

account for and track user fees. MDUFMA requires the submission of the user fees concurrently with applications (21 U.S.C. 379j(a)(2)(C)). If

the required fees are not submitted, the review of the application will not begin. The User Fee Cover Sheet provides the

information necessary to either initiate or defer the application review.

FDA estimates the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN

Form FDA No.	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
3601	5,214	1	5,214	0.30	1,564

Dated: February 1, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-02613 Filed 2-5-13; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2003-N-0453]

Training Program for Regulatory Project Managers; Information Available to Industry

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) is announcing the continuation of the Regulatory Project Management Site Tours and Regulatory Interaction Program (the Site Tours Program). The purpose of this document is to invite pharmaceutical companies interested in participating in this program to contact CDER.

DATES: Pharmaceutical companies may submit proposed agendas to the Agency by April 8, 2013.

FOR FURTHER INFORMATION CONTACT: Dan Brum, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 4160, Silver Spring, MD 20993-0002, 301-796-0578, dan.brum@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

An important part of CDER's commitment to make safe and effective drugs available to all Americans is optimizing the efficiency and quality of the drug review process. To support this primary goal, CDER has initiated various training and development programs to promote high performance in its regulatory project management

staff. CDER seeks to significantly enhance review efficiency and review quality by providing the staff with a better understanding of the pharmaceutical industry and its operations. To this end, CDER is continuing its training program to give regulatory project managers the opportunity to tour pharmaceutical facilities. The goals are to provide the following: (1) Firsthand exposure to industry's drug development processes and (2) a venue for sharing information about project management procedures (but not drug-specific information) with industry representatives.

II. The Site Tours Program

In this program, over a 2- to 3-day period, small groups (five or less) of regulatory project managers, including a senior level regulatory project manager, can observe operations of pharmaceutical manufacturing and/or packaging facilities, pathology/toxicology laboratories, and regulatory affairs operations. Neither this tour nor any part of the program is intended as a mechanism to inspect, assess, judge, or perform a regulatory function, but is meant rather to improve mutual understanding and to provide an avenue for open dialogue. During the Site Tours Program, regulatory project managers will also participate in daily workshops with their industry counterparts, focusing on selective regulatory issues important to both CDER staff and industry. The primary objective of the daily workshops is to learn about the team approach to drug development, including drug discovery, preclinical evaluation, tracking mechanisms, and regulatory submission operations. The overall benefit to regulatory project managers will be exposure to project management, team techniques, and processes employed by the pharmaceutical industry. By participating in this program, the regulatory project manager will grow professionally by gaining a better understanding of industry processes and procedures.

III. Site Selection

All travel expenses associated with the site tours will be the responsibility of CDER; therefore, selection will be based on the availability of funds and resources for each fiscal year. Selection will also be based on firms having a favorable facility status as determined by FDA's Office of Regulatory Affairs District Offices in the firms' respective regions. Firms interested in offering a site tour or learning more about this training opportunity should respond by submitting a proposed agenda to Dan Brum (see **DATES** and **FOR FURTHER INFORMATION CONTACT**).

Dated: January 31, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-02523 Filed 2-5-13; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Advancing Translational Sciences (NCATS): Cooperative Research and Development Agreement (CRADA) and Licensing Opportunity for Small Molecule Agonists of the Relaxin Hormone Receptor (RXFP1) for Treatment of Heart Failure and Fibrosis

SUMMARY: The National Center for Advancing Translational Sciences (NCATS), the National Institutes of Health (NIH), is seeking Cooperative Research and Development Agreement (CRADA) partners to collaborate in the final stages of lead optimization, in vitro and in vivo evaluation, and preclinical development of a novel series of potent, selective, and orally bioavailable small molecule agonists of the relaxin hormone receptor, RXFP1, for the treatment of heart failure and fibrosis. Interested potential CRADA collaborators will receive detailed information on the current status of the project after signing a confidentiality

disclosure agreement (CDA) with NCATS.

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 will 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 Lauren Nguyen-Antczak, Ph.D., Licensing and Patenting Manager, Office of Technology Transfer, NIH, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804, Telephone: (301) 435–4074; Email: lauren.nguyen-antczak@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 or small molecule compounds that are in an early phase of development. Respondents interested in submitting a CRADA proposal should be aware that it may be necessary for them to secure a patent license to the above-mentioned patent 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.

Recombinant relaxin hormone has been extensively investigated for the treatment of acute heart failure and is currently in phase III clinical trials for this indication. Related to its antifibrotic role in pregnancy, relaxin appears to be unique in promoting the active remodeling of heart lesions. However, this remodeling capacity of the natural hormone is difficult to study in chronic settings due to the short half-life and the need for intravenous administration of the recombinant hormone. The clinically observed physiological effects of relaxin are mediated through its interaction with a G protein-coupled receptor (RXFP1) leading to the modulation of several signal transduction pathways. Activation of RXFP1 by relaxin induces (1) up-regulation of the endothelin system which leads to vasodilation; (2) extracellular matrix remodeling through regulation of collagen deposition, MMPs and TIMPs expression, and overall tissue homeostasis; (3) a moderation of inflammation by reducing levels of inflammatory cytokines, such as TNF- β and TGF- β ; and, (4) angiogenesis by activating transcription of VEGF. The development of small-molecule agonists of RXFP1 would have numerous benefits and will allow investigating additional therapeutic applications where chronic administration is required. NCATS has identified a series of small-molecule agonists of RXFP1 which are potent, highly selective, easy to synthesize, and with reasonable metabolic and physical properties. Our molecules display similar efficacy as the natural hormone in several functional assays. Mutagenesis studies have mapped the specific regions responsible for relaxin receptor activation by these compounds to an allosteric site on the receptor. Finally, these compounds display good *in vivo* pharmacokinetic properties and are currently being evaluated *in vivo*.

Under the CRADA, further *in vitro* and *in vivo* ADME and activity studies will be conducted on current and new small molecule leads, using rodent and non-rodent species. Pharmacokinetics and PEP image studies in monkey are on-going to better characterize compound tissue distribution. But further *in vivo* characterization of select compounds is needed and will be part of the CRADA program. Based on the results of these experiments and other data, the program will then develop a target product profile. The chemical series might 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 IND application. Collaborators should have experience in the pre-clinical development of small molecules and with the successful submission of IND applications to the FDA for cardiovascular and/or fibrotic diseases.

The full CRADA proposal should include a capability statement with a detailed description of (1) Collaborators' chemistry expertise in the area of modulation of small molecule physical properties and formulation of small molecules, and their ability to manufacture sufficient quantities of chemical compounds according to FDA guidelines and under GMP; (2) expertise with cardiovascular and/or fibrotic diseases; (3) expertise in regulatory affairs, particularly at the IND filing and early stage clinical trials stages; (4) collaborator's ability to support, directly or through contract mechanisms, and upon the successful completion of relevant milestones, 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 pre-clinical studies of the project.

Publications

1. “Identification of small molecule agonists of the relaxin 1 receptor by utilizing a homogenous cell-based cAMP assay,” Chen CZ, Southall N, Xiao J, Marugan JJ, Ferrer M, Agoulnik A, Zheng W, *Journal Biomolecular Screening*, Accepted.

2. Identification and optimization of small molecule agonists of the relaxin hormone receptor RXFP1,” Xiao J, Chen CZ, Huang Z, Agoulnik IU, Ferrer M, Southall N, Hu X, Zheng W, Agoulnik AI, and Marugan JJ, *Nature-Communications*, Submitted.

Patent Status:

“Modulators of the Relaxin receptor 1”, Marugan JJ, Xiao J, Ferrer M, Chen CZ, Southall N, Zheng W, Agoulnik A, Agoulnik IU, U.S. Patent Application # 61/642,986, NIH Reference # E-072–2012/0-US-1.

Dated: January 30, 2013.

Christopher P. Austin,
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