4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-0012]

Linking Marketplace Heparin Product Attributes and Manufacturing Processes to Bioactivity and Immunogenicity

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of grant funds for the support of a sole source award to the University of North Carolina. The goal of the award is to identify what component(s) of the complex heparin mixtures have the propensity to cause heparin induced thrombocytopenia (HIT) to improve the safety of heparin drug products. The FDA seeks to identify the components of the heparin mixture that are associated with HIT so that actions may be taken to reduce these events and improve patient outcomes with this widely used drug.

DATES: Important dates are as follows:

1. The application due date is July 15, 2013.
2. The anticipated start date is August, 2013.
3. The opening date is the date this announcement is published in the Federal Register.
4. The expiration date is July 16, 2013.

ADDRESSES: Submit the paper application to: Gladys Melendez at the Food and Drug Administration, Grants Management (HFA-500), 5630 Fishers Lane, Rockville, MD 20857. For

more information, see section III of the SUPPLEMENTARY INFORMATION section of this notice.

FOR FURTHER INFORMATION CONTACT: David Keire, Center for Drug Evaluation and Research, Food and Drug Administration, 1114 Market St., rm. 1002, St Louis, MO, 63130, 314-539-3850; or Gladys Melendez, Office of Acquisition Support and Grant Services, Food and Drug Administration, 5630 Fishers Lane, Rockville, MD 20857, 301-827-7175, email: Gladys.bohler@fda.hhs.gov.

For more information on this funding opportunity announcement (FOA) and to obtain detailed requirements, please contact Gladys.bohler @fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Funding Opportunity Description

Request for Application: FDA RFA-13-007

Catalog of Federal Domestic Assistance: 93.103]

A. Background

The goal of this Research Project is to identify which components of heparin drug mixtures have the propensity to cause heparin induced thrombocytopenia (HIT) in order to improve the safety profile of this widely used anticoagulant. Heparin is a heterogeneous mixture of polysaccharides of varying length, sulfation pattern, acylation and conformation that has been in clinical use since the 1930s. HIT is a drug-dependent immune disorder caused by antibodies to complexes formed between platelet factor 4 (PF4) and heparin which can occur in patients who undergo major trauma (e.g. broken bones and cardiovascular surgery) and receive heparin. The condition leads to formation of abnormal blood clots and concomitant complications associated with clots. PF4-heparin antibodies are observed in all patients with HIT. In addition,

low molecular weight heparins or the synthetic pentasaccharide (fondaparinux) have also been shown to cause HIT antibody formation although these smaller chain length heparins are much less likely to lead to clinical HIT symptoms.

The major limitation in the available reagents for studies aimed at identifying the components of heparin that lead to the pathogenesis of HIT is the lack of pure component heparin standards. Therefore, this collaboration brings together the following capabilities and laboratories: 1) synthesis of heparin chains of the same length, sulfation pattern and conformation (Dr. Liu at the University of North Carolina and Dr. Linhardt at Rensselaer Polytechnical Institute), 2) synthesis and physicochemical characterization of heparin and heparin-PF4 complexes (Keire FDA/DPA St Louis) and 3) a HIT-immunogenicity animal model (Dr. Arepally at Duke University). FDA believes that this combination of skills and expertise has the potential to make pure standards, fully characterize the standards, create and characterize PF4-heparin standard aggregates and assess their propensity to elicit an immune response in an animal model. This research is unique and not otherwise available. The ability to make pure heparin standards in gram quantities and fully characterize their properties is only available from the Liu and Linhardt laboratories. Furthermore, Dr. Arepally's mouse model of HIT immunogenicity is not available in any other laboratory. When completed the study will identify heparin components that enhance HIT propensity and which could potentially be minimized in heparin manufacturing, leading to safer heparin drugs with better patient outcomes.

B. Research Objectives

The research objective is to identify the components of the heparin mixture that have the propensity to lead to HIT pathogenesis.

C. Eligibility Information

This is a sole source RFA because the investigators identified in this document have unique skills and expertise necessary to perform the proposed work.

II. Award Information/Funds Available

A. Award Amount

Only one award will be available to the University of North Carolina in the amount of $250,000 (Total Cost) in the first year.

B. Length of Support

Depending on research progress and subject to the availability of funds additional funds may be awarded under this grant for up to a five year project period reflecting $250,000 Total Cost per year.

III. Paper Application, Registration, and Submission Information

To submit a paper application in response to this FOA, applicants should first review the full announcement. Persons interested in applying for a grant may obtain an application at http://grants.nih.gov/grants/forms.htm

For all paper application submissions, the following steps are required:

- Step 1: Obtain a Dun and Bradstreet (DUNS) Number
- Step 2: Register With Central Contractor Registration
- Step 3: Register With Electronic Research Administration (eRA) Commons

Steps 1 and 2, in detail, can be found at http://www07.grants.gov/applicants/organization_registration.jsp. Step 3, in detail, can be found at https://commons.era.nih.gov/commons/registration/registrationInstructions.jsp. After you have followed these steps, submit paper applications to: Gladys Melendez; Grants Management, Food and Drug Administration, 5630 Fishers Lane, rm. 2032; HFA-500; Rockville, MD 20857.

Dated: June 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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