Drug Screening Program

Request for Proposals

New Program Announcement

2020

I. BACKGROUND

Drug testing in chordoma animal models:
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 the mission to find systemic treatments for chordoma patients, in 2015 the Foundation developed a centralized Drug Screening Program operated through a partnership with South Texas Accelerated Research Therapeutics (now known as Xeno-START), a contract research laboratory that specializes in preclinical cancer drug development in animal models. 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. 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 Foundation has developed or acquired 11 PDX models and 2 CDX models, which are available for drug testing. To date, over 45 drugs as single agents and/or 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.

Expansion of drug screening services in 2020-New program announcement:
The chordoma research community continues to expand its knowledge about the biology of the disease and identify new targets that may be important in regulating tumor cell growth and/or progression. In many cases, repurposed drugs from other indications directed against these targets exist that could be rapidly tested for effects on chordoma cell growth. In addition, as with many other cancers, the need for rationally designed combination approaches have to be explored for their ability to more effectively inhibit chordoma growth and potentially induce cell killing.

To support these needs and complement the existing *in vivo* program, the Foundation is now offering a new *in vitro* drug screening service to rapidly assess new drugs and combination approaches.. Nominated drugs can be tested for their effects on chordoma cell viability in a number of validated cell lines in a rapid and efficient manner through a centralized laboratory. Additional assay formats including cell killing and mechanistic readouts will be considered.

II. PURPOSE

The primary intent of these studies is to generate *in vitro* or *in vivo* preclinical data that can help validate new therapeutic targets and corresponding drug classes, and, ideally, provide evidence to justify advancing promising drugs into 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. Through this request for proposals, the Foundation aims to identify well-justified therapeutic concepts to evaluate for *in vitro* and/or *in vivo* activity:

- *In vitro* screening for compounds or combinations with strong mechanistic rationale requiring preclinical data in chordoma cell lines to support advancement into animal models
- *In vivo* screening for concepts that have strong mechanistic rationale with existing preclinical data demonstrating *in vitro* activity

III. MECHANISM OF SUPPORT

***In vitro* evaluation:**
For approved therapeutic concepts, the Foundation will provide ***in vitro* evaluation** of the drug(s) in up to **3-5** chordoma cell lines. The preferred cell lines that will be used are listed in Section VII below.

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

- Drugs are tested in the Alamar Blue cell viability assay at 8-12 doses run in quadruplicate in each cell line tested.

- For each cell line selected, each drug is tested twice on separate batches of cells.

- A known test compound is included in each run as a positive control in addition to vehicle controls.

- Drugs that have activity in the cell viability assay can have additional testing in appropriate cell killing and/or mechanistic assays.

- All data is prepared with an automated analysis and reporting template. A dose curve, IC_{50} estimate, and raw data is sent electronically once the screening is performed.

Please note: Encouraging data generated from *in vitro* assessment of a given drug(s) can be used to support submission of a subsequent *in vivo* screening application.

***In vivo* evaluation:**
For approved therapeutic concepts, the Foundation will provide ***in vivo* evaluation** of the drug(s) in up to **3** PDX/CDX 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.
- Data collected from the *in vivo* experiments include 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.
- Tumor tissue from both the control and drug-treated groups is collected at the end of the study for potential pharmacodynamic (PD) analyses. **Note:** START will collect and preserve the tissue as requested but will not be involved in the actual PD analysis. Tumor tissue and blood can be sent back to the PI's lab for different types of analyses.
    - **<u>For non-profit laboratories only:</u> Starting in 2020, the Foundation will offer an award of up to $10,000 to support PD studies to evaluate target engagement, mechanism of action, and biomarker assessments. Drugs that demonstrate tumor growth inhibition of at least 60% will be eligible for this funding. Following the completion of the *in vivo* study, investigators whose concepts meet this threshold will be invited to submit a one-page proposal to request this funding.**

For both *in vitro* and *in vivo* studies, 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 cell lines and models.

IV. APPLICATION INFORMATION

Applications will be accepted from investigators at academic institutions, nonprofit research institutions and for-profit companies on a rolling basis throughout the year starting in September 2020.

To apply, complete the application form (separate *in vitro* and *in vivo* applications accompany this RFP) with all of the information requested. The application should be returned to Joan Levy, Director of Research, via email at: grants@chordoma.org at your earliest convenience.

Inquiries concerning the application process, drugs being proposed and the experimental design should be directed to Joan Levy at joan@chordoma.org.

V. 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**: For *in vitro* and *in vivo* testing in chordoma cell lines and models, respectively, there should be 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:** For *in vivo* testing, 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.

VI. 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 publicly 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 data/study reports, the Chordoma Foundation will provide the Principal Investigator with a written report summarizing study results with the accompanying raw data files. 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.

VII. AVAILABLE MODELS

The following cell lines will be used for *in vitro* testing (subsequent to change as more cell lines are added):

Cell line	Tumor Location	Disease Status	Adult(>19)/pediatric
UCH-1*	Sacral	Recurrent	Adult
UCH-2*	Sacral	Recurrent	Adult
CH22*	Sacral	Recurrent	Adult
JHC7*	Sacral	Primary	Adult
UMChor1*	Clival	Primary	Adult
UMChor5**	Clival	Primary	Pediatric

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
CF459^{P}	PDX	Clival	Primary	Pediatric
CF555^{P}	PDX	Clival	Metastatic	Pediatric
CF539^{P}	PDX	Clival	Metastatic	Pediatric
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

^{P}= progression model with primary tumor sample and 2 separate metastatic lesions from the same pediatric patient

*WGS and/or RNAseq performed and data stored in Cavatica

** RNAseq data soon to be available on Cavatica

Additional cell line and model information can be found on our website.