Seike, Xin Wei Wang (NCI).

Patent Status: PCT Application No. PCT/US2007/073637 filed 16 Jul 2007, which published as WO 2008/009028 on 17 Jan 2008; claiming priority to 14 Jul 2006 (HHS Reference No. E-263-2006/1-PCT-01).

Licensing Status: Available for non-exclusive or exclusive licensing.

Licensing Contact: Susan Ano, PhD; 301-435-5515; anos@mail.nih.gov.

Dated: October 14, 2008.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804; telephone: 301/496-7057; fax: 301/402-0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Catalytic Domains of [beta](1,4)-galactosyltransferase I Having Altered Donor and Acceptor Specificities, Domains That Promote In Vitro Protein Folding, and Methods for Their Use

Description of Technology: [beta](1,4)-galactosyltransferase I catalyzes the transfer of galactose from the donor, UDP-galactose, to an acceptor, N-acetylglucosamine, to form a galactose-[beta](1,4)-N-acetylglucosamine bond. This reaction allows galactose to be linked to an N-acetylglucosamine that may itself be linked to a variety of other molecules. The reaction can be used to make many types of molecules having great biological significance. For example, galactose-[beta](1,4)-N-acetylglucosamine linkages are very important for cellular recognition and binding events as well as cellular interactions with pathogens, such as viruses. Therefore, methods to synthesize these types of bonds have many applications in research and medicine to develop pharmaceutical agents and improved vaccines that can be used to treat disease.

The present invention is based on the surprising discovery that the enzymatic activity of [beta](1,4)-galactosyltransferase can be altered such that the enzyme can make chemical bonds that are very difficult to make by other methods. These alterations involve mutating the enzyme such that the mutated enzyme can transfer many different types of sugars from sugar nucleotide donors to many different types of acceptors. Therefore, the mutated [beta](1,4)-galactosyltransferases of the invention can be used to synthesize a variety of

products that, until now, have been very difficult and expensive to produce.

The invention also provides amino acid segments that promote the proper folding of a galactosyltransferase catalytic domain and mutations in the catalytic domain that enhance folding efficiency and make the enzyme stable at room temperature. The amino acid segments may be used to properly fold the galactosyltransferase catalytic domains of the invention and thereby increase their activity. The amino acid segments may also be used to increase the activity of galactosyltransferases that are produced recombinantly. Accordingly, use of the amino acid segments according to the invention allows for production of [beta](1,4)-galactosyltransferases having increased enzymatic activity relative to [beta](1,4)-galactosyltransferases produced in the absence of the amino acid segments.

Applications: Synthesis of polysaccharide antigens for conjugate vaccines, glycosylation of monoclonal antibodies, and as research tools.

Development Status: The enzymes have been synthesized and preclinical studies have been performed.

Inventors: Pradman K. Qasba, Boopathy Ramakrishnan, Elizabeth Boeggeman (NCI).

Patent Status: U.S. Patent Application No. 11/178,230 filed 08 Jul 2005, allowed (HHS Reference No. E-230-2002/2-US-03); Foreign rights also available.

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: John Stansberry, PhD; 301-435-5236; stansbej@mail.nih.gov.

Collaborative Research Opportunity: The National Cancer Institute's Nanobiology Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize the use of galactose and modified galactose to be linked to an N-acetylglucosamine that may itself be linked to a variety of other molecules. Please contact John D. Hewes, PhD, at 301-435-3121 or hewesj@mail.nih.gov for more information.

Methods of Glycosylation and Bioconjugation

Description of Technology: Eukaryotic cells express several classes of oligosaccharides attached to proteins or lipids. Animal glycans can be N-linked via beta-GlcNAc to Asn (N-glycans), O-linked via -GalNAc to Ser/Thr (O-glycans), or can connect the carboxyl end of a protein to a phosphatidylinositol unit (GPI-anchors) via a common core glycan structure.

Beta (1,4)-galactosyltransferase I catalyzes the transfer of galactose from the donor, UDP-galactose, to an acceptor, N-acetylglucosamine, to form a galactose-beta (1,4)-N-acetylglucosamine bond, and allows galactose to be linked to an N-acetylglucosamine that may itself be linked to a variety of other molecules. Examples of these molecules include other sugars and proteins. The reaction can be used to make many types of molecules having great biological significance. For example, galactose-beta (1,4)-N-acetylglucosamine linkages are important for many recognition events that control how cells interact with each other in the body, and how cells interact with pathogens. In addition, numerous other linkages of this type are also very important for cellular recognition and binding events as well as cellular interactions with pathogens, such as viruses. Therefore, methods to synthesize these types of bonds have many applications in research and medicine to develop pharmaceutical agents and improved vaccines that can be used to treat disease.

The invention provides *in vitro* folding methods for a polypeptidyl-alpha-N-acetylgalactosaminyltransferase (pp-GalNAc-T) that transfers GalNAc to Ser/Thr residue on a protein. The application claims that this *in vitro*-folded recombinant ppGalNAc-T enzyme transfers modified sugar with a chemical handle to a specific site in the designed C-terminal polypeptide tag fused to a protein. The invention provides methods for engineering a glycoprotein from a biological substrate, and methods for glycosylating a biological substrate for use in glycoconjugation. Also included in the invention are diagnostic and therapeutic uses.

Application: Enzymes and methods are provided that can be used to promote the chemical linkage of biologically important molecules that have previously been difficult to link.

Development Status: Enzymes have been synthesized and characterization studies have been performed.

Inventors: Pradman Qasba and Boopathy Ramakrishnan (NCI).

Patent Status: PCT Application No. PCT/US2008/006248 filed 14 May 2008, claiming priority to 14 May 2007 (HHS Reference No. E-204-2007/0-PCT-02).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: John Stansberry, PhD; 301-435-5236; stansbej@mail.nih.gov.

Collaborative Research Opportunity: The National Cancer Institute is seeking

statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize this technology. Please contact John D. Hewes, PhD, at 301-435-3121 or hewesj@mail.nih.gov for more information.

Alpha 1-3 N-Acetylgalactosaminyltransferases With Altered Donor and Acceptor Specificities, Compositions, and Methods of Use

Description of Technology: The present invention relates to the field of glycobiology, specifically to glycosyltransferases. The present invention provides structure-based design of novel glycosyltransferases and their biological applications.

The structural information of glycosyltransferases has revealed that the specificity of the sugar donor in these enzymes is determined by a few residues in the sugar-nucleotide binding pocket of the enzyme, which is conserved among the family members from different species. This conservation has made it possible to reengineer the existing glycosyltransferases with broader sugar donor specificities. Mutation of these residues generates novel glycosyltransferases that can transfer a sugar residue with a chemically reactive functional group to N-acetylglucosamine (GlcNAc), galactose (Gal) and xylose residues of glycoproteins, glycolipids and proteoglycans (glycoconjugates). Thus, there is potential to develop mutant glycosyltransferases to produce glycoconjugates carrying sugar moieties with reactive groups that can be used in the assembly of bio-nanoparticles to develop targeted-drug delivery systems or contrast agents for medical uses.

Accordingly, methods to synthesize N-acetylglucosamine linkages have many applications in research and medicine, including in the development of pharmaceutical agents and improved vaccines that can be used to treat disease.

This application claims compositions and methods based on the structure-based design of alpha 1-3 N-Acetylgalactosaminyltransferase (alpha 3 GalNAc-T) mutants from alpha 1-3galactosyltransferase (a3Gal-T) that can transfer 2'-modified galactose from the corresponding UDP-derivatives due to mutations that broaden the alpha 3Gal-T donor specificity and make the enzyme alpha3 GalNAc-T.

Application: Development of pharmaceutical agents and improved vaccines.

Development Status: Enzymes have been synthesized and preclinical studies have been performed.

Inventors: Pradman Qasba, Boopathy Ramakrishnan, Elizabeth Boeggman, Marta Pasek (NCI).

Patent Status: PCT Application No. PCT/US2007/018678 filed 22 Aug 2007 (HHS Reference No. E-279-2007/0-PCT-01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: John Stansberry, PhD; 301-435-5236; stansbej@mail.nih.gov.

Collaborative Research Opportunity: The National Cancer Institute's Nanobiology Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize structure-based design of novel glycosyltransferases. Please contact John D. Hewes, PhD, at 301-435-3121 or hewesj@mail.nih.gov for more information.

Beta 1,4-Galactosyltransferases With Altered Donor and Acceptor Specificities, Compositions and Methods of Use

Description of Technology: The present invention relates to the field of glycobiology, specifically to glycosyltransferases. The present invention provides structure-based design of novel glycosyltransferases and their biological applications.

The structural information of glycosyltransferases has revealed that the specificity of the sugar donor in these enzymes is determined by a few residues in the sugar-nucleotide binding pocket of the enzyme, which is conserved among the family members from different species. This conservation has made it possible to reengineer the existing glycosyltransferases with broader sugar donor specificities. Mutation of these residues generates novel glycosyltransferases that can transfer a sugar residue with a chemically reactive functional group to N-acetylglucosamine (GlcNAc), galactose (Gal) and xylose residues of glycoproteins, glycolipids and proteoglycans (glycoconjugates). Thus, there is potential to develop mutant glycosyltransferases to produce glycoconjugates carrying sugar moieties with reactive groups that can be used in the assembly of bio-nanoparticles to develop targeted-drug delivery systems or contrast agents for medical uses.

Accordingly, methods to synthesize N-acetylglucosamine linkages have many applications in research and medicine, including in the development

of pharmaceutical agents and improved vaccines that can be used to treat disease.

The invention claims beta (1,4)-galactosyltransferase I mutants having altered donor and acceptor and metal ion specificities, and methods of use thereof. In addition, the invention claims methods for synthesizing oligosaccharides using the beta (1,4)-galactosyltransferase I mutants and to using the beta (1,4)-galactosyltransferase I mutants to conjugate agents, such as therapeutic agents or diagnostic agents, to acceptor molecules. More specifically, the invention claims a double mutant beta 1, 4 galactosyltransferase, human beta-1, 4-Tyr289Leu-Met344His-Gal-T1, constructed from the individual mutants, Tyr289Leu-Gal-T1 and Met344His-Gal-T1, that transfers modified galactose in the presence of magnesium ion, in contrast to the wild-type enzyme which requires manganese ion.

Application: Development of pharmaceutical agents and improved vaccines.

Development Status: Enzymes have been synthesized and preclinical studies have been performed.

Inventors: Pradman Qasba, Boopathy Ramakrishnan, Elizabeth Boeggman (NCI).

Patent Status: PCT Application No. PCT/US2007/018656 filed 22 Aug 2007 (HHS Reference No. E-280-2007/0-PCT-01).

Licensing Status: Available for exclusive or non-exclusive licensing.

Licensing Contact: John Stansberry, PhD; 301-435-5236; stansbej@mail.nih.gov.

Collaborative Research Opportunity: The National Cancer Institute's Nanobiology Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize glycosyltransferases. Please contact John D. Hewes, PhD, at 301-435-3121 or hewesj@mail.nih.gov.

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