[Billing Code 4140-01-P]

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.

FOR FURTHER INFORMATION: 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.

A Novel Immortalized Human Adrenal Cell Line with Inactive Protein Kinase A for Studies on cAMP Signaling and Endocrine Tumorigenesis

Description of Technology: The first known immortalized cell line with a naturally-occurring inactivating mutation in PRKAR1A, the regulatory subunit type 1A (R1alpha) of protein kinase A (PKA), which is associated with tumor formation.

PKA isozyme balance is critical for the control of cAMP signaling and related cell cycle and proliferation changes. Aberrant cAMP signaling has been linked to adrenocortical and other, mostly endocrine, tumors. Inactivating mutations in the PRKAR1A gene are a known cause of Carney Complex - an autosomal dominant multiple neoplasia syndrome associated with skin, heart, and other myxomas and a variety of endocrine tumors.

Potential Commercial Applications:

• Studies on multiple tumor formation associated with Carney Complex.

• Characterization of cAMP-mediated mechanisms of endocrine tumor formation.

• Studies of a large variety of cAMP-mediated processes in normal physiology and disease.

Competitive Advantages: First known immortalized cell line with a naturally-occurring inactivating mutation in the PRKAR1A gene.

Development Stage: In vitro data available

Inventor: Constantine A. Stratakis (NICHD)

Publication: Nesterova M, et al. An immortalized human cell line bearing a PRKAR1A-inactivating mutation: effects of overexpression of the wild-type Allele and

other protein kinase A subunits. J Clin Endocrinol Metab. 2008 Feb;93(2):565-71. [PMID 18056771]

Intellectual Property: HHS Reference No. E-267-2012/0 — Research Material. Patent protection is not being pursued for this technology.

Licensing Contact: Patrick McCue, Ph.D.; 301-435-5560; mccuepat@mail.nih.gov

Collaborative Research Opportunity: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development 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 Joseph Conrad III, Ph.D. at jmconrad@mail.nih.gov.

Modulation of Regulatory T-Cell and B-Cell Lymphocytes for the Treatment of Autoimmune and Other Disease Indications

Description of Technology: A method of modulating the immune response by affecting the activity of the regulatory lymphocytes through targeting of the Hepatitis A Virus receptor 1 (HAVCR1) receptor. This methodology can be developed for the treatment of autoimmune diseases, allergies, prevention of transplant rejection, and incorporated into therapeutic strategies for cancer.

Regulatory lymphocytes, such as regulatory T-cells (Tregs) and B-cells (Bregs), play a significant role in suppressing and controlling immune responses to antigens, including allergens and self-antigens that induce autoimmune diseases. The Tregs and Bregs also control the immune responses to microbial pathogens thereby limiting

excessive damage to tissue. HAVCR1 is expressed on these regulatory lymphocytes and functions as a master regulator of these cells.

Potential Commercial Applications:

• Treatment of Autoimmune Diseases

• Treatment of Allergies

• Prevention of Rejection of Allogenic Transplants

• Cancer Therapy

• Immunotherapies

• Stimulate Response to Vaccines (adjuvant)

Competitive Advantages: Can be used to target multiple disease states.

Development Stage:

• Early-stage

• Pre-clinical

• In vitro data available

Inventors: Gerardo Kaplan, Mohanraj Manangeeswaran, Jerome Jacques, Krishnamurthy Konduru (all of FDA)

Publication: Manangeeswaran M, et al. Binding of hepatitis A virus to its cellular receptor 1 inhibits T-regulatory cell functions in humans. Gastroenterology. 2012 Jun;142(7):1516-25.e3. [PMID 22430395]

Intellectual Property: HHS Reference No. E-095-2012/0 — U.S. Provisional Application No. 61/611,437 filed 15 Mar 2012

Related Technology: HHS Reference No. E-150-1994/0 — U.S. Patent 5,622,861 issued 22 Apr 1997 (Hepatitis A Virus Receptor)

Licensing Contact: Kevin W. Chang, Ph.D.; 301-435-5018; changke@mail.nih.gov

Collaborative Research Opportunity: The Center for Biologics Evaluation and Research, Laboratory of Emerging Pathogens, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize targeting of HAVCR1 to control Treg and Breg function in human diseases. For collaboration opportunities, please contact Gerardo Kaplan at gerardo.kaplan@fda.hhs.gov.

A Method to Expand a Population of Regulatory T Cells Optimal for the Treatment of Autoimmune Diseases

Description of Technology: The transfusion of regulatory T cells (Tregs) has been used in the clinic to successfully prevent graft vs. host disease and is currently being evaluated in the treatment of other autoimmune diseases, such as organ graft rejection, type 1 diabetes and multiple sclerosis. Prior to transfusion, adoptive regulatory T cell transfer requires the expansion of regulatory T cells in culture; this results in a mixed population of regulatory T cells that limits the effectiveness of the transferred cells.

Scientists at the NIH have developed a method that promotes the expansion of regulatory T cells that are longer lived, more stable, and more suppressive of the autoimmune response. By supplementing T cell cultures with DNA oligonucleotides, the inventors were able to enrich the regulatory T cell population that enhanced the suppression of the autoimmune response. This method has the potential to more effectively generate regulatory T cells for the treatment of autoimmune diseases.

Potential Commercial Applications: Treatment of autoimmune diseases, such as Graft vs. Host Disease, Organ Graft Rejection Type 1 Diabetes, Multiple Sclerosis.

Competitive Advantages:

• More effective therapy when compared to traditional T cell expansion methods.

• Expansion method is inexpensive and similar to current methods.

Development Stage: In vitro data available

Inventors: Yong Chan Kim and Ethan M. Shevach (NIAID)

Publication: Kim Y, et al. Oligodeoxynucleotides stabilize Helios-expressing Foxp3+ human T regulatory cells during in vitro expansion. Blood. 2012 Mar 22;119(12):2810-8. [PMID 22294730]

Intellectual Property: HHS Reference No. E-279-2011/0 — U.S. Provisional Application No. 61/576,837 filed 16 Dec 2011

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

Peptides for Treatment of Tumor Necrosis Factor alpha Mediated Inflammatory Disease

Description of Technology: Tumor Necrosis Factor alpha (TNF-alpha) is a multifunctional cytokine that mediates inflammation, immune regulation, and cellular proliferation. This cytokine is converted to its active form by TNF-alpha converting enzyme (TACE). Pathological increases in TNF-alpha activity have been associated with a wide variety of inflammatory diseases, including inflammatory bowel disease,

rheumatoid arthritis, and cancer. Inhibiting the conversion of TNF-alpha to its active form by inhibiting TACE represents a potential treatment for these diseases.

The current technology provides peptides, derived from an N-terminal fragment of the TACE protein, that inhibit TACE activity. Also described are methods of using these peptides to lower levels of active TNF-alpha. These peptides could be used as a treatment for TNF-alpha-mediated inflammatory diseases.

Potential Commercial Applications: Treatment of TNF-alpha mediated inflammatory diseases.

Competitive Advantages: Inhibition of TACE activity represents a novel mechanism to treat inflammatory disease.

Development Stage:

• Early-stage

• In vitro data available

Inventors: Stewart J. Levine et al. (NHLBI)

Publication: Buckley CA, et al. Amino-terminal TACE prodomain attenuates TNFR2 cleavage independently of the cysteine switch. Am J Physiol Lung Cell Mol Physiol. 2005 Jun;288(6):L1132-8. [PMID 15749738]

Intellectual Property: HHS Reference No. E-208-2003/0 — US Patent No. 7,655,752 issued 02 Feb 2010

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

Human Antibodies and Fusion Proteins with Potent and Broad HIV-1 Neutralizing Activity

Description of Technology: The inventions listed below provide multiple novel human anti-HIV-1 domain antibodies (m36 and its affinity- matured versions) and their fusion proteins with two-domain or single-domain human soluble CD4 (sCD4) that can potentially be used alone or synergistically with other anti-HIV-1 antibodies and antiretroviral drugs as therapeutics and/or preventatives for infection by different HIV-1 strains.

Some of the inventions listed below also describe some fusion proteins as vaccine immunogens that could elicit broadly neutralizing antibodies against HIV-isolates from different clades. One invention also describes the methods to prepare and use the immunogens in the vaccination for prevention of HIV-1 infections. More specifically, the later invention provides a vaccine composed of a primary immunogen and a secondary immunogen, and a method for making the vaccine which could be effective in eliciting desired broadly neutralizing antibodies. The primary immunogen could be effective in activating B cell receptors (BCRs) that are on the maturational pathways of the desired antibodies and have an intermediate degree of somatic mutational diversity. The secondary immunogen contains epitopes of the desired antibodies and could be effective in further diversifying the BCRs sufficiently to form mature BCRs that have the identical or substantially identical sequence as the desired antibodies.

Potential Commercial Applications: Treatment and prevention of HIV-1 infections.

Competitive Advantages:

• Elicits broadly neutralizing antibodies against HIV-1 isolates from different clades.

• Potentially elicits antibodies that are not regulated by tolerance mechanisms.

• Novel methods to design vaccines for HIV-1 treatment and prevention.

• May also be used for designing vaccines for cancer treatment.

• Relatively small size allows for potential penetration into lymphoid tissues.

Development Stage:

• In vitro data available

• In vivo data available (animal)

Inventors: Dimiter Dimitrov and Weizao Chen (NCI)

Publications:

1. Chen W, et al. Human domain antibodies to conserved sterically restricted regions on gp120 as exceptionally potent cross-reactive HIV-1 neutralizers. Proc Natl Acad Sci USA. 2008 Nov 4;105(44):17121-6. [PMID 18957538]

2. Chen W, et al. Engineered single human CD4 domains as potent HIV-1 inhibitors and components of vaccine immunogens. J Virol. 2011 Sep;85(18):9395-405. [PMID 21715496]

3. Chen W, et al. Bifunctional fusion proteins of the human engineered antibody domain m36 with human soluble CD4 are potent inhibitors of diverse HIV-1 isolates. Antiviral Res. 2010 Oct;88(1):107-15. [PMID 20709110]

4. Chen W, Dimitrov DS. Human monoclonal antibodies and engineered antibody domains as HIV entry inhibitors. Curr Opin HIV AIDS. 2009 Mar;4(2):112-7. [PMID 19339949]

Intellectual Property:

• HHS Reference No. E-043-2008/0 — U.S. Patent Application No. 12/811,998 filed 07 Jul 2010; related international applications

• HHS Reference No. E-322-2008/0 — U.S. Patent Application No. 13/123,659 filed 11 Apr 2011

• HHS Reference No. E-103-2010/1 — PCT Application No. PCT/US2011/037439 filed 20 May 2011, which published as WO 2011-146891 on 31 May 2012

Licensing Contact: Sally Hu, Ph.D.; 301-435-5606; hus@mail.nih.gov

Collaborative Research Opportunity: The NCI CCR Nanobiology Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize m36, single domain sCD4, and related fusion proteins as candidate therapeutics against HIV-1. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

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Date

Richard U. Rodriguez, M.B.A.
Director
Division of Technology Development and Transfer
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National Institutes of Health

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