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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, 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. 209 and 37 CFR Part 404 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.

SUPPLEMENTARY INFORMATION: Technology descriptions follow.

Highly Sensitive Tethered-Bead Immune Sandwich Assay

Description of Technology: This technology is a highly sensitive tethered-bead immune sandwich assay. Analyte molecules are captured between two antibodies, a capture antibody and a detection antibody. The capture antibody on a micron-size bead binds analyte from a sample fluid. The bead-captured analyte is then exposed to a "detection" antibody that binds to the bead-captured analyte, forming a "sandwich". The sandwiched analyte-bead complex then connects to a flexible polymer (such as DNA) anchored on a solid surface to form tethered particles. Binding the analyte-bead complex to a flexible polymer forms tethered particles and may be done, for example, by streptavidin biotin. Motion of the tethered beads easily identifies bound analyte. The tethered beads are quantified using low-magnification light microscopy. Prior enhanced sensitivity tethered bead technologies require expensive and cumbersome detection equipment. This assay is inherently single molecule, low background, and works with simple inexpensive imaging formats, but is automatable and potentially adaptable to portable technologies. A prototype design using prostate specific antigen (PSA) shows detection sensitivity of ~.03ng/ml, compared with normal PSA sensitivity of ~< 4ng/ml. Design refinements further improve sensitivities.

Potential Commercial Applications: Diagnostics and research.

Competitive Advantages: Highly sensitive single molecule adaptable format, specific, low background, inexpensive, simple to use, automatable for image analysis.

Development Stage:

• Early-stage

• Prototype

Inventors: Jonathan Silver (NHLBI), Zhenyu Li (George Washington Univ.), Keir Neuman (NHLBI)

Publication: Silver J, et al. Tethered-bead, immune sandwich assay. Biosens Bioelectron. 2015 Jan 15;63:117-23. [PMID 25064819]

Intellectual Property: HHS Reference No. E-188-2014/0 - US Provisional Application No. 62/015,122 filed June 20, 2014

Licensing Contact: Edward (Tedd) Fenn; 424-297-0336; Tedd.fenn@nih.gov

Polyketal Nanoparticle Delivery of CpG Oligodeoxynucleotide for Treatment of Lung Cancer

Description of Technology: This technology delivers oligodexoynucleotide locally to lung tumors using polyketal nanoparticles. CpG ODNs (oligonucleotides with CpG motifs) stimulate anti-tumor immune cells via Toll-like receptor 9 and show promise as cancer therapeutics in preclinical and clinical trials. However, previous systemic CpG ODN treatments of lung tumors progressed only to Phase 3 trials. Local CpG ODN delivery appears to have superior antitumor effect compared to earlier systemic treatments. Adsorbing CpG ODNs onto biodegradable polyketal (CpG-NP) creates 1-3 micron nanoparticles that can reach distal alveoli by inhalation. This localized treatment improves uptake and persistence in the tumor microenvironment, resulting in decreased immunosuppressive T-Cells and increased macrophages. *In vivo*

data indicate this therapy reduces tumor growth and enhances survival rate in lung cancer. Mice treated with CpG-NP had fewer and smaller tumor nodules (reduced by >90%). In Lewis lung carcinoma model, CpG-NP therapy significantly improved the survival; 80% of CpG-NP-treated mice survived (some for >1 yr). CpG-NP represents a promising potential lung cancer therapy.

Potential Commercial Applications: Therapeutic or combination therapy for lung cancer treatment.

Competitive Advantages:

• Superior therapeutic effect versus systemic administration.

• CpG ODN treatments have well studied safety profile in phase 1-3 clinical trials.

Development Stage: In vivo data available (animal)

Inventors: Dennis Klinman and Takashi Sato (NCI)

Publication: Klinman D, et al. Synthetic oligonucleotides as modulators of inflammation. J Leukoc Biol. Oct 2008; 84(4): 958-64. [PMID 18430787]

Intellectual Property: HHS Reference No. E-159-2014/0 - US Provisional Application No. 62/024,657 filed July 15, 2014

Licensing Contact: Edward (Tedd) Fenn; 424-297-0336; Tedd.fenn@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 optimizing delivery of immunostimulatory CpG oligonucleotides to patients with lung cancer. For collaboration opportunities, please contact John D. Hewes, Ph.D. at john.hewes@nih.gov.

Aza-Englerin Analogues - Novel Natural Product-Based Nitrogen-Containing Anti-Cancer Agents

Description of Technology: Available for licensing are synthetic compounds developed as novel cancer therapeutics. Scientists at the National Institutes of Health and University of Hawaii have designed and synthesized novel aza-englerin analogues that have shown great inhibitory effects on cancer cell growth. Englerin A is a natural compound from the African plant *Phyllanthus engleri* that displays potent and selective anti-cancer properties in several cancer types and has been found to be active in several mouse xenograft experiments with human tumor cells when injected intraperitoneally. The invention provides compositions, methods of synthesis and methods of using the aza-derivatives of englerin for cancer treatment. These englerin analogues show significant bioavailability after oral administration in mice, making them attractive as cancer therapeutics.

Potential Commercial Applications: Potential therapeutics for cancer, particularly kidney cancer, Ewing's sarcoma, and other cancers with a glycolytic phenotype. Potential in diabetes and HIV infection.

Competitive Advantages:

• Novel compounds with great inhibitory effect on select cancer cells, designed/synthesized as analogues to natural products that show striking anti-cancer properties.

• Parent compounds are effective in in vivo cancer models.

• Novel syntheses of the compounds of the invention are provided.

• Bioavailability after oral administration in mouse model demonstrated, making it suitable for clinical usage.

Development Stage:

• Early-stage

• In vitro data available

• In vivo data available (animal)

Inventors: John A Beutler (NCI), Douglas Figg (NCI), William Chain (Univ. of Hawaii-Manoa)

Publications:

1. Ratnayake R, et al. Englerin A, a selective inhibitor of renal cancer cell growth, from Phyllanthus engleri. Org Lett. 2009 Jan 1;11(1):57-60. [PMID 19061394]

2. Li Z, et al. A brief synthesis of (-)-englerin A. J Am Chem Soc. 2011 May 4;133(17):6553-6. [PMID 21476574]

3. Akee R, et al. Chlorinated englerins with selective inhibition of renal cancer cell growth. J Nat Prod. 2012 Mar 23;75(3):459-63. [PMID 22280462]

4. Sourbier C, et al. Englerin A stimulates PKC theta to inhibit insulin signaling while simultaneously activating HSF1: A case of pharmacologically induced synthetic lethality. Cancer Cell 23 (2):228-237, 2013. [PMID 23352416]

Intellectual Property:

• HHS Reference No. E-090-2014/0 - US Provisional Patent Application No. 61/936,285 filed February 5, 2014

• HHS Reference No. E-090-2014/1 - US Provisional Patent Application No. 62/018,381 filed June 27, 2014

Related Technologies:

• HHS Reference No. E-064-2008/2-US-06 - US Patent No. 8,410,292 issued April 2, 2013

• HHS Reference No. E-042-2012/0-US-06 - U.S. Patent Application No. 14/370,140 filed July 1, 2014

• HHS Reference No. E-201-2012/0-PCT-02 - PCT Application No. PCT/US2013/069796 filed November 13, 2013, which published as WO 2014/078350 on May 22, 2014

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

Collaborative Research Opportunity: The National Cancer Institute, Molecular Targets Development Program, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize aza-englerin analogues as cancer inhibitors. For collaboration opportunities, please contact John D. Hewes, Ph.D. at john.hewes@nih.gov.

Nicotine Conjugate Treatment for Parkinson's Disease

Description of Technology: It has been known since 1959 that tobacco use has protective effects against Parkinson's disease. However, efforts to turn that knowledge into a safe and effective treatment, divorced from tobacco use, have had little success. An inventor at FDA now has *in vitro* evidence that nicotine promotes a protein clearance system, thereby halting Parkinson's disease progression. In addition to using nicotine as the treatment, the inventor has created a coated conjugate of nicotine and nanoceria. This

conjugate not only harnesses the power of nicotine but also takes advantage of the anti-oxidant effect of the nanoceria to reduce the oxidant environment, which is also a major mechanism of neuronal damage in Parkinson's disease.

Potential Commercial Applications: Treatment for Parkinson's disease.

Competitive Advantages: Improved mechanism to use nicotine as a treatment.

Development Stage:

• Early-stage

• In vitro data available

Inventor: Syed Z. Imam (FDA)

Intellectual Property: HHS Reference No. E-016-2014/0 - US Provisional Application No. 62/010,033 filed June 10, 2014

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

Collaborative Research Opportunity: The FDA National Center for Toxicological Research, Division of Neurotoxicology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize A Nicotine-NanoCeria Conjugate named NIC-NANO for treatment of Parkinson's disease. For collaboration opportunities, please contact Syed Z Imam at syed.imam@fda.hhs.gov.

cGAP-PNA Multivalent Ligand Display at the Nanoscale

Description of Technology: Scientists at the NIH are developing new types of peptide nucleic acids (PNAs) that maintain aqueous solubility at longer lengths. This new

type of PNA is called "cGAP-PNA" because it contains a sequence complementary to the L-PNA sequence, which is a PNA with one or more gamma-sidechains that displays a ligand. The investigators have synthesized cGAP-PNAs that are 60 nucleobases long that can support the assembly of 5 complementary L-PNAs (each with 12 nucleobases) that bear specific ligands. This platform can replace more traditional multivalent scaffolds, such as dendrimers and gold nanoparticles.

Potential Commercial Applications: Multivalent ligand display.

Competitive Advantages:

• Decreased hydrophobicity

• Increased water solubility

• Can be used at very long lengths

• More stable and resistant to degradation than existing PNAs

Development Stage:

• Early-stage

• In vitro data available

Inventors: Daniel H. Appella, Andrew V. Dix, Ethan A. Englund, Kara M. George Rosenker (all of NIDDK)

Publication: Dix A, et al. Programmable nanoscaffolds that control ligand display to a G-protein-coupled receptor in membranes to allow dissection of multivalent effects. J Am Chem Soc. 2014 Sep 3;136(35):12296-303. [PMID 25116377]

Intellectual Property: HHS Reference No. E-761-2013/0 - US Provisional Application No. 61/929,893 filed January 21, 2014

Related Technologies:

• HHS Reference No. E-308-2006/3 - US Application No. 13/592,490 filed August 23, 2012

• HHS Reference No. E-129-2010/0 - EP Application No. 11721899.0 filed May 11, 2011; US Application No. 13/697,123 filed November 9, 2012

Licensing Contact: Charlene S. Maddox, Ph.D.; 301-435-4689; charlene.maddox@nih.gov

Collaborative Research Opportunity: The National Institute of Diabetes and Digestive and Kidney Diseases 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 Marguerite Miller at Marguerite.Miller@nih.gov or 301-496-9003.

Dated: January 9, 2015.

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Richard U. Rodriguez,
Acting Director,
Office of Technology Transfer,
National Institutes of Health.

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