[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.

Cell Lines Expressing Nuclear and/or Mitochondrial RNase H1

Description of Technology: RNase H1 has been shown to remove RNA/DNA hybrids and either too much or too little enzyme can lead to undesirable effects such as deletions of DNA. The gene encoding RNase H1 in mammalian cells produces two forms of the protein. One is targeted to the nucleus of the cell and the other to the mitochondrial organelle. To study the effects of expression as well as to understand the regulation of the frequency with which each form is made, NIH investigators constructed cells derived from HEK293 cells where expression of each or both forms is/are expressed only after addition of doxycycline as a small molecule inducer compound. The set of cell lines could be important in the process of analysis of RNA/DNA hybrids as each cell line expresses different amounts of each form.

Potential Commercial Applications: Research materials to study RNA/DNA hybrids

Competitive Advantages: Not available elsewhere

Development Stage:

• Prototype

• Pre-clinical

• In vitro data available

Inventors: Robert J. Crouch and Yutaka Suzuki (NICHD)

Publication: Suzuki Y, et al. An upstream open reading frame and the context of the two AUG codons affect the abundance of mitochondrial and nuclear RNase H1. Mol Cell Biol. 2010 Nov;30(21):5123-34. [PMID 20823270]

Intellectual Property: HHS Reference No. E-273-2012/0 — Research Material. Patent protection is not being pursued for this technology.

Licensing Contact: Betty B. Tong, Ph.D.; 301-594-6565; tongb@mail.nih.gov

Collaborative Research Opportunity: The Program in Genomics of Differentiation, NICHD, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize small molecule inhibitors of RNase H1, genome instability, or transcription and translation. For collaboration opportunities, please contact Joseph Conrad III, Ph.D. at jmconrad@mail.nih.gov.

Improved Transposase Compositions for Whole Genome Sequencing

Description of Technology: The invention provides improved transposase enzymes engineered to exhibit reduced sequence biases, and to operate more efficiently than wildtype transposases.

Scientists at NIDDK and John Hopkins University jointly developed mutant transposases that are superior to wildtype transposases in whole genome sequencing applications. Transposases facilitate the cleavage of certain DNA segments, called transposons, at specific sites within a genome and their subsequent insertions at random sites. Addition of transposases and labeled transposons to whole genome preparations allow for one-pot, simultaneous fragmentation and identification of targeted DNA sequences.

Mutations introduced by the inventors facilitate formation of dimeric enzyme complexes with enhanced activity and stability. These modifications result in more efficient fragmentation and tagging of genomic DNA.

Potential Commercial Applications: Kits for whole genome sequencing.

Competitive Advantages:

• Can easily be expressed in the bacterium, *E. coli*, and purified in large quantities.

• Are soluble, stable and exist as smaller active complexes compared to native enzymes.

• Are fully active at room temperature (23 - 30°C).

• Have a higher transposition activity and show minimal insertional sequence bias in-vitro compared to the wild type.

Development Stage:

• Prototype

• Pilot

• In vitro data available

Inventors: Fred Dyda (NIDDK), Alison Hickman (NIDDK), Nancy Craig (Johns Hopkins School of Medicine), Sunil Gangadharan (Johns Hopkins School of Medicine)

Intellectual Property: HHS Reference No. E-194-2012/0 — U.S. Provisional Application No. 61/652,560 filed 29 May 2012

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301-435-4074; nguyenantczakla@mail.nih.gov

Improved Monoclonal Antibodies Against Neuregulin 2

Description of Technology: The invention provides highly selective monoclonal antibodies against the extracellular domain (ECD) or intracellular domain (ICD) of neuregulin-2, a ligand for the ErbB receptors in adult human brain. Neuregulins regulate a diverse array of neurological process in the central nervous system and are implicated in schizophrenia and other psychiatric disorders. However, an understanding of the specific role of neuregulin 2 has been hindered by a lack of specific antibodies useful in immunoblotting and immunohistology studies. Commercially available antibodies do not perform as well in these applications when compared to the invention antibodies. A mouse monoclonal antibody directed to the ECD is available for licensing (clone 8D11, HHS Ref. No. E-192-2012), and rabbit antibodies directed to the ICD are also available (clone 11-11, HHS Ref. No. E-193-2012; clone 15-10, HHS Ref. No. E-189-2012; and clone 9-2, HHS Ref. No. E-188-2012). Antibodies from clones 8D11 and 11-11 have been validated for immunohistology and antibodies from clones 15-10 and 9-2 have been validated for Western blotting using brain tissue from wild-type and neuregulin 2 deficient mice.

Potential Commercial Applications: Superior monoclonal antibody for Western blotting or immunohistology analysis of tissue sections

Competitive Advantages:

• Superior binding specificity in comparison to commercially available antibodies

• Developed antibodies bind specific, characterized regions on neuregulin 2

Development Stage:

• Prototype

• In vitro data available

Inventors: Detlef Vullhorst, Andres Buonanno, Irina Karavanov (all of NICHD)

Intellectual Property: HHS Reference Nos. E-188-2012/0, E-189-2012/0, E-190-2012/0, E-191-2012/0, E-192-2012/0, E-193-2012/0. This is a Research Tool — patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301-435-4074; nguyenantczakla@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 neuregulin-2 monoclonal antibodies. For collaboration opportunities, please contact Charlotte McGuinness at mcguinnc@mail.nih.gov.

Glucocerebrosidase Activators for the Treatment of Gaucher Disease, Parkinson's Disease, and Other Proteinopathies

Description of Technology: Gaucher disease is a rare lysosomal storage disease that is characterized by a loss of function of the glucocerebrosidase (GCase) enzyme, which results in a decreased ability to degrade its lipid substrate, glucocerebroside. The intracellular build up of this lipid causes a broad range of clinical manifestations, ranging from enlarged spleen/liver and anemia to neurodegeneration. In Gaucher disease, the loss of GCase function has been attributed to low levels of the protein in the lysosomal compartment, resulting from improper GCase folding and transport. Also, mutations in the GCase gene have been linked to some forms of Parkinson's disease, and may also be involved in other proteinopathies.

This technology describes a collection of salicylic acid-derived small molecules that act as chaperones to activate proper GCase folding and subsequent transport from the endoplasmic reticulum into the lysosome. Unlike many other small molecule chaperones, these salicylic acid derivatives do not inhibit the activity of the GCase enzyme. These small molecules have been tested for the ability to activate GCase *in vitro* and show chaperone activity in a patient-derived fibroblast translocation assay.

Potential Commercial Applications:

• Treatment of Gaucher disease

• Treatment of Parkinson's disease

• Treatment of other lysosomal storage diseases

Competitive Advantages: The compounds are novel small molecules that enhance proper GCase folding and transport without inhibiting enzyme activity in the lysosome.

Development Stage:

• Early-stage

• In vitro data available

Inventors: Juan Marugan (NCATS), Wei Zheng (NCATS), Samarjit Patnaik (NCATS), Noel Southall (NCATS), Ellen Sidransky (NHGRI), Ehud Goldin (NHGRI), Wendy Westbroek (NHGRI)

Publication: Related publication is currently in preparation.

Intellectual Property:

• HHS Reference No. E-144-2012/0 — U.S. Provisional Application No. 61/616,758 filed 28 Mar 2012

• HHS Reference No. E-144-2012/1 — U.S Provisional Application No. 61/616,773 filed 28 Mar 2012

Licensing Contact: Tara Kirby, Ph.D.; 301-402-0220; tarak@mail.nih.gov

Collaborative Research Opportunity: The National Center for Advancing Translational Sciences 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 Dr. Juan Marugan at maruganj@mail.nih.gov.

Cyclodextrins as Therapeutics for Lysosomal Storage Disorders

Description of Technology: Cyclodextrins (CD), alone or in combination with other agents (e.g., vitamin E), as therapeutics for the treatment of lysosomal storage disorders (LSDs) caused by the accumulation of non-cholesterol lipids.

CDs are sugar molecules in a ring form. The alpha-CD (6 sugars), beta-CD (7 sugars) and gamma-CD (8 sugars) are commonly used cyclodextrins. The hydroxypropyl-beta cyclodextrin (HPbCD) has been approved for pharmaceutical use. Recent reports show that beta-cyclodextrin including HPbCD and beta-methyl-cyclodextrin reduced cholesterol accumulation and neuronal cell loss in the mouse model of NPC1 disease.

NCATS investigators found that CD (alpha-, beta- and gamma-CDs) increased intracellular Ca2+ and lysosomal exocytosis in both wild type cells and cells with Wolman disease, and reduced the size of enlarged lysosomes in six patient cell lines with LSDs. Further, CD in combination with tocopherol synergistically/additively reduced

cholesterol accumulation in cells of NPC and Wolman diseases. Based on these results, they propose treatment of LSDs with cyclodextrins (such as alpha and gamma forms) alone or in combination with Vitamin E and its analogues for better efficacy and less side effects.

Potential Commercial Applications:

• treatment of lysosomal storage diseases

• treatment of disorders caused by accumulation of non-cholesterol lipids

Competitive Advantages:

• use of cyclodextrins in combination with vitamin-E (e.g., delta-tocopherol) provides additive therapeutic effect

• less side effects than cyclodextrin only or vitamin E only for LSDs because of reduced doses for both compounds in combination

Development Stage:

• Early-stage

• Pre-clinical

• In vitro data available

Inventors: John McKew, Wei Zheng, Miao Xu, Manju Swaroop, Juan Marugan (all of NCATS)

Intellectual Property: HHS Reference No. E-050-2012/0 — US Provisional Application No. 61/679,668 filed 12 Aug 2012

Related Technology: HHS Reference No. E-294-2009/0 — PCT Patent Application No. PCT/US2011/044590 filed 19 Jul 2011, entitled" “Use of Delta

Tocopherol for the Treatment of Lysosomal Storage Disorders" (Wei Zheng et al., NCATS)

Licensing Contact: Suryanarayana Vepa, Ph.D., J.D.; 301-435-5020; vepas@mail.nih.gov

Collaborative Research Opportunity: The National Center for Advancing Translational Sciences 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 Dr. Juan Marugan at maruganj@mail.nih.gov.

Selective Treatment of Cancer, HIV, Other RNA Viruses and Genetically related Diseases using Therapeutic RNA Switches

Description of Technology: Targeted therapy in cancer or viral infections is a challenge because the disease state manifests itself mainly through differences in the cell interior, for example in the form of the presence of a certain RNAs or proteins in the cytoplasm.

The technology consists of designed RNA switches that activate the RNA interference pathway only in the presence of a trigger RNA or DNA to which they bind, in order to knock down a chosen gene that is not necessarily related to the initial trigger.

This new approach can lead to a new type of drug that has the unique feature of selectively causing a biochemical effect (such as apoptosis) in cells that are infected by RNA viruses (such as HIV), as well as cancer cells. The RNA switch concept can be expanded to selectively treat other genetically related diseases.

Potential Commercial Applications:

• Targeted therapeutic for viral infections, cancer stem cells, and genetically related diseases

• Research tool to study cancer or viral infection

Competitive Advantages

• Fewer side effects because the therapeutic RNA-interference pathway is only activated by the RNA switch when it is intact and in its active conformation

• Selectively kills cells infected by RNA viruses

• Contains a minimal number of single stranded nucleotides, thus minimizing the effects of nucleases

Development Stage: In vitro data available

Inventors: Bruce A. Shapiro (NCI), Eckart Bindewald (SAIC-Frederick, Inc.), Kirill Afonin (NCI), Arti Santhanam (NCI)

Publications:

1. Afonin KA, et al. Co-transcriptional Assembly of Chemically Modified RNA Nanoparticles Functionalized with siRNAs. Nano Lett. 2012 Oct 10;12(10):5192-5. [PMID 23016824]

2. Grabow WW, et al. "RNA Nanotechnology in Nanomedicine," in Nanomedicine and Drug Delivery (Recent Advances in Nanoscience and Nanotechnology), ed. M Sebastian, et al. (New Jersey: Apple Academic Press, 2012), 208-220. [Book Chapter]

3. Shukla GC, et al. A boost for the emerging field of RNA nanotechnology. ACS Nano. 2011 May 24;5(5):3405-18. [PMID 21604810]

4. Afonin KA, et al. Design and self-assembly of siRNA-functionalized RNA nanoparticles for use in automated nanomedicine. Nat Protoc. 2011 Dec 1;6(12):2022-34. [PMID 22134126]

5. Bindewald E, et al. Multistrand RNA secondary structure prediction and nanostructure design including pseudoknots. ACS Nano. 2011 Dec 27;5(12):9542-51. [PMID 22067111]

6. Grabow WW, et al. Self-assembling RNA nanorings based on RNAI/II inverse kissing complexes. Nano Lett. 2011 Feb9;11(2):878-87. [PMID 21229999]

7. Kasprzak W, et al. Use of RNA structure flexibility data in nanostructure modeling. Methods. 2011 Jun;54:239-50. [PMID 21163354]

8. Afonin KA, et al. In vitro assembly of cubic RNA-based scaffolds designed in silico. Nat Nanotechnol. 2010 Sep;5:676-82. [PMID 20802494]

9. Severcan I, et al. "Computational and Experimental RNA Nanoparticle Design," in Automation in Genomics and Proteomics: An Engineering Case-Based Approach, ed. G Alterovitz , et al. (Hoboken: Wiley Publishing, 2009), 193-220. [Book Chapter]

10. Shapiro B, et al. "Protocols for the In silico Design of RNA Nanostructures," in Nanostructure Design Methods and Protocols, ed. E Gazit, R Nussinov. (Totowa, NJ: Humana Press, 2008), 93-115. [Book Chapter]

11. Bindewald E, et al. Computational strategies for the automated design of RNA nanoscale structures from building blocks using NanoTiler. J Mol Graph Model. 2008 Oct;27(3):299-308. [PMID 18838281]

12. Yingling YG, Shapiro BA. Computational design of an RNA hexagonal nanoring and an RNA nanotube. Nano Lett. 2007 Aug;7(8): 2328-34. [PMID 17616164]

Intellectual Property:

• HHS Reference No. E-038-2012/0 — U.S. Provisional Application No. 61/561,247 filed 17 Nov 2011

• HHS Reference No. E-038-2012/1 — U.S. Provisional Application No. 61/678,434 filed 01 Aug 2012

Related Technology: HHS Reference No. E-039-2012/0 — U.S. Provisional Application No. 61/561,257 filed 17 Nov 2011

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

Collaborative Research Opportunity: The NCI Center for Cancer Research Nanobiology Program is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize therapeutic RNA switches. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

Activation of Therapeutic Functionalities with Chimeric RNA/DNA Nanoparticles for Treatment of Cancer, Viruses and Other Diseases

Description of Technology: A new strategy based on RNA/DNA hybrid nanoparticles, which can be generally used for triggering multiple functionalities inside diseased cells is presented. Individually, each of the hybrids is functionally inactive and functional representation can only be activated by the re-association of at least two

cognate hybrids simultaneously present in the same cell. Overall, this novel approach allows (i) the triggered release of therapeutic siRNAs or miRNAs inside the diseased cells, (ii) activation of other split functionalities (e.g. FRET, different aptamers, rybozymes, split proteins) intracellularly, (iii) higher control over targeting specificity (e.g. if two hybrids are decorated with two different tissue specific recognition moieties), (iv) biosensing and tracking of the delivery and re-association of these hybrids in real-time inside cells, (v) increasing the number of functionalities by introducing a branched hybrid structure, (vi) introduction of additional functionalities without direct interference of siRNA processivity, (vii) increasing the retention time in biological fluids by fine-tuning chemical stability through substituting the DNA strands with chemical analogs (e.g. LNA, PNA, etc.), (viii) conditional release of all functionalities.

Potential Commercial Applications:

• Therapeutic siRNA for cancer, viruses and other diseases

• Therapeutic for delivery of multiple functionalities

• Diagnostic to visualize cancer cells, virus infected cells, or diseased cells, or track the delivery and effectiveness of siRNA treatment or other treatments associated with the particle

• Research tool to study cancer, viral infections or other diseases

Competitive Advantages:

• Novel way for multiple functionality delivery and activation

• Enhanced chemical stability and pharmacokinetics due to the average size of nanoparticles exceeding 10nm

• Increased specificity for selecting cells of interest using more than one target gene

Development Stage:

• In vitro data available

• In vivo data available (animal)

Inventors: Bruce A. Shapiro (NCI), Kirill Afonin (NCI), Arti Santhanam (NCI), Mathias Viard (SAIC-Frederick, Inc.), Eckart Bindewald (SAIC-Frederick, Inc.), Luc Jaeger (U of Cal. Santa Barbara)

Publications:

1. Afonin KA, et al. Co-transcriptional Assembly of Chemically Modified RNA Nanoparticles Functionalized with siRNAs. Nano Lett. 2012 Oct 10;12(10):5192-5. [PMID 23016824]

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Intellectual Property: HHS Reference No. E-039-2012/0 — U.S. Provisional Application No. 61/561,257 filed 17 Nov 2011

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• HHS Reference No. E-038-2012/1 — U.S. Provisional Application No. 61/678,434 filed 01 Aug 2012

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

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November 5, 2012
Date

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

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