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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.

Thioxothiazolidinone Derivatives — A Novel Class of Anti Cancer Agents

Description of Technology: The invention provides for a novel class of heterocyclic compounds (i.e. thioxothiazolidinone derivatives) that exhibit anticancer activity in a unique mechanism. More specifically, the compounds of the invention act as inhibitors of the enzyme human tyrosyl DNA phosphodiesterase1 (Tdp1), a DNA repair enzyme involved in topoisomerase1 (Top1) mediated DNA damage, such as damage induced by the Top1 inhibitors and chemotherapeutic agents, camptothecins. As such, these compounds can serve as potentiators of camptothecins. The experimental data indeed point at a synergistic effect achieved in a combination therapy of the thioxothiazolidinone derivatives of the invention and the established anticancer agents camptothecins. Moreover, due to this synergistic effect, a lower therapeutic dose of the latter may be needed, resulting in reduced side effects. In addition, it is possible that the Tdp1 inhibitors of the invention may be effective as anti tumor agents on their own. This is based on the fact that Tdp1 is involved also in repairing DNA damage resulting from oxygen radicals, and the observation that tumors contain excess free radicals.

Potential Commercial Applications:

• Effective cancer therapy in combination with camptothecins

• Cancer therapy as standalone anti cancer agents

Competitive Advantages: The compounds of the invention act in unique mechanism that can enhance the therapeutic efficacy of the anticancer drugs camptothecins, and at the same time can serve as standalone anticancer agents.

Development Stage: In vitro data available

Inventors: Yves G. Pommier (NCI) et al.

Publications:

1. Marchand C, et al. Identification of phosphotyrosine mimetic inhibitors of human tyrosyl-DNA phosphodiesterase I by a novel AlphaScreen high-throughput assay. Mol Cancer Ther. 2009 Jan;8(1):240-248. [PMID 19139134]

2. Dexheimer TS, et al. Tyrosyl-DNA phosphodiesterase as a target for anticancer therapy. Anticancer Agents Med Chem. 2008 May;8(4):381–389. [PMID 18473723]

3. Dexheimer TS, et al. 4-Pregnen-21-ol-3,20-dione-21-(4-bromobenzenesufonate) (NSC 88915) and related novel steroid derivatives as tyrosyl-DNA phosphodiesterase (Tdp1) inhibitors. J Med Chem. 2009 Nov 26;52(22): 7122–7131. [PMID 19883083]

Intellectual Property: HHS Reference No. E-239-2011/0 — U.S. Provisional Patent Application No. 61/545,308 filed 10 Oct 2011

Licensing Contact: Uri Reichman, Ph.D., MBA; 301-435-4616; reichmau@mail.nih.gov

Monospecific and Bispecific Human Monoclonal Antibodies Targeting IGF-II

Description of Technology: The type 1 insulin-like growth factor (IGF) receptor (IGF1R) is over-expressed by many tumors and mediates proliferation, motility, and protection from apoptosis. Agents that inhibit IGF1R expression or function can potentially block tumor growth and metastasis. Its major ligands, IGF-I, and IGF-II are over-expressed by multiple tumor types. Previous studies indicate that inhibition of IGF-I, and/or IGF-II binding to its cognizant receptor negatively modulates signal

transduction through the IGF pathway and concomitant cell proliferation and growth. Therefore, use of humanized or fully human antibodies against IGFs represents a valid approach to inhibit tumor growth. The present invention discloses two monoclonal antibodies, designated m610.27 and m630, and a bispecific monoclonal antibody, m660, generated by linking domains from m610.27 and m630. All three antibodies display high affinities for IGF-I and IGF-II in the pM to nM range. The antibodies inhibited signal transduction mediated by the IGF-1R interaction with IGF-I and IGF-II and blocked phosphorylation of IGF-IR and the insulin receptor. m610.27 and m630 are the first pair of human antibodies that target nonoverlapping epitopes on IGF-II. All three antibodies in an IgG1 or IgG1-like format could lead to irreversible elimination of IGF-II from circulation making it a viable candidate for cancer treatment.

Potential Commercial Applications:

• Therapeutic for the treatment of various human diseases associated with aberrant cell growth and motility such as breast, prostate, and leukemia cancers.

• Research reagent to study IGF-I and/or IGF-II binding and its association with tumor growth

Competitive Advantages:

• m610.27 and m630 are the first characterized antibodies that target nonoverlapping epitopes on IGF-II

• m660 was generated from two domains; one each from m610.27 and m630

• small size of the m610.27 and m630 domains prevent overlapping in binding to IGF-II

Development Stage:

• Pre-clinical

• In vitro data available

Inventors: Dimiter S Dimitrov, Weizao Chen, Yang Feng (NCI)

Intellectual Property: HHS Reference No. E-212-2011 — U.S. Provisional Application No. 61/548,164 filed 17 Oct 2011

Related Technologies:

• HHS Reference No. E-217-2005/2 — U.S. Patent No. 7,824,681 issued 02 Nov 2010; U.S. Patent Application No. 12/889,345 filed 23 Sep 2010

• HHS Reference No. E-336-2005/0 — U.S. Patent Application No. 12/296,328 filed 07 Oct 2008

• HHS Reference No. E-232-2009/0 — PCT Application No. PCT/US2010/051784 filed 07 Oct 2010

• HHS Reference No. E-068-2011/0 — U.S. Provisional Application No. 61/474,664 filed 12 Apr 2011

Licensing Contact: Whitney Hastings; 301-451-7337; hastingw@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 this technology. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

Genetic Interactions That Predict Attention Deficit Hyperactivity Disorder Outcome and Severity

Description of Technology: Genotyping of attention deficit hyperactivity disorder (ADHD) linked chromosomal regions containing single nucleotide polymorphisms (SNPs) was used by researchers at the National Human Genome Research Institute (NHGRI) to discover gene interactions that increase the risk of developing ADHD and predict ADHD severity.

NHGRI researchers discovered an ADHD linked gene interaction between the latrophilin 3 (*LPHN3*) gene and a haplotype on chromosome 11q that contains the gene coding for the dopamine receptor D2 (*DRD2*) and neural cell adhesion molecule 1 (*NCAM1*). In a similar invention, mutations in *LPHN3* were shown to increase the risk of developing ADHD (HHS E-312-2006, TAB 1504). Expanding on those findings, this invention describes an interaction between *LPHN3* and *11q* that not only doubles the risk of developing ADHD, but also the severity of ADHD. Furthermore, the *LPHN3-11q* interaction correlates with patient response to therapeutic treatments.

In summary, this invention can be used to develop biomarkers for determining susceptibility to and severity of ADHD, as well as, developing theranostic assays for determining prognosis of ADHD treatments. In addition, signaling pathways delineated from these genetic sites can be used to develop better ADHD therapeutics.

Potential Commercial Applications:

• Biomarkers for ADHD susceptibility and severity

• Prognostic assays

• Personalized treatment options

Competitive Advantages: Improved prediction of ADHD susceptibility, severity, and possibly patient response to treatment

Development Stage:

• Early-stage

• In vivo data available (human)

Inventors: Maximilian Muenke, Mauricio Arcos-Burgos, and Maria T. Acosta (NHGRI)

Publications:

1. Jain M, et al. A cooperative interaction between LPHN3 and 11q doubles the risk for ADHD. Mol Psychiatry. 2011 May 24. (Epub ahead of print) [PMID: 21606926]

2. Arcos-Burgos M and Muenke M. Toward a better understanding of ADHD: LPHN3 gene variants and the susceptibility to develop ADHD. Atten Defic Hyperact Disord. 2010 Nov;2(3):139-147. [PMID: 21432600]

Intellectual Property: HHS Reference No. E-187-2011/0 — U.S. Provisional Application No. 61/505,864 filed on 08 July 2011

Related Technology: HHS Reference No. E-312-2006/0 — U.S. Patent No. 8,003,406 issued on 23 August 2011

Licensing Contact: Charlene Sydnor, Ph.D.; 301-435-4689; sydnorc@mail.nih.gov

Modulating Autophagy as a Treatment for Lysosomal Storage Diseases

Description of Technology: Researchers at NIAMS have developed a technology for treatment of lysosomal storage diseases by inhibition of autophagy. Pompe disease is an example of a genetic lysosomal storage disease caused by a reduction or absence of acid alpha-glucosidase (GAA). Patients with Pompe disease

have a lysosomal buildup of glycogen in cardiac and skeletal muscle cells and severe cardiomyopathy and skeletal muscle myopathy. Treatment of Pompe disease by GAA enzyme replacement therapy is quite ineffective for the skeletal muscle myopathy. Skeletal muscle resistance to therapy is associated with increased cellular buildup of autophagic debris. Inactivation of autophagy results in effective GAA replacement therapy and a reduction in glycogen back to normal levels. This technology provides a novel approach for the treatment of Pompe disease as well as other diseases where autophagy is a critical contributor to disease development.

Potential Commercial Applications:

• Development of tools for autophagy suppression and treatment of a variety of diseases

• Development of chemical inhibitors of autophagy

• Development of animal models to study lysosomal storage diseases

Competitive Advantages:

• This technology is the first use of autophagy disablement to reverse an intracellular pathology

• More effective than enzyme replacement therapy alone for the treatment of the lysosomal storage disease, Pompe disease

Development Stage: In vivo data available (animal)

Inventors: Nina Raben, Cynthia N. Schreiner, Paul H. Plotz, Shoichi Takikita, Tao Xie, Rebecca Baum (NIAMS)

Publications:

1. Raben N, et al. Suppression of autophagy permits successful enzyme replacement therapy in a lysosomal storage disorder--murine Pompe disease. Autophagy. 2010 Nov;6(8):1078-1089. [PMID 20861693]

2. Raben N, et al. Suppression of autophagy in skeletal muscle uncovers the accumulation of ubiquitinated proteins and their potential role in muscle damage in Pompe disease. Hum Mol Genet. 2008 Dec 15;17(24):3897-3908. [PMID 18782848]

Intellectual Property: HHS Reference No. E-210-2009/0 — PCT Application No. PCT/US2010/047730 filed 02 Sep 2010

Licensing Contact: Jaime Greene, M.S.; 301-435-5559; greenejaime@mail.nih.gov

Collaborative Research Opportunity: The National Institutes of Health is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize the technology for disabling autophagy as a treatment for lysosomal storage diseases. For collaboration opportunities, please contact Cecilia Pazman at pazmance@mail.nih.gov.

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Date

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

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