The Mark Foundation for Cancer Research
and
The Chordoma Foundation

Joint Request for Proposals:

Therapeutic Innovation Award

February 2018

I. PURPOSE

The Mark Foundation for Cancer Research funds groundbreaking research integrating discoveries in biology with innovative technology to deliver breakthroughs to patients. The Chordoma Foundation works to improve the lives of those affected by chordoma by accelerating the development of better treatments for this orphan disease. Together, we are offering this funding opportunity with the goal of catalyzing research using innovative approaches and technologies to enable the development of therapies targeting brachyury - a transcription factor that plays a key role in chordoma and other cancers.

II. BACKGROUND

Brachyury is a key developmental transcription factor that plays a central role in embryonic notochord formation and mesoderm development. After development, brachyury serves no known function in the adult body, and is absent from virtually all healthy tissues. However, it has been implicated in the initiation and progression of a variety of cancers, most notably chordoma - a rare tumor arising from notochordal cells that reside in the base of the skull and along the spine.

The master regulator of notochord cell fate, brachyury is highly expressed in virtually all chordoma tumors and is essential for the survival of chordoma cells. Moreover, nearly all chordoma patients harbor a predisposing germline SNP in brachyury, and somatic amplification of brachyury is common in chordoma tumors, suggesting that gain of function of brachyury plays an important role in driving the disease. In a variety of other cancers - including breast, lung, colon, and prostate cancers - expression of brachyury is associated with disease progression, metastasis and resistance to therapy.

Mounting evidence suggests that targeting brachyury could represent a promising therapeutic strategy both for chordoma and other tumor types. However, as a transcription factor, brachyury is conventionally regarded as challenging drug target. Fortunately, a convergence of new technologies and therapeutic approaches, coupled with enhanced understanding of transcriptional regulation, has created new opportunities to target transcription factors in cancer. This funding opportunity is meant to capitalize on those opportunities and accelerate the discovery of therapies that target brachyury. If successful, approaches and technologies that enable brachyury drug discovery could serve as a template for accelerating drug discovery for other transcription factors, which represent key drivers and a significant fraction of “undruggable” targets across most cancers.

III. GOALS AND SCOPE OF THIS AWARD

The goal of this funding opportunity is to support research that will explore innovative ways to target transcriptional pathways that drive cancer, and lay the foundation for drug discovery efforts directed at this critical target.

Relevant areas of study include but are not limited to:

- Interaction of brachyury with other proteins and/or small molecules
- Direct degradation of brachyury
- Functional implications of the chordoma-associated SNP in brachyury
- Therapeutic manipulation of upstream regulators of brachyury, or downstream brachyury targets
- Immunogenic properties of brachyury

Of particular interest are projects that employ innovative or emerging approaches and technologies, or that apply techniques from other domains of science.

Projects involving cell-based assays or preclinical studies should be conducted in the context of chordoma models; however, further evaluation can be performed in relevant models from other cancers. The Chordoma Foundation has 14 chordoma cell lines and 6 xenograft models that are available to researchers. Detailed information on these resources can be found using the following link:
https://www.chordomafoundation.org/research/disease-models/

IV. MECHANISM OF SUPPORT

This funding opportunity is offered in two phases. The first funding phase, described in this RFP, will support a one-year pilot study to assess feasibility of an approach and generate preliminary data. Based on the results generated in the first funding phase, awardees may be invited to apply for a second phase of funding which will support a multi-year continuation of the project.

For the first funding phase, applicants may request up to $150,000 over a 12-month funding period. Indirect costs not to exceed 10% of direct costs can be included in the budget. Applications that are scored favorably but not funded during the initial award cycle may be funded as additional money becomes available. Proposals involving meaningful collaboration among investigators with complementary capabilities are encouraged; awards can be split among investigators' institutions as needed.

Information on the second phase award will be announced at a later date. Invitation to apply for the second phase award will be limited to recipients of the first phase award.

V. ELIGIBILITY AND APPLICATION INFORMATION

Applications will be accepted from investigators at academic institutions, nonprofit research institutions and for-profit companies. Investigators with no specific expertise in chordoma, but who have significant expertise in the proposed approach or methodology, are welcome to apply.

Interested applicants should submit a **1 page letter of intent (LOI)** describing the aims of a one-year feasibility study, the proposed approach, and how funding from this award will lay the groundwork for subsequent brachyury drug discovery.

- Email the following to grants@chordoma.org no later than **Friday, April 6th**:
  - One page letter of intent
  - Principle investigator biosketch(s)
  - Names and contact information of up to three recommended reviewers
- All documents should be in Microsoft Word format.
- Invitations to submit a full application will be made within 10-14 days after the LOI deadline date. Application template will be sent to invitees at that time.

Inquiries concerning the application and process should be directed to Joan Levy, Director of Research, via email at: joan@chordoma.org.

VI. KEY DATES

- **RFP release**: February 16, 2018
- **LOI due**: April 6, 2018
- **Full application due***:* June 1, 2018
- **Award notification**: September 2018

VII. CRITERIA FOR CONCEPT SELECTION

Proposals will be reviewed by a committee with expertise in chordoma biology, transcription and/or translation, and drug discovery. Criteria that will be used in scoring and prioritizing applications include but are not limited to:

- Incorporation of innovative and novel approaches and/or technologies
- Clear path forward for future drug discovery efforts targeting brachyury and/or related proteins in chordoma and/or other cancers
- Assembly of the appropriate expertise to conduct the proposed research
- Realistic aims to be achieved in the 12-month award period