Request for Applications: Development of a Genome Editing Strategy for Myotonic Dystrophy Type 1

Solicitation Name: 2018-MDF Genome Editing for Myotonic Dystrophy
Contracting Office Address:

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Date Issued: 24-July-2018
Applications Due: 30-Nov-2018
Notification of Selection: 28-Jan-2019
Period of Award: 2 years
Anticipated overall award: up to $250,000 per award for a total not to exceed $500,000
Number of awards to be issued: up to two

Synopsis

Through this Request for Applications (RFA), the Myotonic Dystrophy Foundation (MDF) recognizes a need to advance genome editing technology and evaluate its potential as a candidate therapy for use in myotonic dystrophy type 1 (DM1). MDF intends to issue up to two 2-year awards of up to $250,000 total cost for projects that address the evaluation of genome editing strategies, means of delivery, specificity, efficiency, functionality, and safety for *in vivo* treatment of DM1.

Although gene editing technologies are rapidly evolving, significant hurdles remain for *in vivo* clinical testing of genome editing reagents. Many of these hurdles are not specific to any one disease. Thus, bold and innovative approaches to advance genome editing platforms are needed in order to develop fundamentally new ways to treat DM1.

This RFA is based in part upon expertise on: (a) the state-of-the-art for genome editing and (b) the development of a genome editing initiative for DM1 in a workshop convened by MDF. A summary of that expert advice is listed in Important References and Resources below. Applicants are encouraged to review this information in preparing applications for the RFA.

Collaborations between experts in genome editing technologies and those with strong track records in myotonic dystrophy research are strongly encouraged.

Goal

The focus of this RFA is on early stage discovery and development of *in vivo* genome editing technologies in academic laboratories or other nonprofit research institutions, utilizing state-of-the-art

knowledge. This solicitation is strategy, platform and delivery vehicle agnostic, as MDF seeks the best path forward to identify optimal tools and processes to develop a therapy for DM1. The goal is to establish a proof of concept for a therapeutic that is not incremental, but has a substantial level of effect across the multiple body systems impacted by the DM1 disease. Developing and testing improvements in current gene editing technology will be needed to achieve the goal of an effective *in vivo* therapy for DM1. Grantees will be selected through a competitive application peer reviewed process. At the end of the award period, there is the potential that additional funding may be available through MDF.

Background

DM Overview:

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. Currently, there are no approved therapies, only palliative therapies are available for this progressive and life-threatening disease.

DM1 is caused by an expansion of a CTG trinucleotide repeat in the 3'-untranslated region of *DMPK*. Beyond a threshold length (approximately >50 repeats), the expanded CUG RNA repeat sequence forms hairpin structures that act to sequester MBNL proteins. Since MBNL is a key regulator of alternative splicing, much of the pathogenesis of DM1 can be linked to mis-splicing. There are, however, other downstream consequences of the expanded repeat, including effects on other splicing regulators and triggering of RAN translation, some of which are not fully understood at this time. The CTG repeat is also located in the promoter/enhancer of the downstream *SIX5* gene in a very gene dense region of chromosome 19. Repeat expansion can lead to epigenetic changes that impact expression of *SIX5* and this may have some additional impact on disease severity.

Longer CTG repeats result in earlier age of onset and more severe form of the disease. The expanded CTG repeats are highly unstable in both the germ line and soma, with a strong bias toward expansion. Intergenerational expansions explain the striking anticipation of 20 to 30 years per generation frequently observed in DM1 families. Somatic expansions of the CTG repeats are often very large (>3,000 repeats) and contribute toward the tissue specificity and progressive nature of the symptoms. Several features of the *DMPK* locus are relevant to applying genome editing strategies for DM1. These include: near homogeneity of CTG expansions (approximately 90 to 95% of patients have pure CTG expansion tracts); high density of genes in the *DMPK* locus on chromosome 19; very low degree of SNPs in the immediate vicinity of the CTG repeat tracks.

Opportunities and Challenges for DM1:

In developing a genome editing program for DM1, a clear understanding of both the disease and the target is essential. This focus will ensure that the outcomes from research supported by this RFA will be directly applicable for therapy development for DM1.

Although genome editing is entering clinical testing, the earliest clinical trials involve *ex vivo* editing of autologous cells and return of the selected, edited cells to the trial subject, thereby avoiding many delivery and safety issues. Given the multiple organ systems involved in DM1 (skeletal muscle, cardiac muscle, brain, GI system, etc.), *ex vivo* editing is not considered a viable therapeutic option at this time. *In vivo* use of genome editing technology faces multiple potential hurdles to success. These include, but are not limited to, selection and optimization of a platform/strategy, choice of an effective delivery vehicle, and objective evaluation of efficacy and safety.

Recognizing that many of the potential hurdles to achieving *in vivo* genome editing are not unique to its applicability to any one disease but wanting to understand how the technology can be applied to DM1, the MDF convened a Genome Editing Workshop. A summary of the participants in and discussions from that workshop is now available (see Important References and Resources list below).

Based on feedback from the Genome Editing Workshop, MDF has developed this RFA to solicit applications from investigators at academic and non-profit organizations. This strategy to focus on early stage discovery/development efforts was chosen since current generation genome editing technology is likely to fall short of achieving a meaningful cure for DM1. Applications will be solicited, evaluated, and awarded according to the processes described below. Awards will be managed as cooperative agreements, with regular interactions between grantees and an MDF-appointed project advisory committee.

Important References and Resources

This section includes recent publications where genome editing technology was applied to DM1, as well as links to resources from MDF, NIH, and NIST that will be valuable in preparing applications.

Recent Publications Using Genome Editing in DM1:

Dastidar S, Ardui S, Singh K, Majumdar D, Nair N, Fu Y, Reyon D, Samara E, Gerli MFM, Klein AF, De Schrijver W, Tipanee J, Seneca S, Tulalamba W, Wang H, Chai YC, In't Veld P, Furling D, Tedesco FS, Vermeesch JR, Joung JK, Chuah MK, VandenDriessche T. Efficient CRISPR/Cas9-mediated editing of trinucleotide repeat expansion in myotonic dystrophy patient-derived iPS and myogenic cells. Nucleic Acids Res. 2018 Jun 27. doi: 10.1093/nar/gky548.

van Agtmaal EL, André LM, Willemse M, Cumming SA, van Kessel IDG, van den Broek WJAA, Gourdon G, Furling D, Mouly V, Monckton DG, Wansink DG, Wieringa B. CRISPR/Cas9-Induced (CTG· CAG)_n Repeat Instability in the Myotonic DystrophyType 1 Locus: Implications for Therapeutic Genome Editing. Mol Ther. 2017 Jan 4;25(1):24-43. doi: 10.1016/j.ymthe.2016.10.014. Epub 2017 Jan 4.

MDF Genome Editing Workshop Summary:
http://www.myotonic.org/sites/default/files/pages/program/MDF_Genome_Editing_Workshop_Full_Notes_FNL_2018-04-27.pdf
Summary of discussions at a workshop of genome editing experts convened by MDF. Provides information on opportunities and hurdles in applying genome editing to DM1.

NIH Common Fund Somatic Cell Genome Editing Program:
https://commonfund.nih.gov/editing
NIH's analysis and initiatives directed toward genome editing technologies and resources. Includes important information on strengths and liabilities of the various genome editing platforms and the collection of tools, methods, data, and best practices to accelerate development and testing of genome editing therapeutics.

NIST Genome Editing Consortium:
https://www.nist.gov/programs-projects/nist-genome-editing-consortium
Contains information on outputs of a consortium put together by the National Institute of Standards and Technology to increase confidence and lower risks of using genome editing technologies in research and commercial project. Includes information from expert workshops convened by NIST in partnership with FDA. The talk by Dr. Anna Kwilas, CMC Reviewer/CBER/FDA may be particularly informative for applicants as to regulatory perspectives (https://www.nist.gov/sites/default/files/documents/2018/05/21/4_anna_kwilas_fda_cber_april_2018.pdf).

Applications

1. Eligibility for RFA

Applications are limited to those from academic institutions and/or non-profit research institutes. For-profit organizations are not eligible for this RFA. Collaborative projects are strongly encouraged, particularly those that propose partnering between experts in genome editing technologies and investigators with strong track records in myotonic dystrophy research. Such applications ensure a combination of state-of-the-art genome editing expertise and practical knowledge of the genetics and pathogenesis of myotonic dystrophy.

- Applicants or teams of applicants must have proficiency in the knowledge, resources and skills necessary to carry out the proposed research;
- Submitting PIs and Co-PIs must:
    - Be a professional or faculty member at an appropriate educational, medical, or other non-profit research institution and be qualified to conduct and supervise a program of original research;
    - Have both administrative and financial responsibility for the grant;
    - Have access to organizational resources necessary to conduct the proposed research project; and
    - Hold a Doctor of Medicine, Doctor of Philosophy, Doctor of Science or equivalent degree.
- Applications from non-U.S. academic institutions or non-profit organizations are permitted.

2. Study Requirements

Project Direction:

Projects must focus on early stage therapy discovery and development of genome editing strategies for DM1 that target the *DMPK* gene. Although genome editing with CRISPR/Cas9 has been the subject of several recent publications, that platform may or may not prove to be the best approach for DM1.

Successful applications must not only address fundamental hurdles to applying genome editing but must include strategies that specifically address the complexities of the *DMPK* locus, including use of appropriate DM1 models at each stage of evaluation of a candidate therapeutic. Because of the nature of DM1, only projects directed toward *in vivo* delivery of genome editing reagents will be considered (*ex vivo* editing and introduction of edited cells is deemed insufficient to treat a multi-system disease like DM). Since an approved therapy for DM1 is the ultimate goal, the value of *in vitro* and *in vivo* models must be justified in the research plan.

Due to the size and duration of this award, it is not anticipated that investigators will be able to move a candidate therapeutic into clinical testing without additional resources. Applicants should, however, provide a transition plan as to how they intend to move a successful program to subsequent stages of development.

Scope of Research Plan:

Emphasis in the research plan should be on preclinical discovery and development activities to include but not limited to:

- Evaluating competing strategies/platforms/targets for genome editing to move forward the most effective plan for DM1;
- Advancing means of delivery of genome editing reagents to all disease-relevant tissues;
- Advancing efficiency of genome editing at all target tissues;

- Addressing safety of genome editing reagents, including minimizing off-target editing and potential immunologic responses to genome editing reagents;
- Developing/optimizing DM1 models needed for assessing genome editing candidate therapies;
- Conducting preclinical proof of concept studies of candidate genome editing strategies.

In the proposed research plan, successful applicants will have addressed multiple hurdles, such as those listed here, in advancing a candidate genome editing therapy for ultimate *in vivo* use in treating DM1.

Intellectual Property:

Grantees must ensure to the extent possible, that any intellectual property generated during the course of the research is protected in order to ensure the possibility of ultimate commercialization of a therapeutic for DM1.

3. Submission Process and Requirements

Applications cannot exceed 20 pages in length, and must be submitted in 11-point font. Applications should be submitted via email to MDF Grants Manager Elizabeth Habeeb-Louks (elizabeth.habeeb-louks@myotonic.org) no later than November 30th, 2018.

The requested budget for proposed studies is not to exceed $250,000 in direct costs distributed over a two-year project period. Funding of two awards is anticipated. MDF does not pay indirect costs.

The application must include the following (within the 20-page limit):

1. Brief lay abstract of 200 words or less;
2. Technical abstract of 400 words or less;
3. Description of the background and scientific rationale for project;
4. Detailed description of the research plan—include caveats, contingencies, and appropriateness of both methods and *in vitro* / *in vivo* models;
5. Description of the transition plan. Specifically, detail what steps the grantee would take to continue the work beyond the two-year award period. Include a transition plan for seeking additional funding and include other resources (including potential partners) that may be available to move a candidate therapeutic forward;
6. If the application involves a collaboration, description of the rationale for, and logistics of the collaboration, including contributions of all parties, plan for communication and sharing of equipment and/or team members;
7. A timeline that includes milestones—applicants should propose appropriate milestones at approximately 6, 12, 18 and 24-month timepoints from project initiation to help drive decision making as projects progress; milestones are required in order to provide clear indicators of a project's continued success or emergent difficulties; progress reports will be required at each milestone; final milestones will be negotiated with recipients prior to any award;
8. Figures (may be embedded in text or included at the end).

In addition, (not included in the 20-page count) applications must include:

9. References;
10. Detailed budget in spreadsheet or table format (see “Other Requirements” for instructions on dividing the budget between collaborators);
11. Accompanying budget description and justification;
12. Description of facility(ies) and equipment, if any, that will be used for the project;
13. IUCAC documentation

14. Very brief (maximum of 2 pages): Names, degrees, training/qualifications, experience, role in project and percent effort for team members from both groups in the collaboration (may be submitted as a table);
15. CVs of all key personnel;
16. Letters from collaborators and/or in support of the application (required to document collaborations and/or availability of resources not already in hand); and
17. Face page provided by MDF for this RFA (see attached).

Submit applications as a single PDF file, including the signed face page, and all supporting documents to MDF Grants Manager Elizabeth Habeeb-Louks (elizabeth.habeeb-louks@myotonic.org) by the designated deadline with the subject line "RFA: 2018 MDF Genome Editing for Myotonic Dystrophy."

4. Review and Selection

Projects will be reviewed by *an ad hoc* committee composed of individuals with expertise in one or more areas relevant to this RFA including, but not restricted to, mechanistic and clinical aspects of the disease and genome editing technology. All reviewers will sign confidentiality agreements and conflict of interest statements. In their cover letter, applicants may suggest that particular individuals or individuals from particular organizations not be used as reviewers.

Review criteria:

- Impact/relevance for proposed work to drive genome editing therapy development for DM1;
- Rationale for and feasibility of research plan, including appropriateness of the approach for DM1 and adequacy of any proposed *in vitro / in vivo* models;
- Innovation in addressing the disease and gaps in current genome editing strategies;
- Potential for proposed research to ultimately transition to the clinic; adequacy of applicant's transition plan;
- Experience and expertise of applicants and strength of preliminary data;
- Adequacy of facilities and resources;
- Feasibility of collaboration, if applicable, including balance of responsibilities and intellectual contribution; and
- Adequacy of timeline and proposed milestones.

5. Other Award Conditions

The cooperative agreement nature of the awards means that there will be substantial and regular interactions between grantees and the MDF-appointed project advisory committee. The advisory committee will include MDF staff and individuals with basic, translational, and clinical development expertise in genome editing technology and/or DM1. The advisory committee will provide oversight and guidance of funded projects.

Budget: Total costs are not to exceed $250,000, distributed across a two-year grant period; no indirect expenses are permitted. If the project involves a collaboration, one collaborator should be identified as the submitting PI and the other as the Co-PI. The award will be made to the organization of the submitting PI and the organization of the Co-PI will be considered a subcontractor. It will be the responsibility of the submitting PIs organization to manage the agreement with the subcontractor.

Applicants must confirm that the funds awarded will be used only for the research project described in the application; indirect costs and overhead charges are not allowed for these applications. Equipment charges are allowed upon written approval from MDF.

Awards will be managed as cooperative agreements, with milestones. MDF's interest is in advancing research toward an approved therapy. Thus, MDF will exercise flexibility in assessment of milestones or in updating milestones based on emerging data, and only seeking termination on projects that reach the point of no feasible path forward.