[Billing Code: 4140-01-P]

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.

DATE: Interested candidate partners must submit a statement of interest and capability to the NCATS point of contact before [Insert Due DATE as 30 days after published in FR] 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; E-mail: 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 CONACT: 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.

January 30, 2013

Date

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

[FR Doc. 2013-02611 Filed 02/05/2013 at 8:45 am; Publication Date: 02/06/2013]