DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute (NHLBI); Opportunity for a Cooperative Research and Development Agreement (CRADA) To Identify Small Molecule Inhibitors of Human Macrophage Cholesterol Accumulation for Therapy of Atherosclerotic Cardiovascular Diseases

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: Macrophage cholesterol accumulation in blood vessels leads to the development of atherosclerotic plaques, the cause of most heart attacks and strokes. Recently, research from Dr. Howard Kruth, head of the Experimental Atherosclerosis Section of NHLBI has elucidated a novel mechanism of receptor-independent macrophage cholesterol accumulation[1,2]. In this pathway, human macrophages take up low-density lipoprotein (LDL), the main carrier of blood cholesterol, by fluid-phase endocytosis, an uptake pathway that can be activated in macrophages. Activated macrophages show greatly stimulated uptake of fluid and LDL contained in the fluid through macropinocytosis, a fluid-phase endocytic uptake pathway unique to macrophages. This mechanism of LDL uptake and macrophage cholesterol accumulation does not depend on binding of LDL to receptors. Macrophage macropinocytosis of LDL produces levels of cholesterol accumulation similar to that observed for macrophages isolated from atherosclerotic plaques, something that does not occur when human macrophages take up LDL by receptor-mediated mechanisms in these macrophages.

The NHLBI is seeking CRADA collaborators to work with investigators in the Experimental Atherosclerosis Section of NHLBI to identify inhibitors of this cholesterol uptake pathway. The collaborator will provide high throughput screening capabilities coupled with small molecule and/or siRNA libraries of test compounds, or other methodologies to identify potential inhibitors of this pathway. A cell-based screening assay that will have predictive value with human macrophages will be developed jointly by the NHLBI investigators and the collaborator based on published and unpublished research findings of the NHLBI investigators. The goal of this collaboration will be to identify compounds that selectively inhibit macrophage macropinocytosis and consequently macrophage uptake of LDL and cholesterol accumulation. Compounds identified will be further tested in a suitable animal model of atherosclerosis to determine their effect on macrophage cholesterol accumulation and atherosclerotic plaque development. Macropinocytosis also mediates entry of microorganisms such as HIV into macrophages. Thus, discovery of macropinocytosis inhibitors may be relevant not only to atherosclerosis treatment but also to certain infectious disease treatments.

References

1. Kruth, H.S., Huang, W., Ishii, I., and Zhang, W.Y.: Macrophage foam cell formation with native low density lipoprotein. J. Biol. Chem. 277:34573–34580, 2002.

2. Kruth, H.S., Jones, N.L., Huang, W., Zhao, B., Ishii, I., Chang, J., Combs, C.A. Malide, D., and Zhang, W.Y.: Macropinocytosis is the endocytic pathway that mediates macrophage foam cell formation with native LDL. J. Biol. Chem. 280:2352–2360, 2005.

Contact: Inquiries concerning this CRADA opportunity should be directed to Ms. Peg Koelble, Technology Transfer Specialist, Office of Technology Transfer and Development, NHLBI, NIH; 6705 Rockledge Drive, Suite 6018, MSC 7992; Bethesda, Maryland 20892–7992, Telephone: 301–594–4095; Fax: 301–594–3080; E-mail: *Koelblep@nhlbi.nih.gov.* Inquires must be received no later than 60 days after March 22, 2005.

Dated: March 11, 2005.

Dr. Carl Roth,

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Agency Information Collection Activities: Submission for OMB Review; Comment Request

Periodically, the Substance Abuse and Mental Health Services Administration (SAMHSA) will publish a summary of information collection requests under OMB review, in compliance with the Paperwork Reduction Act (44 U.S.C. Chapter 35). To request a copy of these documents, call the SAMHSA Reports Clearance Officer on (240) 276–1243.

Government Performance and Results Act Client/Participant Outcome (OMB No. 0930–0208)—Revision

The mission of SAMHSA is to improve the effectiveness and efficiency of substance abuse and mental health treatment and prevention services across the United States. All of SAMHSA's activities are designed to ultimately reduce the gap in the availability of substance abuse and mental health services and to improve their effectiveness and efficiency.

Data currently are collected from all SAMHSA best practices and targeted capacity expansion grants and contracts where client outcomes are to be assessed at intake (or initial contact), 6 and 12 months post admission or post-intervention. SAMHSA-funded projects are required to submit these data as a contingency of their award. The analysis of the data will also help determine whether the goal of reducing health and social costs of drug use to the public is being achieved.

The primary purpose of this data collection activity is to meet the reporting requirements of the Government Performance and Results Act (GPRA) by allowing SAMHSA to quantify the effects and accomplishments of SAMHSA programs. In addition, the data will be useful in addressing goals and objectives outlined in ONDCP's *Performance Measures of Effectiveness.* The revision of this data collection affects only the Center for Substance Abuse Treatment (CSAT). The proposed revision will modify the CSAT services instrument to include new questions on family characteristics, specific services and social connectedness to align with the SAMHSA Administrator's seven domains for national outcomes measures. In addition, the data collection time points will change to intake, discharge, and 6 months post admission.

The following is the estimated annual response burden for this collection.