[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, 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.

Compositions for Modification of Genomic DNA and Exogenous Gene Expression

Description of Technology: A novel method of targeted insertion of transgenes at CLYBL locus directly in human cells is disclosed. Also, methods and compositions for increasing targeted insertion of a transgene into a specific location within the cell or increasing the frequency of gene modification in a targeted locus are disclosed. Genome modification by precise gene targeting at specific sequence/locus has great advantages over conventional transient expression or random integration methodologies and, therefore, has tremendous therapeutic potential. NIH investigators identified CLYBL gene in Chromosome 13 as a potential safe harbor locus. To directly target CLYBL safe-harbor in human cells without pre-engineering, they identified a unique transcription activator-like effector nuclease (TALEN) target sequence at CLYBL locus. The CLYBL TALENs (also termed as C13 TALENs) constructed using pZT backbone showed high gene editing efficiency in human 293T cells measured by both T7E1 mismatch assay and targeted sequencing. The inventors have used TALENs to simultaneously knock-in multiple reporter genes at up to four alleles of PPP1R12C/AAVS1 and new CLYBL safe-harbors in human induced pluripotent stem cells (iPSCs) and neural stem cells (NSCs). The engineered safe-harbor knock-in cell lines maintain robust transgene expression during iPSC/NSC self-renewal and differentiation, and CLYBL locus allowed 10-fold stronger transgene expression than other loci. NSC lines engineered by this methodology as well as constructs and protocols for evaluation are also available.

Potential Commercial Applications:

• Human stem cell-based gene therapy

• Drug screening

Competitive Advantages: CLYBL safe harbor on Chromosome 13 allows 5~10-fold stronger transgene expression than AAVS1 safe harbor, providing an alternative and potentially better solution for targeted gene transfer/knock-in and drug-screening, especially for weak promoter-driven transgenes.

Development Stage:

• Early-stage

• In vitro data available

Inventors: Jizhong Zou and Mahendra S. Rao (NIAMS)

Intellectual Property: HHS Reference No. E-763-2013/0-US-01 – US Application No. 61/905,002 filed 15 Nov 2013

Related Technology: HHS Reference No. E-762-2013/0-US-01 – US Application No. 61/904,999 filed 15 Nov 2013

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

Engineering Neural Stem Cells Using Homologous Recombination

Description of Technology: Methods for modifying the genome of a Neural Stem Cell (NSC) are disclosed. Also, methods for differentiating NSCs into neurons and glia are described. NSCs are multipotent, self-renewing cells found in the central nervous system, capable of differentiating into neurons and glia. NSCs can be generated efficiently from pluripotent stem cells (PSCs) and have the capacity to differentiate into any neuronal or glial cell type of the central nervous system. Improvements in genome engineering of NSCs can potentially facilitate cellular replacement therapies for the

treatment of neurodegenerative disorders. Recently, NIH investigators have developed a procedure to efficiently engineer NSCs through homologous recombination by introducing TAL effector nucleases (TALENs) and donor vectors. They have designed TALENs that efficiently generate double stranded breaks at two safe harbor loci (AAVS1 and CLYBL). These TALENs facilitate homologous recombination without silencing at these loci. The TALENs were delivered along with a DNA donor vector with a ubiquitous promoter driving expression of a cDNA using a nucleofector to get high transfection efficiencies. NSCs modified in this manner have therapeutic potential in treating neurodegenerative diseases. NSC lines engineered by this methodology as well as constructs and protocols for evaluation are also available.

Potential Commercial Applications: Cellular replacement therapies for neurodegenerative disorders.

Competitive Advantages:

• The novel methods provide highly pure engineered NSC populations which maintain the capacity to self-renew and differentiate to neurons and astrocytes suitable for cell replacement therapies.

• Safe harbor TALEN-mediated homologous recombination is a high-efficiency method to generate targeted mini-gene transfer or reporter knock-in cell lines in both human iPSCs and NSCs.

Development Stage:

• Early-stage

• In vitro data available

Inventors: Nasir S. Malik, Mahendra S. Rao, Jizhong Zou, Raymond Funahashi (all of NIAMS)

Intellectual Property: HHS Reference No. E-762-2013/0-US-01 – US Application No. 61/904,999 filed 15 Nov 2013

Related Technology: HHS Reference No. E-763-2013/0-US-01 – US Application No. 61/905,002 filed 15 Nov 2013

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

Role of Novel Hepatitis Delta Virus Variant in Sjögren's Syndrome

Description of Technology: Sjögren's is a chronic autoimmune disease characterized by dry mouth and eyes, fatigue, and musculoskeletal pain resulting from the attack of the moisture-producing glands by the body's own white blood cells. The subject invention is based on the discovery of an association between infection by a novel clade 1 variant of hepatitis delta virus (HDV) and primary Sjögren's syndrome. The association was made after detection of the HDV nucleic acid in the salivary glands of patients diagnosed with Sjögren's syndrome and *in vivo* studies in mice that developed Sjögren's syndrome-like pathogenesis after expression of HDV antigen. The discovery of this link opens the possibilities for developing diagnostics against HDV to determine who are at risk for developing Sjögren's syndrome. The novel HDV variant can also serve as a potential therapeutic target for preventing or treating Sjögren's.

Potential Commercial Applications:

• Diagnostic for novel HDV clade 1 variant as a risk factor for developing Sjögren's

• Therapeutics against this newly discovered HDV clade 1 variant for prevention and/or treatment of Sjögren's syndrome

Competitive Advantages:

• Novel diagnostic for a potentially significant risk factor in developing Sjögren's syndrome

• Newly discovered potential targets for treatment of Sjögren's

Development Stage:

• Early-stage

• In vitro data available

• In vivo data available (animal)

Inventors: Melodie L. Weller and John Chiorini (NIDCR)

Intellectual Property: HHS Reference No. E-736-2013/0 – US Provisional Application No. 61/888,706 filed 09 Oct 2013

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

Collaborative Research Opportunity: The National Institute of Dental and Craniofacial Research is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize Role of Novel Hepatitis Delta Virus Variant. For collaboration opportunities, please contact David W. Bradley, Ph.D. at bradleyda@nidcr.nih.gov.

Treating or Inhibiting JC Polyomavirus Infection and JC Polyomavirus-Associated Progressive Multifocal Leukoencephalopathy

Description of Technology: Available for licensing are novel findings to generate immune response to JC polyomavirus (JCV). An immunogenic composition with a single JCV subtype VP1 polypeptide generates neutralizing antibodies to all JCV subtypes, including JCV with variant VP1 polypeptides. The invention is useful for the prevention, treatment, or inhibition of JCV infection and JCV-associated pathologies, such as progressive multifocal leukoencephalopathy (PML).

Also available for licensing are techniques for identifying a subject at risk for developing PML, based on detecting the absence of JCV neutralizing antibodies in the subject.

Potential Commercial Applications:

• Pharmaceutical treatments of JC virus infection

• Pharmaceutical treatments or prevention of PML

• Prediction or early diagnosis of the development of PML

Competitive Advantages:

• Generating an immune response to all JC virus subtypes utilizing a JC virus capsid polypeptide from a single subtype.

• No known methods for identifying a subject at risk for developing PML by detecting the absence of JC virus neutralizing antibodies in the subject.

Development Stage:

• Early-stage

• In vitro data available

• In vivo data available (animal)

• In vivo data available (human)

Inventors: Christopher B. Buck (NCI), Upasana Ray (NCI), and Diana V. Pastrana

Publication: Buck CB. Developing vaccines against BKV and JCV. Presentation, 5th International Conference on Polyomaviruses and Human Diseases: Basic and Clinical Perspectives, Stresa, Italy, May 9-11, 2013. Abstract published online in June 2013 in J Neurovirol. 2013;19:307. [DOI 10.1007/s13365-013-0171-0]

Intellectual Property: HHS Reference No. E-549-2013/0 – US Provisional Application No. 61/919,043 filed 20 Dec 2013

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

Collaborative Research Opportunity: The National Cancer Institute, Laboratory of Cellular Oncology, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize methods of treating JC polyomavirus-related disorders. For collaboration opportunities, please contact John D. Hewes, Ph.D. at hewesj@mail.nih.gov.

Therapeutic for Sickle Cell Disease and Beta Thalassemias

Description of Technology: Sickle-cell disease and beta thalassemia are among the most common hereditary blood disorders in the world. It has been shown that patients exhibit less severe symptoms of these disorders when they produce unusually high levels of fetal hemoglobin (HbF). HbF production, which normally shuts off after birth, has been considered as a viable treatment because of inability to form hemoglobin aggregates within red blood cells responsible for painful episodes in patients.

Researchers at the National Institute of Diabetes and Digestive and Kidney Diseases have identified a method of regulating the expression of fetal hemoglobin in adult red blood cells. The lead inventor and colleagues have developed novel expression vectors designed to reactivate production of HbF proteins through increased erythroid-specific expression of Lin28 or decreased expression of Let-7 micro-RNAs. This technology could lead to development of multiple types of therapeutics that ameliorate or eliminate the pathologies associated with human sickle-cell anemia and beta thalassemia.

Potential Commercial Applications: *Ex vivo* and *in vivo* therapeutics for treatment of sickle-cell anemia and beta thalassemias.

Competitive Advantages:

• Amplification of HbF expression 10-fold higher than existing methods.

• Reduced production of symptom-associated adult hemoglobin.

• Regulation of Lin28 and Let-7 expression with no immunogenic effects.

• Potential for viral and non-viral gene delivery.

• Potential for Genome Editing Therapy.

Development Stage:

• Early-stage

• In vitro data available

• In vivo data available (animal)

Inventors: Jeffery L. Miller (NIDDK), Yuanwei T. Lee (NIDDK), Colleen Byrnes (NIDDK), Jaira Vasconcellos (NIDDK), Stefan A. Muljo (NIAID)

Publication: Lee YT, et al. LIN28B-mediated expression of fetal hemoglobin and production of fetal-like erythrocytes from adult human erythroblasts ex vivo. Blood. 2013 Aug 8;122(6):1034-41. [PMID 23798711]

Intellectual Property: HHS Reference No. E-456-2013/2 – International Application No. PCT/US2013/067811 filed 31 Oct 2013

Licensing Contact: Vince Contreras, Ph.D.; 301-435-4711; contrerasv@mail.nih.gov

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