Combination Cancer Therapy Using an IL13-Targeted Toxin and an HDAC Inhibitor

Description of Technology: Typical cancer treatments such as chemotherapy, radiation therapy and surgical resection are non-specific processes that kill healthy cells as well as diseased cells, ultimately resulting in discomfort and undesirable side-effects for patients. In an effort to reduce the burden on cancer patients, a tremendous effort has been placed on developing ways to increase the specificity of cancer treatments. One way to increase specificity is to identify proteins which are present on the surface of cancer cells but absent on normal healthy cells, and use that protein as a target for delivering a therapeutic agent. Because the therapeutic agent only reaches the diseased cell, patients are less likely to experience non-specific side-effects, reducing their pain burden during treatment.

IL13-receptor-alpha-2 (IL13–Rα2) is a cell surface protein that is selectively expressed on certain diseased cells, including cancer cells. IL13–Rα2 binds to the cytokine IL13, suggesting that a therapeutic agent fused to IL13 can target and kill only those cancer cells which express IL13–Rα2. Our inventors previously constructed fusion proteins comprising (1) IL13 and (2) an active fragment of the bacterial toxin *Pseudomonas* exotoxin A (PE). These IL13–PE fusion proteins demonstrated the ability to selectively kill cancer cells that overexpressed IL13–Rα2, as well as other types of diseased cells (asthma, pulmonary fibrosis) which overexpressed IL13–Rα2. This suggested that IL13–PE fusion proteins were excellent candidates for new therapeutic agents.

In an effort to increase the effectiveness of these IL13–PE fusion proteins, the inventors sought ways to increase the expression of IL13–Rα2 on cancer cells, thereby increasing the rate at which the therapeutic agent could kill the diseased cell. Histone deacetylase (HDAC) inhibitors have been employed as anti-cancer agents for several years, and a number of HDAC inhibitors are currently in clinical trials. Although the exact mechanism by which HDAC inhibitors function is unclear, it is believed that the ability of these molecules to increase the expression of anti-cancer genes is behind their therapeutic effect.

This invention concerns a means of improving specific cancer therapy through the combination of (a) IL13–PE fusion proteins and (b) HDAC inhibitors. The inventors surprisingly found that the expression of IL13–Rα2 increased in several types of pancreatic cancer cells in response to HDAC inhibitors, whereas normal, healthy cells did not experience such an increase in IL13–Rα2 expression. The use of IL13–PE fusion proteins in combination with HDAC inhibitors improved specific killing of pancreatic cancer cells relative to the use of IL13–PE fusion proteins in the absence of the HDAC inhibitors. This suggested that the use of IL13–PE fusion proteins along with HDAC inhibitors was a strong candidate combinatorial therapeutic for the treatment of various cancers (e.g., pancreatic, glioblastoma multiforme) and other diseases characterized by overexpression of IL13–Rα2 (e.g., asthma, pulmonary fibrosis).

Applications:

- Treatment of diseases associated with the increased expression of IL13–Rα2
- Relevant diseases include pulmonary fibrosis, asthma and cancers such as pancreatic cancer, glioblastoma multiforme and other head and neck cancers

Advantages:

- HDAC inhibitors only increased IL13–Rα2 expression in diseased cells, leaving normal healthy cells unaltered
- IL13–PE fusion proteins only kill cells that overexpress IL13–Rα2, allowing specific targeting of treatment
- Targeted treatment decreases non-specific killing of healthy, essential cells, resulting in fewer side-effects and healthier patients

Development Status: Preclinical stage of development

Inventors: Puri *et al.* (FDA)

Patent Status: US provisional application 61/494,779 (HHS reference E–107–2011/0–US–01)

For more information, see:

- US Patents 5,614,191, 5,919,456 and 6,518,061 (HHS technology reference E–266–1994/0)
- US Patent Publication US 20040136959 A1 (HHS technology reference E–032–2000/0)
- US Patent 7,541,040 (HHS technology reference E–296–2001/0)

Licensing Status: Available for licensing

Licensing Contact: David A. Lambertson, PhD; 301–435–4632; *lambertsond@mail.nih.gov*

Dated: July 26, 2011.

Richard U. Rodriguez,

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

[FR Doc. 2011–19378 Filed 7–29–11; 8:45 am]

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.

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.

Methods and Software for the Quantitative Assessment of Vasculature in Allantois and Retina Explants

Description of Technology: The invention relates to methods and software that can facilitate and improve quantification, accuracy and standardization in the assessment of vasculature in angiogenesis assays such as in the allantois explants and the retina explants assays. The software of this invention can aid in the analysis of images resulting from these assays and thus enhance the accuracy and effectiveness of research in the area of angiogenesis. This in turn will lead to enhanced progress in the development of medical methods and drugs to treat diseases related to angiogenesis such as cancer, macular degeneration, and some pregnancy disorders.

Applications: The software can be integrated with a variety of imaging systems used in conjunction with angiogenesis assays to enhance the assessment and the quality of research in the area of angiogenesis.

Advantages:

- The method and software of the invention will make analysis of angiogenesis assays more accurate, better standardized, and less

cumbersome than existing analysis systems.

• This method and software will eliminate the user-dependent bias which is characteristic of existing methods.

• This method and software will generally improve the quality of analysis of angiogenesis assays.

• The software is suitable for integration in a variety of existing imaging systems and software as well as readily usable as an independent complementary technology in the research and biomedical fields.

Development Status: The software is fully developed.

Inventor: Enrique Zudaire (NCI).

Relevant Publications:

1. Pitulescu ME, Schmidt I, Benedito R, Adams RH. Inducible gene targeting in the neonatal vasculature and analysis of retinal angiogenesis in mice. Nat Protoc. 2010 Sep;5(9):1518–1534. [PMID: 20725067].

2. Gambardella L, *et al.* PI3K signaling through the dual GTPase-activating protein ARAP3 is essential for developmental angiogenesis. Sci Signal 2010 Oct 26;3(145):ra76. [PMID: 20978237].

3. Zudaire E, Gambardella L, Kurcz C, Vermeren S. A computational tool for quantitative analysis of vascular networks. PLoS One (Submitted).

Patent Status: HHS Reference No. E–176–2011/0—Software/Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: The software is available for licensing.

Licensing Contacts:

• Uri Reichman, Ph.D., MBA; 301–435–4616; *UR7a@nih.gov.*

• Michael Shmilovich, *Esq.;* 301–435–5019; *shmilovm@mail.nih.gov.*

Pyruvate as a Transient Hypoxia Inducer for Anti-cancer Therapies

Description of Technology: Human solid tumors, such as breast cancer, lung cancer, ovarian cancer, pancreatic cancer and prostate cancer, etc. frequently have substantial volumes with low oxygen concentration, i.e. hypoxic. These hypoxic tumors show resistance to radiation and chemotherapies. To overcome such resistance, novel classes of agents have been designed and developed that are specifically active or activated under hypoxic conditions, in hypoxic tumors. The instant invention describes a novel idea to improve anti-cancer effect of hypoxia-sensitive therapeutics by using a rapidly oxidized reducing agent such as pyruvate or succinate. In the instant invention, the NIH investigators found that pyruvate, an endogenous substrate for energy production by mitochondria, induced severe hypoxia in tumors within 30 minutes of intravenous injection, and the tumor oxygen level reversibly returned to basal level within a few hours. Since pyruvate seems to induce only transient hypoxia, and its safety profiles are known, it may have significant advantages over other hypoxia inducers reported to date for improving the efficacy of hypoxia-sensitive anti-cancer therapies.

Applications:

• Provide a novel way to target various cancers, especially solid tumors for treatment;

• Improve the efficacy of using hypoxic toxins for cancer treatment;

• *In vivo* screening of oxygen-status dependent drugs.

Market: Cancer is the second leading cause of death in the U.S. The National Cancer Institute estimates the overall annual costs for cancer in the U.S. at $107 billion; $37 billion for direct medical costs, $11 billion for morbidity costs (cost of lost productivity), and $59 billion for mortality costs. There is an ongoing need for innovative approaches to anticancer therapy.

Development Status: Pre-clinical stage of development.

Inventors: Drs. Shingo Matsumoto (NCI), James B. Mitchell (NCI), and Robert J. Gillies (H. Lee Moffitt Cancer Center and Research Institute) *et al.*

Publication: Poster presentation in the International Society for Magnetic Resonance in Medicine (ISMRM) meeting in May 2011. Manuscript is *in press.*

Patent Status: U.S. Provisional Application No. 61/478,465 filed April 22, 2011 (HHS Reference No. E–144–2011/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Betty B. Tong, PhD; 301–594–6565; *tongb@mail.nih.gov.*

Multivalent Vaccines for Rabies Virus and Filoviruses

Description of Technology: No vaccine candidates against Ebola virus (EBOV) or Marburg virus (MARV) are nearing licensure and the need to develop a safe and efficacious vaccine against filoviruses continues. Whereas several preclinical vaccine candidates against EBOV or MARV exist, their further development is a major challenge based on safety concerns, pre-existing vector immunity, and issues such as manufacturing, dosage, and marketability. The inventors have developed a new platform based on live or chemically inactivated (killed) rabies virus (RABV) virions containing EBOV glycoprotein (GP) in their envelope. In preclinical trials, immunization with such recombinant RABV virions provided excellent protection in mice against lethal challenge with the mouse adapted EBOV and RABV. More specifically, the inventors have developed a trivalent filovirus vaccine based on killed rabies virus virions for use in humans to confer protection from all medically relevant filoviruses and RABV. Two additional vectors containing EBOV Sudan GP or MARV GP are planned to be constructed in addition to the previously developed EBOV Zaire GP containing vaccine. The efficiency of these vaccines against challenge with EBOV, MARV and RABV will be studied in multiple preclinical studies. Live attenuated vaccines are being developed for use in at risk nonhuman primate populations in Africa and inactivated vaccines are being developed for use in humans.

Potential Commercial Applications:

• Biodefense vaccine.

• Developing country vaccine.

• Multivalent prophylactic Ebola/Marburg/rabies vaccine.

Competitive Advantages:

• Vaccines are replication deficient and/or inactivated.

• Protection against rabies and Ebola.

• Reliable and cost-effective manufacture.

• No preexisting immunity to vectors.

• No potential vaccine reactogenicity.

Development Stage:

• Pre-clinical.

• *In vitro* data available.

• *In vivo* data available (animal).

Inventors: Joseph Blaney, Jason Paragas, Peter Jahrling, Reed Johnson (NIAID).

Intellectual Property: HHS Reference No. E–032–2011/0 — U.S. Patent Application No. 61/439,046 filed 03 Feb 2011.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Layered Electrophoretic Transfer for Analysis of Low or Medium Abundant Proteins in Tissue Samples

Description of Technology: The subject invention is a method to selectively process the protein content from a two dimensional sample, such as a tissue section, for more detailed analysis. It is particularly useful for analysis of a subset of proteins from a complex protein mixture. The method employs a layer of polyacrylamide gels and an electric field. Proteins from the sample are transferred and sieved through a stack of polyacrylamide gels of varying concentrations. Thus, it is possible to analyze specific subsets of

proteins in the different gel layers and maintain the two dimensional location of the proteins within the original sample. One of the advantages of this technology is that it allows for isolation and subsequent analysis of low abundant or medium abundant proteins by a number of different methodologies such as imaging mass spectrometry.

Applications:

- Protein Analysis of Tissue Samples.
- Histology and Pathology.

Advantages:

- Isolation of low or moderately-abundant proteins in tissue sections.
- Method maintains 2-dimensional location of proteins in tissue samples.

Development Status: In vitro data can be provided upon request.

Market:

- Diagnostic.
- Pathology.
- Basic Research.

Inventors: Michael Emmert-Buck, Liang Zhu, and Michael Tangrea (NCI).

Publication: Zhu L, Tangrea MA, Mukherjee S, Emmert-Buck MR. Layered electrophoretic transfer—A method for pre-analytic processing of histological sections. Proteomics. 2011 Mar;11(5):883–889. [PMID: 21280224].

Patent Status: U.S. Provisional Application No. 61/420,258 filed December 6, 2010 (HHS Reference No. E–020–2011/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Kevin W. Chang, PhD; 301–435–5018; *changke@mail.nih.gov.*

Collaborative Research Opportunity: The Center for Cancer Research, Laboratory of Pathology, Pathogenetics Unit, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize layered electrophoretic transfer (LET). Please contact John Hewes, PhD at 301–435–3121 or hewesj@*mail.nih.gov* for more information.

Pertussis Vaccine

Description of Technology: Despite mass vaccination, reported pertussis cases have increased in the United States and other parts of the world, probably because of increased awareness, improved diagnostic means, and waning vaccine-induced immunity among adolescents and adults. Licensed vaccines do not kill the organism directly; the addition of a component inducing bactericidal antibodies would improve vaccine efficacy. This application claims *Bordetella pertussis* and *Bordetella bronchiseptica* LPS-derived core oligosaccharide (OS) protein conjugates. *B. pertussis* and *B. bronchiseptica* core OS were bound to aminooxylated BSA via their terminal Kdo residues. The two conjugates induced similar anti-*B. pertussis* LPS IgG levels in mice. Conjugate-induced antisera were bactericidal against *B. pertussis.*

Potential Commercial Applications:

- Pertussis prophylactic conjugate vaccine.
- Use of vaccine to generate neutralizing antibodies.

Competitive Advantages: Conjugates are easy to prepare and standardize; added to a recombinant pertussis toxoid, they may induce antibacterial and antitoxin immunity.

Development Stage:

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

Inventors: Joanna Kubler-Kielb (NICHD), Rachel Schneerson (NICHD), John B. Robbins (NICHD), Ariel Ginzberg (NICHD), Teresa Lagergard (NICHD), *et al.*

Publication: Kubler-Kielb J, Vinogradov E, Lagergård T, Ginzberg A, King JD, Preston A, Maskell DJ, Pozsgay V, Keith JM, Robbins JB, Schneerson R. Oligosaccharide conjugates of Bordetella pertussis and bronchiseptica induce bactericidal antibodies, an addition to pertussis vaccine. Proc Natl Acad Sci U S A. 2011 Mar 8;108(10):4087–4092. [PMID: 21367691].

Intellectual Property: HHS Reference No. E–006–2011/0—U.S. Application No. 61/438,190 filed 31 Jan 2011.

Related Technology: HHS Reference No. E–183–2005/0 —U.S. Application No. 12/309,428 filed 16 Jan 2009.

Licensing Contact: Peter A. Soukas, J.D.; 301–435–4646; *soukasp@mail.nih.gov.*

Collaborative Research Opportunity: The NICHD is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize vaccines against pertussis. For collaboration opportunities, please contact Joseph Conrad, III, PhD at *jmconrad@mail.nih.gov.*

Novel Methods for the Reversible Incorporation of Functional Groups Into RNA and DNA: Synthesis and Uses for 2′-O-aminooxymethyl Nucleoside Derivatives

Description of Technology: The delivery of DNA/RNA therapeutic drugs is still a major hurdle for the clinical application of DNA/RNA-based drugs. Also, developments in silencing the expression of specific genes, through RNA interference pathways, have led to an increased demand for synthetic RNA sequences and have created a pressing need for rapid and efficient methods for RNA synthesis. Recently, FDA scientists have developed a novel phosphoramidite, 2′-O-aminooxymethyl ribonucleoside (2′-O-protected compounds). The 2′-O-aminooxymethyl ribonucleoside can be modified with any type of functional group using an oximation reaction as long as the functional group contains an aldehyde, ketone, or acetal group. Modification of the 2′-O-aminooxymethyl with an aldehyde results in a conjugated 2′-phosphoramidite that could be readily converted back to the native ribonucleoside and its corresponding by-product. On the other hand, the oximation of 2′-O-aminooxymethy with a ketone results in an irreversible conjugated form of the phosphoramidite.

The 2′-O-protected compounds of the present technology have several advantages, for example, the 2′-O-protected compound is stable during the various reaction steps involved in oligonucleotide synthesis; and the protecting group can be easily removed after the synthesis of the oligonucleotide, for example, by reaction with tetrabutylammonium fluoride; and the O-protected groups do not generate DNA/RNA alkylating side products, which have been reported during removal of 2′-O-(2-cyanoethyl)oxymethyl or 2′-O-[2-(4-tolylsulfonyl)ethoxymethyl groups under similar conditions.

Applications:

- Incorporation of a potentially large array of functional groups into RNA and DNA oligonucleotides for diagnostic and/or therapeutic applications.
- Conjugation of a variety of sugars or complex carbohydrates to DNA/RNA therapeutic oligonucleotides.
- Attachment of cell membrane-penetrating peptides to therapeutic DNA/RNA oligonucleotides.

Inventors: Serge L. Beaucage and Jacek Cieslak (FDA).

Patent Status: U.S. Provisional Application No. 61/471,451 filed 04 April 2011 (HHS Reference No. E–262–2010/0–US–01).

Licensing Status: Available for licensing.

Licensing Contact: Suryanarayana Vepa, PhD, J.D.; 301–435–5020; *vepas@mail.nih.gov.*

Dated: July 26, 2011.

Richard U. Rodriguez,

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

[FR Doc. 2011–19377 Filed 7–29–11; 8:45 am]

BILLING CODE 4140–01–P