Drug Screening Program
Request for Proposals

2019

I. BACKGROUND

The Chordoma Foundation is a nonprofit organization dedicated to improving the lives of chordoma patients and leading the search for a cure. In service of this mission, the Foundation has developed a centralized Drug Screening Program to enable rapid and efficient evaluation of potential new treatments for chordoma in preclinical models of the disease. Through this service, academic researchers and companies can more easily evaluate promising drug candidates without the time and expense of acquiring, establishing and expanding preclinical models.

The Drug Screening Program is operated through a partnership with South Texas Accelerated Research Therapeutics (START), a contract research laboratory that specializes in preclinical cancer drug development. The Foundation contracts with START to develop, bank, and expand patient-derived xenograft (PDX) and cell line-derived xenograft (CDX) models and to perform *in-vivo* efficacy studies in these models. Centralizing these experiments in a single lab generates efficiencies and economies of scale that reduce the overall cost of evaluating new therapeutic approaches.

Since 2015, the Foundation has developed or acquired 9 PDX models and 2 CDX models, which are now available for drug testing. To date, over 36 drugs and drug combinations have been evaluated in one or more of these models. The results from the majority of the completed studies are available on the Foundation's website and in the public data repository Figshare. Now, the Foundation is seeking proposals for additional promising drug candidates to evaluate.

II. PURPOSE

Through this request for proposals, the Foundation aims to identify well-justified therapeutic concepts to evaluate in chordoma xenograft models through the Drug Screening Program in 2019. The primary intent of these studies is to generate preclinical data that can help validate new therapeutic targets and corresponding drug classes, and, ideally, provide evidence to justify or prioritize future clinical trials. Therefore, though all applications will be considered, priority will be given to drugs in clinical development or marketed agents. Additionally, these studies may help to identify specific molecular subtypes of chordoma that may be most sensitive to particular therapies and identify biomarkers that could predict response in patients.

III. MECHANISM OF SUPPORT

For approved therapeutic concepts, the Foundation will provide *in vivo* evaluation of the drug(s) in up to 3 PDX/CDX models. Once a concept is approved, the Foundation will work with each investigator to design the study, including determination of drug dosing and selection of desired models.

Generally, *in vivo* evaluation will be conducted as described below; however, modifications to the study design may be possible if necessary.

- Experiments are performed in immunodeficient mice implanted subcutaneously with tumors grown to the size of 150-250 mm^3 at study initiation. Each treatment group consists of 5 mice.
- Treated animals are compared to an untreated control group to calculate tumor growth inhibition.
- Drugs are administered po, sc, or via tail vein injection.
- Tumor tissue from both the control and drug-treated groups is collected at the end of the study for subsequent PD analyses. (Note: START will collect and preserve the tissue as requested but will not be involved in the actual PD analysis. Furthermore, funding for PD analysis will not be provided by the CF as part of this award and, if needed, must be secured from other sources.)
- Data collected from the *in vivo* experiments includes animal weights, observations, and tumor dimensions. This information will be used to determine agent tolerability based on weight change and gross physiologic changes; and anticancer activity based on tumor growth inhibition or regression.

IV. KEY DATES

- Proposal due: May 10, 2019
- Applicant Notification: June 28, 2019
- Finalizing study design: July-August 2019
- *In vivo* testing in Q3-Q4 2019

V. APPLICATION INFORMATION

Applications will be accepted from investigators at academic institutions, nonprofit research institutions and for-profit companies.

To apply, complete the accompanying application form with all of the information requested. The application should be returned to Joan Levy, Director of Research, via email at: joan@chordoma.org no later than May 10, 2019 by 8PM EST. Applications arriving after this deadline will not be accepted for review.

Inquiries concerning the application process, drugs being proposed and the experimental design should also be directed to Joan Levy via email.

VI. CRITERIA FOR CONCEPT SELECTION

Proposals will be reviewed by a scientific committee with expertise in chordoma biology as well as preclinical drug evaluation. Applications will be scored and prioritized on the basis of the following criteria:

- **Strong molecular rationale**: There is compelling evidence that the drug target plays a critical role in chordoma disease biology or is essential for chordoma cell survival. Drug combination approaches are also encouraged with the appropriate supporting rationale.
- **Preclinical evidence:** The drug or drug class demonstrates activity in functional *in vitro* assays (e.g. proliferation or apoptosis) and/or mechanistic on-target effects in chordoma cell lines.
- **Drug availability:** Nominated drug is commercially available or available through applicant's institution or can easily be obtained from the company that owns it. In the latter case, a letter of commitment to supply drug should be obtained from the respective company and submitted with the application.
- **Development stage:** The Foundation will consider drugs at any stage of development. However, a preference is given to drugs that are in clinical development or beyond. At minimum, the formulation, dose and administration schedule for *in vivo* testing should be established from studies in other preclinical animal models.

VII. DATA SHARING

Consistent with its nonprofit mission, the Chordoma Foundation provides in-kind drug screening services to accelerate the development and dissemination of knowledge about potential treatment approaches for chordoma. As such, data generated through the Drug Screening Program is intended to be made publically available as rapidly as possible, preferably through a peer reviewed publication. To enable investigators to publish resulting data, the Foundation offers an embargo period during which data will be kept confidential as a manuscript is being prepared and reviewed. The length of the desired embargo should be clearly stated in the accompanying application. When necessary, for certain proprietary drug candidates, the terms for data sharing should be included as part of an accompanying Material Transfer Agreement.

Within thirty (30) days of receiving the final study report from START, the Chordoma Foundation will provide the Principal Investigator with a written report summarizing study results. Interim updates may be provided upon request. The Foundation will maintain confidentiality of the results consistent with the pre-agreed embargo. By default, the embargo will last for a period of 6 months from the date of the report, unless the Principal Investigator waives this confidentiality in writing, or a longer confidentiality period is agreed to in advance. Once the embargo period is waived or expires, summarized data will be posted on the Foundation's website and published on the public data repository Figshare.

VIII. AVAILABLE MODELS

The following PDX/CDX models are available for testing:

Model Name	Model Type	Tumor Location	Disease Status	Adult (>19)/ Pediatric
SF8894*	PDX	Clival	Recurrent	Adult
CF322*	PDX	Clival	Recurrent	Adult
CF365*	PDX	Clival	Metastatic	Pediatric
CF359*	PDX	Clival	Metastatic	Pediatric
CF382	PDX	Clival	Recurrent	Adult
CF459	PDX	Clival	Primary	Pediatric
CF427	PDX	Clival	Primary	Adult
CF466	PDX	Sacral	Metastatic	Adult
SF10792	PDX	Clival	Primary	Adult
UCH1	CDX	Sacral	Recurrent	Adult
CH22	CDX	Sacral	Recurrent	Adult

PDX=Patient derived xenograft; CDX: Cell-line derived xenograft

*WGS and/or RNAseq performed and data stored in Cavatica (www.cavatica.org)

All models have been validated by histology with confirmed T (brachyury) expression and nuclear localization.