The Children’s Tumor Foundation (CTF) is pleased to announce public release of data from the Synodos for NF2 project in its entirety. The data sets are available through nfdataportal.org and easily located on this LINK. Concomitant to the release of the project data, the Foundation is also pleased to announce the initiation of an extensive research program in neurofibromatosis type 2 (NF2) totalling over $2 million in three years. Part of this program will begin through the launch of a special NF2 Drug Discovery Initiative (DDI) round, with the goal to fund up to three studies that will bring new therapeutic agents to the clinic. Funding for each study will be aligned with the Drug Discovery Initiative program, with a duration of two years.

BACKGROUND

Neurofibromatosis 2 (NF2) is a rare neurogenetic disorder that affects roughly 1 in 25,000 people worldwide, and is characterized by multiple schwannomas and meningiomas. These are histologically benign tumors, but their multiplicity, involving several cranial nerves, spinal nerve roots, and peripheral nerves in people with NF2 results in severe cumulative morbidity and can ultimately lead to death. Although bilateral vestibular schwannomas are pathognomonic for NF2, meningiomas are the second most common tumor type in NF2 and their presence is associated with increased mortality. Importantly, meningiomas are the most common brain tumors worldwide and many sporadic meningiomas have somatic NF2 mutations. In most non-NF2 patients, meningiomas and schwannomas are effectively treated with surgery or radiation therapy. In the setting of NF2, surgery and radiation therapy are associated with reduced efficacy and increased toxicity, and there are no effective drug therapies for these tumors. Hence, effective treatments for NF2-associated schwannomas and meningiomas are a major unmet medical need for both the broad population with sporadic forms of these tumors as well as for people with the rare syndrome of NF2.¹

Introduction to Synodos for NF2

The Foundation’s Synodos for NF2 project started in 2014 and concluded recently. It was a large scale collaborative initiative that assembled a team of basic, translational, and clinical research experts from twelve world-class labs and medical centers who joined forces to work together, free of bureaucratic obstacles and institutional competition.

The goal of Synodos for NF2 was to discover novel therapeutic long-term tolerable agents for clinical treatment that either successfully shrink NF2 tumor types, or halt tumor growth.

Synodos for NF2 aimed to deliver multiple new and advanced cell and animal models to accelerate drug screening, new target pathways, and an increased understanding of response and resistance to treatment.

The primary outcomes of the Synodos for NF2 project were the identification of drugs that can enter clinical trials. One of them is Brigatinib, a drug that showed to be very effective in reducing meningioma and schwannoma in animal models (manuscript in preparation). As a result, Takeda, the pharma company that owns Brigatinib, is currently working with CTF and the Synodos NF2 clinicians to launch an innovative trial for NF2 patients. The adaptive platform trial design will provide the flexibility to react to clinical evidence as it is being collected, and modify the design and enrollment in trials by including more patients to generating evidence. As recently reported in two draft guidances issued by the FDA, the final protocol will make use of group sequential design, sample size adaptations, adaptive enrichment, treatment arm selection or patient allocation adjustments (Adaptive Designs for Clinical Trials of Drugs and Biologics, Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics).

The innovative protocol will allow a dynamic allocation of patients dependent on how they will respond to the treatment and the introduction of new drug agents or drug combinations to the platform as they are being identified.

The original deliverables from the Synodos NF2 project included:

1) results from systematic pre-clinical in vitro and in vivo screening in meningioma and VS cell culture systems of biologically rational compounds amenable to clinical development;
2) results from an in vitro and in vivo unbiased screen with drug in late clinical development drugs;
3) detailed integrated analysis of genetic, genomic, transcriptome and kinome data from multiple cell culture systems with and without treatment to identify new target pathways; to investigate tumor-type and species-specific therapeutic targets and differential responses to treatment, to implicate mechanisms of acquired resistance and to reveal opportunities for combination therapies;
4) improved screening paradigms based upon human genetic findings and genome modification of target cell lines;
5) detailed clinical trial design(s) for the best performing drugs in this advanced preclinical pipeline.
Description of Available Data

The Synodos NF2 project has generated several types of ‘omic and drug screening data from NF2 tumor models of schwannoma and meningioma, including:

**Low throughput drug screening data:** A panel of rationally-selected small molecules and drugs such as mTOR and HDAC inhibitors were tested against human and mouse cell line models of meningioma and schwannoma.

**Single-agent and combination high throughput drug screening data:** A panel of 1912 drugs and drug-like molecules (the MIPE 4.0 library from NCATS) was screened in 6 cell line models of meningioma and schwannoma with NF2 wildtype or NF2 deficient status. In addition, 4 of these cell lines were screened with 6x6 and 10x10 point combination dose-response assays with this panel of drugs. Both raw and processed data are available.

**Genomic variant data (structural rearrangement):** Jumping library sequencing facilitates detection of chromosomal abnormalities such as pathogenic breakpoints. There are processed data (bam files) from 11 human and mouse cell line models of meningioma and schwannoma with NF2 wildtype or NF2 deficient status.

Gene expression: Raw (fastq files) and processed (bam, count, and differential expression files) RNAseq data were generated from an \( N\text{f}_2^{\text{fl/fl}} \) mouse model dorsal root ganglion tissue and cell line models of meningioma and schwannoma. In addition, data were generated from cell line models of meningioma and schwannoma with vehicle control, or 12 different single agent or combinations of small molecule inhibitors. Data from the 2017 release and the 2019 release are both now available for exploration.

Kinomics: Processed data are available from NF2 mouse model dorsal root ganglion tissue several cell line models of meningioma and schwannoma after treatment with a vehicle control or one of seven small molecules. Data from the 2017 release and the 2019 release are both now available for exploration.

We encourage you to explore the Synodos NF2 project for more details, or the NF Data Portal to find this and other related data.
OBJECTIVE AND SCOPE

The focus of this Request for Application (RFA) is to support exploratory and developmental research projects involving secondary data analysis of the Synodos for NF2 data set and selection of the next active drug or combination of drugs to be included as the next candidate in the ongoing NF2 platform trial.

Applicants are strongly encouraged to start with the analysis of the available dataset and propose the next set of experiments to validate or generate new data that will lead to the selection of the most promising agent or combination to treat NF2-deficient meningioma, schwannoma or ependymoma. Validation of the proposed drug for clinical studies will have to take into account the Synodos for NF2 dataset.

It is expected, at the end of the grant and after an agreed embargo period, that the data generated in the funded application will integrate and enrich the existing data on NF2, being deposited and annotated in accordance with the ontology in use on the NF Data Portal. To help applicants to meet this goal, CTF will provide assistance through Sage Bionetwork.

The type of studies this proposal is considering to fund are, but not limited to:

- Secondary analyses of Synodos NF2 data
- In-vitro testing and new model system generation
- In-vivo testing studies in appropriate NF2 animal models
- Target or MoA validation experiments
- PK/PD
- OMICS or other NGS studies

APPLICANT ELIGIBILITY

- Applicants should have an MD, PhD, or equivalent, with an established record of independent research, and must have full access to, or identified collaborators with, all required resources.
- Applications are welcome from both the academic and private sectors. Partnerships between the two are actively encouraged, pending patent policy agreement (see below). If applicants are partnering with a contract research organization, a quote for service fees should be included in the application. However, CTF will not be responsible for any additional expenses incurred by the CRO.
- Non-NF2 researchers with expertise in target validation or translational studies are encouraged to apply. The non-NF2 expert applicant can either decide to include an NF2 expert in the team or contact CTF to evaluate opportunities to work in collaboration with an established NF2 lab.
● More than one investigator from an institution can apply as long as the research hypothesis and team composition are distinct. Multiple applications from the same PI will not be considered.
● There are no citizenship requirements for this award. Qualified individuals from within and outside the United States are eligible to apply.

Special Note for federal employees (e.g. NIH intramural researchers)

CTF requires its patent policy to be signed by all awardees and recipient institutions. Since the National Institutes of Health is prohibited from accepting the terms of CTF’s patent policy by congressionally enacted federal law, the patent policy may be waived for federal employees, such as NIH intramural researchers, depending on the project being funded. Federal employees wishing to apply for this award are, therefore, invited to discuss their project with CTF prior to submitting their proposal. Any information shared with CTF will be treated confidentially.

AWARD AMOUNT AND DURATION

Following the DDI funding scheme, funding will be available for the following types:

● Up to $40,000* DDI in vitro Awards:
  ○ In-silico analysis and in-vitro screening studies
● Up to $85,000* DDI in vivo Awards:
  ○ Animal-based preclinical drug testing studies (this can also include in-vitro studies)

CTF funding policy allows max 10% indirect costs. Total amounts for all the awards are inclusive of 10% indirect costs. (i.e. max $3,636.30 IDC costs are allowed within a $40,000 award).

* We will consider funding higher budgets for applications that will propose (and justify) more complex analysis and testing of combinations of drugs. We will not accept any proposal that will exceed a maximum of $180,000 (inclusive of 10% indirect costs).

The duration for the in-vitro awards will be 12 months, and max 24 months for the in-vivo awards.

The final number of funded applications will depend on the submission of a sufficient number of meritorious applications.
APPLICATION PROCESS

Applications will be selected through a two-stage peer-reviewed process comprising submission of a letter of intent (LOI) followed by a full application submission upon approval of the LOI.

Letter of Intent

Applicants must submit a LOI formatted in Arial 11 point detailing –

- Project outline describing key aims/approaches of the study (1-page maximum)
- Composition of the team/personnel involved (1-page maximum)
- Commitment to data-sharing and general statements on how the generated data will be made available at the end of the study (half-page maximum).

Please review the NF Open Science Initiative (NF-OSI) guidelines here, and state your agreement to adhere to the authorship and data sharing plan.

LOIs will be due by 11:59 pm EST on Monday, July 1, 2019 and must be emailed to grants@ctf.org AND slarosa@ctf.org.

LOIs that meet the qualifications will be invited to submit a full application.

Full application

All invited full applications must be formatted in Arial 11 point and must contain –

- Abstract
  Please provide a lay abstract and a technical abstract summarizing the proposed research. Each abstract should be no more than 2500 characters in length.

- Project description (5 pages max)
  The project description section should include pertinent background, specific aims, preliminary data (if any), experimental design, and figures where necessary.

- Data Sharing Plan (DSP)
  Instruction on how to register the study and submit a complete DSP can be found here.
● **References** (no page limit)
  Please provide a list of references for the research cited.

● **Detailed implementation plan** (2 pages max.)
  Please provide specific research milestones to be met within each 6-month interval.

● **NIH biosketch**
  Please submit an NIH biographical sketch for each investigator, including (in section A) description of the role of that investigator in the project and his/her relevant expertise.

● **Other support**
  Please submit information on current, pending, and institutional financial support for all members of the team and any collaborators who will receive salary support from this award. All funding sources including intramural and extramural sources must be disclosed. Please indicate if there is overlap between any funded/pending grant and the current proposed research.

● **Budget pages**
  Please provide a detailed, itemized budget for all tasks proposed in the project plan. CTF will cover direct costs and 10% indirect costs (see “Award Amount and Duration” section).

● **Organizational certifications and letters of support**
  Appropriate certifications and letters of support are required for consideration of submitted proposals. In cases where ethical/regulatory approval is required to perform the work, such approvals must be provided before award activation.

Invited full applications will be due within 6-8 weeks of receiving notification of LOI approval. The exact due date will be indicated in the notification email.
REVIEW PROCESS

Full applications will be evaluated by a review panel comprised of experts in NF2, drug development, data analysis, and clinicians, taking the following elements into consideration –

- Inclusion of existing data into decision/selection/validation process
- Likelihood that the findings of the proposed research will allow the selection of an agent to enter NF2 clinical trial
- Feasibility of proposed study
- Alignment of budget
- Scientific merit of application and applicant

NOTIFICATION TO APPLICANTS

Applicants will be notified of the outcomes of both stages of applications within a tentative timeline of 2 weeks from submission of LOI’s, and 8 weeks from submission of full applications. All applicants who submitted full applications, both funded and not funded, will be provided with a summary of the key comments of the reviewers.

AWARD ACTIVATION

For applications selected for funding, awardees will be requested to complete and return the following documentation to CTF before the award can be activated –

- **Acceptance of award**
  An award acceptance letter will be sent requesting information on applicant, institution, and contact officials for award disbursement.

- **Patent policy**
  All awardee institutions will be required to sign CTF’s patent policy. CTF strongly recommends agreeing to and signing the patent policy at the time of application submission to expedite award activation. The patent policy is intended to ensure that any inventions or patented technologies arising from CTF-funded research are commercialized where possible. We anticipate recouping some revenues arising from such commercialization, in proportion to the initial funding, to support further research initiatives at CTF.
STATUS OF AWARDEE

The awardee shall be considered an employee of the awardee’s institution, and not of CTF.

PERIODIC REPORTING

Awardees are required to submit two types of reports periodically, the templates of which will be provided –

- **Progress report**
  Updates on the development of the funded research must be provided to CTF according to a reporting schedule that will be generated based on the timelines of the proposed deliverables. CTF may use high-level contents of such updates in summary reports to its constituents such as Board of Directors and donors, unless the awardee requests contents to be kept confidential.

- **Expenditure report**
  A financial statement itemizing expenses for each year of funding must be provided to CTF within 60 days of completion of the funded year. All expenses must be reported in US dollars only. Expenditure reports must be signed by the institution’s financial officer. Any unexpended and uncommitted funds in the possession of the awardee at the end of the award period must be returned to CTF within 60 days of the end of the award. In addition to the above, interim accounting may be requested.

DATA AND RESOURCE SHARING

**Data:** CTF believes in making data from all its funded project freely accessible irrespective of whether the findings were positive or negative. Data sharing policy will be discussed with grant recipients, prior to award activation. Normally CTF allows for 12 months embargo on the data from the end of the award. During this period only the awardees have access to the data. After the embargo ends, the data will be open to the community.

**Resources:** CTF incentivizes the sharing of resources (reagents, cell lines, etc), especially for those developed during the grant. It is an optional opportunity for the awardee to make this resource available to the community and list the resources on our website and the data portal.
EXTENDED LEAVE OF ABSENCE

Should the awardee need to take a leave of absence for over a month for family reasons or illness, CTF must be informed of the date of departure and expected date of return.

AWARD CANCELLATION OR EARLY TERMINATION

CTF reserves the right to terminate the award at any time prior to the end of the award term if the progress of the project is not timely or adequate to meet the proposed goals, or if the awardees fail to comply with the terms and conditions of the award. In the event the award is cancelled or terminated, the award amount will be pro-rated based on the number of months it was in effect. A final report of expenditures and a refund of any unspent funds must be submitted to CTF within 60 days after cancellation or termination. Failure to provide the final expenditure report by the required date will result in refusal to be admitted to participate in any future RFA launched by CTF.

AWARD PURPOSE CHANGE OR TRANSFER

Any fundamental change in the objective for which the award was originally made must have prior written consent of CTF. Awards may also not be transferred from one institution to another without CTF’s prior written authorization.

NO-COST EXTENSION

CTF allows awardees to request a No-Cost Extension (NCE) of the final budget period of their award for up to 1 year beyond its original expiration date. All terms and conditions specified in the original contract will apply during the extension period. Once approved, CTF will revise the project end date and provide an acknowledgment to the awardee.
PUBLICATIONS OR EXHIBITS

As an advocate of open data and open science, CTF strongly encourages its awardees to publish their findings in open access journals to allow for faster dissemination of results and for accelerating follow-up research. CTF will consider addressing part or all of the open-access submissions fees on a case by case basis upon request by the authors.

The awardee is also required to notify CTF of all public disclosures, such as scientific publications and presentations (e.g. poster, slide presentation), of CTF-funded research at least 60 days prior to the publication event, and duly acknowledge CTF in such disclosures. CTF also requires that the awardee provides an electronic (PDF or Word) copy of the publication, abstract, slide presentation, or poster materials. This material should be forwarded to grants@ctf.org if possible at the time it is accepted for publication or presentation, along with the name of the journal or the organization accepting it, and the time and place of the meeting. This information shall be considered confidential by CTF until publicly presented or published by the awardee. If prior notification is not possible, this information must be provided to CTF immediately following publication or presentation.

FOLLOW-ON FUNDING

Awardees are required to keep CTF informed about any follow-on funding, collaborations, and publications (posters, papers) generated from the research funded by the award. This information will be requested annually via our online system for a period of 5 years following expiration of the award. Such continuing communications will allow CTF to measure the impact of our research funding more easily.