



[Billing Code 4140-01-P]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Aging (NIA), National Institute of Mental Health (NIMH), and National Center for Advancing Translational Sciences (NCATS): Cooperative Research and Development Agreement (CRADA) and Licensing Opportunity for Ketamine for the Treatment of Depression and Other Anxiety-Related Disorders.

AGENCY: National Institutes of Health

ACTION: Notice.

SUMMARY: The National Institute of Aging (NIA), National Institute of Mental Health (NIMH), and National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH), University of Maryland at Baltimore (UMB) and their collaborators are seeking Cooperative Research and Development Agreement (CRADA) partners to collaborate in the preclinical and clinical development of ketamine metabolite (2R, 6R-HNK) for the treatment of depression and other anxiety-related disorders.

DATES: Interested candidate partners must submit a statement of interest and capability, no more than five pages long, to the NCATS point of contact before [INSERT

DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]
for consideration.

FOR FUTURE INFORMATION CONTACT: Information on licensing and co-development research collaborations, and copies of the U.S. patent applications listed below may be obtained by contacting: Attn: Sury Vepa, Ph.D., J.D., Senior Licensing and Patenting Manager, National Center for Advancing Translational Sciences, NIH, 9800 Medical Center Drive, Rockville, MD 20850, Phone: 301-217-9197, Fax: 301-217-5736, or email NCATSPartnerships@mail.nih.gov. A signed Confidential Disclosure Agreement may be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: As per the Anxiety and Depression Association of the America, Major depressive disorder affects 14.8 million people in America, including children, adults, and the elderly. A number of therapies currently exist to treat depression, although they suffer drawbacks such as requiring weeks to take action. One particular therapy includes the approved drug, ketamine, which has demonstrated robust and acute antidepressant activity. However, its efficacy is bridled with significant disadvantages including its addictive potential and its dissociative activities. This is the case even when administered at low doses, which limits the potential widespread use of ketamine as an antidepressant medication.

In order to improve the treatment of depression, it is important to explore the mechanism by which ketamine exerts its antidepressant effects. That is precisely what the NIH and UMB scientists and collaborators are investigating, and have found that the

metabolism of ketamine is critical to its antidepressant effects, and that the (2R,6R)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone ((2R,6R)-hydroxynorketamine (HNK)) metabolite, reversed depression-like behaviors in mice without triggering anesthetic, dissociative, or addictive side effects associated with ketamine. Specifically, the researchers found that the metabolite does not inhibit the non-competitive glutamatergic N-methyl-D-aspartate (NMDA) receptor, and it exerts rapid actions that activate the α -amino 3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Results indicate a non-NMDA receptor dependent mechanism underlying ketamine's antidepressant properties, which involve bioactivity of a specific metabolite (2R, 6R-HNK) could be exploited for drug development. Additionally, the researchers have established appropriate salt, crystal and polymorph forms of the agent and multiple methods of synthesis. Full ADME and polypharmacology assessment is complete as well as pre-formulations studies.

To expedite the research, development and commercialization of 2R,6R-hydroxynorketamine (a metabolite of ketamine), the National Institutes of Health, UMB and their collaborators are seeking one or more CRADA and/or license agreements with appropriate pharmaceutical or biotechnology companies in accordance with the regulations governing the transfer of Government-developed technology and its public sector objectives, as outlined below. The purpose of a CRADA is to find a partner to collaborate in the development and commercialization of a technology that is in early phases of clinical development. Under the CRADA, key activities related to the clinical development of 2R,6R-HNK as a therapeutic to treat a variety of mental health conditions including depressive disorders will be performed. Collaborators should have proven

experience in drug development with specialized expertise within depression and/or related mental health disorders. Owing to NIH's commitment to public dissemination of data, a key criterion will be that all outcomes from the collaborative effort will be published including the outcomes of all clinical trials. Further, it is the goal of NIH, UMB and other collaborators to develop the technology to the fullest extent (as therapeutic for multiple clinical indications including, but not limited to, anxiety, suicidal ideation, anhedonia, PTSD, addiction, neuropathic pain, among others).

How to Apply: Interested potential CRADA collaborators will receive detailed information on the current status of the project after signing a confidentiality disclosure agreement (CDA) with NIH, UMB and other collaborators. Interested candidate partners must submit a statement of interest and capability, no more than five pages long, to the NCATS point of contact before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER] for consideration. Guidelines for the preparation of a full CRADA proposal will be communicated by the NIH to respondents that have demonstrated sufficient mutual interests and capabilities that indicate the partnering entity will appropriately and substantially contribute to the proposed collaboration. Capability statements submitted after the due date may be considered if a suitable CRADA collaborator has not been identified by NIH and UMB among the initial pool of respondents.

Respondents interested in submitting a CRADA proposal should be aware that it may be necessary for them to secure a patent license to the background-patent applications in order to commercialize products arising from a CRADA. Licensing of background technology patent rights related to this CRADA opportunity and claimed in

the pending patent applications are available for either exclusive or non-exclusive licensing and licensing by NIH is subject to 35 U.S.C. 207 and 37 CFR Part 404.

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.

The full CRADA proposal should include a capability statement with a detailed description of: (1) Collaborator's Expertise with mental health disorders such as depression, (2) Collaborators' expertise in preclinical development efforts including toxicology and chemistry, manufacturing and controls (CMC), (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 therapy 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 as well as clinical trials.

Publications:

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Manickavasagom A, Yuan P, Pribut HJ, Singh NS, Dossou KSS, Fang Y, Huang X-P, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA, Gould TD. NMDA receptor inhibition-independent antidepressant actions of a ketamine metabolite. *Nature*, May 4, 2016, doi: 10:1038/nature17998.

Patent Status:

- 1) “Use Of (2R,6R)-HNK, (S)-Dehydronorketamine and (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain”; Irving W. Wainer, Ruin Moaddel, Michel Bernier, Carlos A. Zarate, Mary Tanga, Marc C. Torjman, Michael Goldberg; Assignees: National Institute of Aging (NIA), National Institute of Mental Health (NIMH), SRI International, University of Medicine and Dentistry of New Jersey (UMDNJ); U.S. Provisional Patent Application # 61/547,336; Filed: October 14, 2011; NIH Reference # E-092-2011.
- 2) “Methods of using (2S,6S)-HNK and (2R,6R)-HNK to treat various depressive disorders and anxiety disorders”; Craig Thomas, Todd D. Gould, Irving W. Wainer, Carlos A. Zarate, Ruin Moaddel, Patrick Morris, Panos Zanos; Assignees: National Institute of Aging (NIA), National Institute of Mental Health (NIMH), National Center for Advancing Translational Sciences (NCATS), University of Maryland at Baltimore(UMB); U.S. Provisional Patent Application # 62/313317; Filed: March 25, 2016; NIH Reference #E-036-2016.

3) “Crystal forms and methods of synthesis of (2R, 6R)-HNK and (2S,6S)-HNK”;
Craig Thomas, Patrick Morris, Carlos A. Zarate, Ruin Moaddel, Todd D. Gould,
Panos Zanos; Assignees: National Center for Advancing Translational Sciences
(NCATS), National Institute of Mental Health (NIMH), National Institute of
Aging (NIA), University of Maryland at Baltimore (UMB); U.S. Provisional
Patent Application #62/313309; Filed: March 25, 2016; NIH Reference #E-116-
2016.

Dated: October 31, 2016

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Deputy Director

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