Dated: January 30, 2013.

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Director, National Center for Advancing Translational Sciences, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Advancing Translational Sciences (NCATS) and National Human Genome Research Institute (NHGRI): Cooperative Research and Development Agreement (''CRADA'') and Licensing Opportunity; Non-inhibitory Chaperones of Glucocerebrosidase for Treatment of Gaucher and Other Diseases

SUMMARY: The National Center for Advancing Translational Sciences (NCATS) and the National Human Genome Research Institute (NHGRI), the National Institutes of Health (NIH), are seeking Cooperative Research and Development Agreement (CRADA) partners to collaborate in the final stages of lead optimization, evaluation and preclinical development of a novel selective series of non-inhibitory chaperones of glucocerebrosidase (GCase) for the treatment of Gaucher and other diseases. Interested potential CRADA collaborators will receive detailed information about the project after signing a confidential disclosure agreement (CDA) with NCATS and NHGRI.

DATES: Interested candidate partners must submit a statement of interest and capability to the NCATS point of contact before March 8, 2013 for consideration. Guidelines for the preparation of a full CRADA proposal will be communicated shortly thereafter to all respondents with whom initial confidential discussions have established sufficient mutual interest. CRADA applications submitted after the due date may be considered if a suitable CRADA collaborator has not been identified by NIH among the initial pool of respondents. Licensing of background technology related to this CRADA opportunity is also available to potential collaborators.

ADDRESSES: Questions about licensing opportunities of related background technology should be addressed to Tara L. Kirby, Ph.D., Senior Licensing and Patenting Manager, Office of Technology Transfer, NIH, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804, Telephone: (301) 435–4426; Email: tarak@mail.nih.gov. Respondents interested in licensing will be required to submit an ''Application for License to Public Health Service Inventions.'' An executed CDA will be required to receive copies of the patent applications.

FOR FURTHER INFORMATION CONTACT: Further details of this CRADA opportunity and statement of interest please contact Lili Portilla, M.P.A., Acting Director, Office of Policy, Communications and Strategic Alliances, National Center for Advancing Translational Sciences, NIH, 6701 Democracy Blvd., Suite 900, Bethesda, MD 20892–4874; Telephone (301) 402–0304; E-Mail: Lilip@nih.gov or Dr. Krishnan Balakrishnan, Technology Transfer Manager, NCATS, Telephone: (301) 217–2336; Email: *balakrik@mail.nih.gov.*

SUPPLEMENTARY INFORMATION: NIH seeks to ensure that technologies developed by NIH are expeditiously commercialized and brought to practical use. The purpose of a CRADA is to find a partner to facilitate the development and commercialization of a technology; in this case, small molecule compounds that are early in the development cycle. Respondents interested in submitting a CRADA proposal should be aware that it may be necessary for them to secure a patent license to the patent rights listed below in order to be able to commercialize products arising from a CRADA. CRADA partners are afforded an option to negotiate an exclusive license from the NIH for inventions arising from the performance of the CRADA research plan.

Gaucher disease, the most common form of lipidosis, is a rare genetic lysosomal storage disease characterized by a loss of function in the GCase enzyme, which is responsible for hydrolyzing glucocerebroside (GC) in the lysosome. Phagocytic cells, such as macrophages, microglia (resident macrophages in the brain), and osteoclasts (resident macrophages in the bone) will clean up dead cells by a mechanism named efferocytosis. The macrophages use GCase to break down GC, a major constituent of cell walls. With deficient functional GCase, GC accumulates within the lysosome of resident macrophages, giving rise to lipid-engorged Gaucher cells, a hallmark of the disease. Many mutant forms of GCase are enzymatically active, but they never reach the lysosome after synthesis in the ribosome. Instead, they accumulate in the endoplasmic reticulum (ER) due to failure in their folding process, which eventually triggers ubiquitination and degradation via the proteasome pathway. One therapeutic strategy under consideration is to develop small molecule chaperones that can promote and accelerate the folding process and increase the transport of mutant protein to the lysosome, where it can then process GC. The main challenge in the development of molecular chaperones for Gaucher disease is that chaperones are inhibitors of the enzyme. This complicates their clinical development, because it is difficult to generate an appropriate *in vivo* exposure at which a compound exhibits chaperone activity, but does not inhibit the enzyme's function. Using high throughput screening, several small-molecule series were identified that do not inhibit the enzyme's action, and through medicinal chemistry optimization, these series were further optimized. These lead molecules were found to increase the specific activity of the enzyme, promote the translocation of GCase to the lysosome in Gaucher fibroblasts and macrophages, reduce the accumulated substrate, and restore efferocytosis of these cells. Further analogs are currently being synthesized to address some of the metabolic liabilities of specific series. Because these compounds can modulate the activity and chaperone the translocation of wild-type GCase as well as different GCase mutants, it is also possible that they might find application in additional settings outside of Gaucher disease. For example, clinical studies have recently shown a clear association between GCase mutants and Parkinson disease. Moreover, the compounds could potentially be used to enhance the efficacy of enzyme replacement therapy.

Under the CRADA, further *in vitro* and *in vivo* absorption, distribution, metabolism, and elimination (ADME) and activity studies will be conducted on current and new small molecule leads, using human macrophages differentiated from isolated Gaucher monocytes or Gaucher induced pluripotent stem cells (iPSCs) and in point mutation Gaucher animal models. Based on this and other data, the program will then develop a target product profile. The chemical series will be further improved to address specific aspects of this target product profile and, if necessary, to optimize its physical properties and formulation. The CRADA scope will also include studies beyond candidate selection including all aspects of pre-clinical studies such as toxicity studies and chemistry GMP scale up of select compound(s) and manufacture of

controls leading to a successful investigational new drug (IND) application. Collaborators should have experience in the pre-clinical development of small molecules and a track record of successful submission of IND applications to the FDA for rare and neglected diseases.

The full CRADA proposal should include a capability statement with a detailed description of (1) collaborator's chemistry expertise in the areas of modulation of small molecule physical properties and formulation of small molecules, and its ability to manufacture sufficient quantities of chemical compounds according to FDA guidelines and under Good Manufacturing Practice (GMP); (2) expertise with Gaucher disease and/or expertise with disorders such as Parkinson disease which might benefit from increases in GCase activity; (3) expertise in regulatory affairs, particularly at the IND filing and early clinical trials stages; (4) collaborator's ability to support, directly or through contract mechanisms, and ability, upon the successful completion of relevant milestones, to support the ongoing pharmacokinetics and biological studies, long term toxicity studies, process chemistry and other pre-clinical development studies needed to obtain regulatory approval of a given molecule so as to ensure a high probability of eventual successful commercialization; and, (5) collaborator's ability to provide adequate funding to support some of the project's pre-clinical studies.

Publications:

1. ''A High Throughput Glucocerebrosidase Assay Using the Natural Substrate Glucosylceramide,'' Motobar O, Goldin E, Leister W, Liu K, Southall N, Huang W, Marugan JJ, Sidransky E, Zheng W, *Anal Bioanal Chem,* 402(2), 731–9, 2012.

2. ''A Novel High Throughput Screening Assay for Small Molecule Therapy for Gaucher Disease Using N370S Mutant Glucocerebrosidase from Patient Tissue,'' Goldin E, Zheng W, Motabar O, Southall N, Marugan JJ, Austin CP and Sidransky E, *PLoS One,* 7(1), e29861, 2012

3. Discovery, SAR and Biological evaluation of Non Inhibitory Small Molecule Modulators of Glucocerebrosidase with Chaperone Activity,'' Patnaik, S, Zheng W, Choi J, Motabar O, Southall N, Westbroek W, Lea W, Velayati A, Goldin E, Sidransky E, Leister W, Marugan J, *J. Med. Chem,* 55(12), 5734–48, 2012.

4. ''A non-inhibitory chaperone reverses impaired function and lipid storage in a patient derived-Gaucher macrophage model,'' Aflaki E, Stubblefield B, Maniwang E, Lopez G, Goldin E, Westbroek W, Marugan JJ, Southall N, Patnaik S, Zheng W, Tayebi N, and Sidransky E, *Blood,* Submitted.

5. ''An induced pluripotent stem cell model that recapitulates the pathologic hallmarks of Gaucher disease,'' Panicker LM, Miller D, Park TS, Patel B, Azevedo JL, Awad O, Masood AM, Veenstra TM, Goldin E, Polumuri SK, Vogel SN, Sidransky E, Zambidis ET, Feldman RA, *Proc Nat Acad Sci USA,* 109(44):18054–9, 2012

Background Technology Available for Licensing:

1. ''Salicylic acid derivatives useful as glucocerebrosidase activators,'' Juan Jose Marugan et al., U.S. Provisional Patent Application No. 61/616,758, HHS Ref. No. E–144–2012/0–US–01.

2. ''Salicylic acid derivatives and additional compounds useful as glucocerebrosidase activators,'' Juan Jose Marugan et al., U.S. Provisional Patent Application No. 61/616,773, HHS Ref. No. E–144–2012/1–US–01.

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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.

FOR FURTHER INFORMATION CONTACT: 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:

Mutations in the G Protein Coupled Receptor (GPCR) Gene Family in Melanoma

Description of Technology: Using exon capture and next generation sequencing approaches to analyze the entire G protein coupled receptor (GPCR) gene family in melanoma, the researchers at the NIH have identified several novel somatic (e.g., tumor-specific) alterations. GPCRs play an integral part in regulating physiological functions and the importance of these molecules is evident by the fact that approximately half of the current FDA approved therapeutics target GPCRs or their direct downstream signaling components.

Many of the GPCR gene mutations identified by the NIH researchers were mutated in a large portion of melanoma patients and already have inhibitors, the most notable being the Glutamate Receptor Metabotropic 3 (GRM3) mutation which could be functionally signification for melanoma tumorigenesis. Therefore, this technology could aid in the development of specific inhibitors of GRM3 as well as the pathway it activates, mitogen-activated protein kinase (MEK), for the treatment of melanoma patients with these mutations. To complement these findings, human melanoma metastatic cell lines harboring GRM3 mutations are also available for licensing.

Potential Commercial Applications:

- Diagnostic array for the detection of GRM3 mutations.
- Method of identifying GRM3 inhibitors as therapeutic agents to treat malignant melanoma patients.
- In vitro and in vivo cell model for the GRM3 mutation in melanoma. This is a useful tool for investigating GRM3 phenotype biology, including growth, motility, invasion, and metabolite production.

Competitive Advantages:

- GPCR mutations, GRM3 in particular, are frequent in melanomas.
- Several inhibitors to GPCR and MEK are already in clinical trials, thus this technology may prove useful for the development of novel diagnostic tests and therapeutics.
- Associated cell lines derived from melanoma patients are available.

Development Stage: Pre-clinical.

Inventors: Yardena Samuels (NHGRI), Todd Prickett (NHGRI), and Steven Rosenberg (NCI).

Publication: Prickett TD, et al. Exon capture analysis of G-protein coupled receptors reveals activating mutations in GRM3 in melanoma. Nat Genet. 2011 Sep 25;43(11):1119–26. [PMID 21946352].