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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.

ADDRESS: 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.

Encapsulated N-Acetylmannosamine or N-Acetylneuraminic Acid as a Therapeutic Agent for Increasing Sialylation in Certain Muscular Atrophies, Kidney Disorders, Cancers or Poor Immune Function

Description of Technology: N-acetylmannosamine is a precursor for the synthesis of sugar molecules known as sialic acids, which play an important role in specific biological processes such as cellular adhesion, cellular communication and signal transduction. Lack of sialic acids also plays a crucial role in disease processes such as inflammation, immune responses, as well as certain muscular atrophies (including hereditary inclusion body myopathy (HIBM) and distal myopathy with rimmed vacuoles (DMRV or Nonaka myopathy)), certain kidney disorders with proteinuria and hematuria (including minimal change nephrosis and focal segmental glomerulosclerosis), and certain cancers (including bladder cancer and myeloid leukemia).

This technology relates to methods of administering liposome-encapsulated N-acetylmannosamine, N-acetylneuraminic acid, or their derivatives to treat human disorders of hyposialylation (by increasing sialic acid production in patients who are deficient in that sugar molecule). Liposome-encapsulated delivery of these monosaccharides enhances successful systemic delivery, including to the central nervous system (crossing the blood-brain barrier), and liposome encapsulation protects against gastrointestinal tract degradation.

Potential Commercial Applications:

- Treatment of rare diseases such as HIBM and Nonaka myopathy (or DMRV).
- Treatment of kidney conditions involving sialic acid deficiencies, resulting in proteinuria and hematuria.

- Treatment of other diseases involving sialic acid deficiencies.
- Use as immune stimulant since adequate sialic acid is important for robust immune function.

Competitive Advantages:

- N-acetylmannosamine is the only uncharged sugar in the sialic acid biosynthesis pathway (thus making it easier to deliver than charged sugars) and is located after the rate-limiting step.
- N-acetyl mannosamine and N-acetylneuraminic acid have been shown to rescue hyposialylation in mouse models of HIBM.
- Encapsulated N-acetylmannosamine or N-acetylneuraminic acid crosses the blood-brain barrier and prevents gastrointestinal tract degradation more efficiently than unencapsulated drug.

Development Stage:

- Pre-clinical
- In vitro data available
- In vivo data available (animal)

Inventors: Marjan Huizing et al. (NHGRI)

Publications:

1. Galeano B, et al. Mutation in the key enzyme of sialic acid biosynthesis causes severe glomerular proteinuria and is rescued by N-acetylmannosamine. *J Clin Invest.* 2007 Jun;117(6):1585-1594. [PMID 17549255]

2. Nemunaitis G, et al. Hereditary inclusion body myopathy: single patient response to intravenous dosing of GNE gene lipoplex. *Hum Gene Ther.* 2011 Nov;22(11):1331-1341. [PMID 21517694]

3. Kakani S, et al. The Gne M712T mouse as a model for human glomerulopathy. *Am J Pathol.*, in press (Dec 2011) (available online in Feb 2012)

Intellectual Property: HHS Reference No. E-270-2011/0 — U.S. Application No. 61/531,934 filed 07 Sep 2011

Licensing Contact: Tara L. Kirby, Ph.D.; 301-435-4426; tarak@mail.nih.gov

Chimeric Antigen Receptors to CD22 for Treating Hematological Cancers

Description of Technology: Chimeric antigen receptors (CARs) are hybrid proteins consisting of an antibody binding fragment fused to protein signaling domains that cause some T-cells to become cytotoxic. Once activated, these cytotoxic T-cells can selectively eliminate the cells which they recognize. Thus, by engineering a T-cell to express a CAR that is specific for a certain cell surface protein, it is possible to selectively target cells for destruction. This is a promising new therapeutic approach known as adoptive cell therapy.

CD22 is a cell surface protein that is expressed on a large number of B-cell lineage hematological cancers. Several promising therapies are being developed which target CD22, including therapeutic antibodies and immunotoxins. This technology concerns the use of a high affinity antibody binding fragment to CD22 as the targeting moiety of a CAR, adding adoptive cell therapy as a new prospective treatment for certain leukemias and lymphomas.

Potential Commercial Applications:

- Treatment of diseases associated with increased or preferential expression of CD22
- Specific diseases include hematological cancers such as chronic lymphocytic leukemia, hairy cell leukemia and pediatric acute lymphoblastic leukemia

Competitive Advantages:

- Targeted therapy decreases non-specific killing of healthy, essential cells, resulting in fewer non-specific side-effects and healthier patients
- Hematological cancers are susceptible to cytotoxic T-cells for treating because they are present in the bloodstream
- Expression of CD22 only on mature cells allows the avoidance of stem cell elimination during treatment
- High affinity of the antibody binding fragment for CD22 increases the likelihood of successful targeting

Development Stage:

- Pre-clinical
- In vitro data available
- In vivo data available (animal)

Inventors: Rimas J. Orentas et al. (NCI)

Intellectual Property: HHS Reference No. E-265-2011/0-US-01 — US provisional application 61/549,516

Related Technology: HHS Reference No. E-129-2001/0-US-03 — US Patent 7,355,012

Licensing Contact: David A. Lambertson, Ph.D.; 301-435-4632;

lambertsond@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 Chimeric Antigen Receptor for CD22, High Affinity. A gene vector to target T cells to B cell leukemia and lymphoma. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

Increased Therapeutic Effectiveness of Immunotoxins That Use Toxin Domains Lacking Both T-cell and B-cell Epitopes

Description of Technology: Immunotoxins can kill cancer cells while allowing healthy, essential cells to survive. As a result, patients receiving an immunotoxin are less likely to experience the deleterious side-effects associated with non-discriminate therapies such as chemotherapy or radiation therapy. Unfortunately, the continued administration of immunotoxins often leads to a reduced patient response due to the formation of neutralizing antibodies against immunogenic B-cell and T-cell epitopes contained within PE. To improve the therapeutic effectiveness of PE-containing immunotoxins through multiple rounds of drug administration, NIH inventors have sought to remove the B-cell and T-cell epitopes within PE. Previous work demonstrated that the removal of the major B-cell epitopes from PE reduced the immunogenicity of PE. This technology involves the identification of major T-cell epitopes on PE, and the removal of the primary T-cell epitope by mutation or deletion. By combining the T-cell epitope mutations with modifications that remove B-cell epitopes, it is possible to create

PE-based immunotoxins that have even greater resistance to the formation of neutralizing antibodies. Immunotoxins containing these new PE-variants are expected to have improved therapeutic efficacy.

Potential Commercial Applications:

- Essential component of immunotoxins
- Treatment of any disease associated with increased or preferential expression a specific cell surface receptor
- Specific diseases include hematological cancers, lung cancer, ovarian cancer, breast cancer, and head and neck cancers

Competitive Advantages:

- PE variants now include the removal of both B-cell and T-cell epitopes, further reducing the formation of neutralizing antibodies against immunotoxins which contain the PE variants
- Less immunogenic immunotoxins result in improved therapeutic efficacy by permitting multiple rounds of administration
- Targeted therapy decreases non-specific killing of healthy, essential cells, resulting in fewer non-specific side-effects and healthier patients

Development Stage: Pre-clinical

Inventors: Ira H. Pastan et al. (NCI)

Patent Status:

- HHS Reference No. E-174-2011/0-US-01 — U.S. Provisional Application 61/495,085

Related Technologies:

- HHS Reference No. E-269-2009/0-PCT-02 — PCT Patent Publication WO 2011/032022

- HHS Reference No. E-292-2007/0-US-06 — US Patent Publication US 20100215656 A1

- HHS Reference No. E-262-2005/0-US-06 — US Patent Publication US 20090142341 A1

- HHS Reference No. E-139-1999/0-US-07 — US Patent 7,081,518

- Multiple additional patent families

Licensing Contact: David A. Lambertson, Ph.D.; 301-435-4632;

lambertsond@mail.nih.gov

Ketamine Metabolites for the Treatment of Depression and Pain

Description of Technology: The market continues to have a need for therapeutics for treating pain and depression that have efficacy in a high percentage of patients but have reduced anaesthetic properties and reduced abuse liability. Ketamine, a drug currently used in human anesthesia and veterinary medicine, has been shown in clinical studies to be effective in the treatment of several conditions, including the of treatment-resistant bipolar depression, major depressive disorder, neuropathic pain, and chronic pain, including complex regional pain syndrome (CRPS). However the routine use of the drug is hindered by unwanted central nervous system (CNS) effects and a patient response rate of ~70%. New data suggests that ketamine metabolites can be used with similar results but with an increase in patient response rates and a decrease in undesirable side effects.

Potential Commercial Applications: Treatment of pain and depression.

Competitive Advantages:

- Increased number of patients able to respond to the treatment because it bypasses the human metabolic machinery needed to convert the drug into its active metabolite(s).

- Decreased CNS side effects.

Development Stage: In vivo data available (animal)

Inventors: Irving W. Wainer, Ph.D. (NIA), Carlos A. Zarate, M.D. (NIMH), Ruin Moaddel, Ph.D. (NIA), Michel Bernier (NIA), Michael E. Goldberg, M.D., Marc C. Toriman, Ph.D.

Publications:

1. Moaddel R, et al. A parallel chiral-achiral liquid chromatographic method for the determination of the stereoisomers of ketamine and ketamine metabolites in the plasma and urine of patients with complex regional pain syndrome. *Talanta*. 2010 Oct 15;82(5):1892-1904. [PMID 20875593]

2. Zarate CA Jr., et al. Relationship of Ketamine's Plasma Metabolites with Response and Diagnosis, and Side Effects in Major Depression. Manuscript in preparation.

3. Ibrahim L, et al. Course of Improvement in Depressive Symptoms to a Single Intravenous Infusion of Ketamine vs. Add-on Riluzole: Results from a Four-Week, Double-Blind, Placebo-Controlled Study. *Neuropsychopharmacology*, in press.

4. Zhao X, et al. Population Pharmacokinetic Modeling of Ketamine and Three Major Metabolites in Patients with Treatment-Resistant Bipolar Depression. *Br. J. Clin. Pharmacol.*, in press.

Intellectual Property: HHS Reference No. E-092-2011/0 — U.S. Provisional Application No. 61/547,336 filed 14 Oct 2011

Related Technologies: HHS Reference No. E-174-2006/0 —

- U.S. Patent Application No. 11/688,603 filed 20 Mar 2007
- Related international applications

Licensing Contact: Jaime M. Greene, M.S.; 301-435-5559;

greenejaime@mail.nih.gov

Collaborative Research Opportunity: The National Institute on Aging, Laboratory of Clinical Investigation, Bioanalytical Chemistry and Drug Discovery Section, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize this technology. For collaboration opportunities, please contact Nicole Guyton, Ph.D. at darackn@mail.nih.gov.

Improved DNA-Protein Vaccination Protocols

Description of Technology: Nucleic acid based vaccines are attractive alternatives to conventional vaccines for a number of reasons. One of the issues with nucleic acid based vaccines is the poor immunogenicity in humans. The subject technology is a method for eliciting improved immune responses with DNA based vaccines. The method involves co-administration of a nucleic acid vaccine with a protein

vaccine for the same antigen of interest that is encoded by the DNA vaccine in a prime-boost protocol. This methodology increased the immune responses in a SIV macaque model to examine DNA based vaccines of HIV and vaccine protocols. The methodology can potentially be applied to other disease indications to elicit greater immune responses.

Potential Commercial Applications: Improve immunogenicity of nucleic acid based vaccines.

Competitive Advantages: The methodology increases the immune response of DNA based vaccines.

Development Stage:

- Early-stage
- Pre-clinical
- In vitro data available
- In vivo data available (animal)

Intellectual Property: HHS Reference No. E-239-2009/0 — International PCT Application No. PCT/US2011/026325 filed 25 Feb 2011

Licensing Contact: Kevin W. Chang, Ph.D.; 301-435-5018;

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Date

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