Request for Proposals: Mouse Drug Testing Facility for Myotonic Dystrophy

Solicitation Name: 2018-MDF Mouse Drug Testing Facility for DM
Contracting Office Address:

Myotonic Dystrophy Foundation
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Contracting Officer: Elizabeth J. Ackermann, Ph.D., Chief Science Officer, MDF
Place of Performance: United States or Canada
Date Issued: March 12, 2018
Proposals Due: May 7, 2018, 5:00 PM PT
Notification of Selection: July 1, 2018
Period of Award: 1 year
Number of Awards: 1
Amount: Not to exceed $200,000.00

Synopsis:

The Myotonic Dystrophy Foundation (MDF) is pleased to announce a Request for Proposals to establish a mouse drug testing facility for myotonic dystrophy type 1 (DM1). MDF intends to support the establishment of a contract-based testing facility by funding activities necessary to set up efficacy testing in the HSA-LR model of DM1 (Mankodi et al., 2000). The facility would then operate under contracts from drug developers and academics to ensure independent and rigorous testing of candidate therapeutics.

MDF, based in San Francisco, CA, is the world's largest patient organization focused solely on myotonic dystrophy (DM). In addition to comprehensive patient support and advocacy work, the Foundation focuses on improving quality of life for those with the disease and advancing the basic and clinical science searching for a cure for DM. MDF partners with, and complements the work of, The Wyck Foundation, the National Institutes of Health (NIH), the Centers for Disease Control and Prevention, and other governmental, advocacy, academic, and philanthropic organizations.

Background:

Myotonic dystrophy is an autosomal dominant, variable, multi-systemic repeat expansion disorder characterized by muscle weakness, fatigue, myotonia, cataracts, cardiac conduction defects and endocrine and gut motility dysfunction. The two forms, DM1 and DM2, are caused by expansions in two unrelated genes, which result in different, but related clinical phenotypes. DM1 is generally more severe and has a very severe congenital form and a juvenile form, while DM2 is usually milder and adult onset. Only palliative therapies are currently available for this progressive and life-threatening disease although there has been increasing industry engagement in DM and multiple experimental treatments are progressing to the clinical testing stage.

Candidate therapeutics require rigorous and thorough efficacy and safety testing in preclinical models prior to identifying the lead candidate and transitioning to clinical evaluation in human subjects. While testing in disease-relevant animal models is not always predictive of clinical success, such testing has been important in developing adequate scientific rationale for both the molecular target and the candidate therapeutic. A key issue in optimization of the predictive value of these studies has been the availability of facilities for independent, unbiased, and rigorous, yet expeditious, animal efficacy testing.

The National Institutes of Health has taken steps to advance rigor and reproducibility in scientific research (Landis et al., 2012; see also: https://www.nih.gov/research-training/rigor-reproducibility/)—many, if not all, of these steps are directly relevant to improving the predictability of animal efficacy testing studies. To ensure that candidate therapeutics that move into clinical evaluation for DM1 have the strongest scientific rationale possible, it is essential that the mouse efficacy testing be done in a rigorous and unbiased manner.

This RFP will provide funding to develop a mouse drug testing facility for DM. The successful applicant is expected to establish standard operating procedures for a specified battery of endpoint measures including determination of mean, variability and potentially timecourse. The overall goal is to ensure readiness of a facility to take on drug efficacy testing contracts from pharmaceutical and biotechnology companies and academic drug developers.

Study Requirements:

Scope: This Request for Proposals is designed to support the implementation of a battery of endpoint measures in blinded, controlled studies that will allow evaluation of efficacy of candidate therapeutics (drugs and biologics) in the HSA-LR mouse (Mankodi et al., 2000) or other model selected in discussion with MDF.

- Endpoint measures to be included are:
    - Panel of approximately 10 splicing events known to correlate with muscle weakness
    - Quantitation of CUGexp RNA in skeletal muscle (RT-qPCR)
    - Detection of RNA foci in skeletal muscle (fluorescence in situ hybridization)
    - Quantitation of Muscleblind (MBNL) protein levels
    - Evaluation of myotonia (in hindlimb and paraspinal, by EMG)
    - Evaluation of histology-quantitation of centralized nuclei in skeletal muscle

    - Evaluation of histology-quantitation of skeletal muscle fiber cross sectional area and fiber size variability (automated imaging)
    - Quantitation of muscle weight
    - Functional studies:
        - Grip strength (grip strength digital dynamometer)
    - Appropriate summary statistics in place for each endpoint
- Development of standard operating procedures (SOPs) for each endpoint measures through interactions with key DM investigators and the MDF and publication of the SOPs on both the contractors and MDF websites
- Publication on the contractors website of the availability of DM1 mouse efficacy testing

Eligibility:

Proposals are welcome from industry, academic institutions, government agencies and/or multidisciplinary teams encompassing several organizations. Submitting organizations or teams must meet the following requirements:

- Organizations or teams must have access to the knowledge, resources and skills necessary to carry out the proposed research;
- The lead investigator must hold a Doctor of Medicine, Doctor of Philosophy, Doctor of Science or equivalent degree;
- Proposals that are incomplete will be excluded from the process, unless evidence is provided of other, external funds to support the proposed budget; and
- The study organization or team must confirm that the funds awarded will only be used to execute the study; indirect costs and overhead charges will not be funded or allowed through this study award.

Submission Process and Requirements:

Proposals must adhere to the page limits listed below and must be submitted in 12-point font. Proposals must be submitted as a single PDF file (including signed cover page) via email, using the subject line "2018-MDF Mouse Drug Testing Facility for DM," to Elizabeth.Habeeb-Louks@myotonic.org by May 7, 2018, 5 PM Pacific time.

The proposal must include the following:

A. Proposal (not to exceed a total of 15 pages)

1. Brief lay abstract (not to exceed a paragraph)
2. Technical abstract
3. Outline of plan for the mouse drug testing facility
4. Documentation of experience/capability to implement a mouse drug testing facility
5. Detailed action plan for identification and implementation of standard operating procedures and conduct of endpoint measure power analysis studies
6. Environment (description of facilities and equipment)
7. Timeline
8. References

B. Personnel (not included in the 15-page count)

1. Listing of names, degrees, role in project, and percentage effort for key team members (1 page)
2. Biographical sketch for each key team member (maximum of 5 pages each, preferably in NIH format)
3. Institutional Animal Care and Use (or equivalent) approval
4. Letters of support (if applicable)

C. Budget and Face Page (not included in the 15-page count)

1. Detailed budget in spreadsheet or table format
2. Accompanying budget description and justification
3. Face page provided by MDF (see attached)

Applicants are encouraged to contact the MDF Chief Science Officer, Dr. Elizabeth Ackermann (elizabeth.ackermann@myotonic.org), with any questions about this RFP or the scientific content of their proposals. Technical issues should be directed to MDF Grants Manager Elizabeth Habeeb-Louks at elizabeth.habeeb-louks@myotonic.org.

Review and Selection Process:

All proposals must be received by the submission deadline and in compliance with the eligibility criteria provided above. Eligible proposals will be peer-reviewed by an ad hoc committee of subject matter experts put together by MDF.

Proposals will be evaluated based on the following criteria:

- Ability of applicant to complete the project and launch a contract facility for mouse drug efficacy testing, including adequacy of resources available, prior experience/expertise, reasonableness of timelines, qualifications of identified study team members and scientific rigor and validity of proposed methods;
- Ability to conduct unbiased, independent, and rigorous mouse efficacy studies for candidate drugs and biologics;
- Potential for applicant to make drug testing services widely available to meet community needs in a timely manner;
- Appropriateness of project budget to project scope; and
- Qualifications of team leadership/principal investigator including previous history of work in the area and successful completion of previous projects.

Other Conditions of Award:

- Recipient must provide approval from their Institutional Animal Care and Use Committee (IACUC) or equivalent before grant funds will be released;
- Upon project completion, the recipient will provide MDF with documentation of endpoint measure SOPs and the data underlying summary statistics for each endpoint; and
- Upon project completion, recipient will undertake a publicity campaign to highlight availability of the mouse drug testing facility in conjunction with the MDF.

Progress Reports:

The recipient must submit regular updates and a final progress report to MDF. Scheduling to be established in the contract.

Expense Reports:

Each recipient must submit an expense report to MDF and the end of the contract period.

Timeline:

Proposals Due: May 7, 2018, 5:00 PM PT
Notification of Selection: July 1, 2018
Period of Award (dependent upon completion of contracting process): September 1, 2018 – August 31, 2019

References:

Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, Crystal RG, Darnell RB, Ferrante RJ, Fillit H, Finkelstein R, Fisher M, Gendelman HE, Golub RM, Goudreau JL, Gross RA, Gubitz AK, Hesterlee SE, Howells DW, Huguenard J, Kelner K, Koroshetz W, Krainc D, Lazic SE, Levine MS, Macleod MR, McCall JM, Moxley RT 3rd, Narasimhan K, Noble LJ, Perrin S, Porter JD, Steward O, Unger E, Utz U, Silberberg SD. A call for transparent reporting to optimize the predictive value of preclinical research. Nature. 2012 Oct 11;490(7419):187-91. doi: 10.1038/nature11556

Mankodi A, Logigian E, Callahan L, McClain C, White R, Henderson D, Krym M, Thornton CA. Myotonic Dystrophy in Transgenic Mice Expressing an Expanded CUG Repeat. Science. 2000; 289; 1769-1772