

NEUROFIBROMATOSIS TYPE 1 (NF1) GENE THERAPY INITIATIVE

REQUEST FOR APPLICATIONS

September 10, 2018

The Children's Tumor Foundation (CTF) is pleased to announce the initiation of a research program in gene-based therapeutic approaches for the treatment of neurofibromatosis type 1 (NF1). This initiative begins through this request for applications (RFA), with the first goal to fund two proof-of-principle studies in *NF1* gene editing. Funding for each study will be \$240,000 total (inclusive of 10% indirect costs) for a duration of two years.

BACKGROUND

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic syndrome affecting 1 in 3,000 people worldwide, with lifelong progression. The hallmark of NF1 is the development of multiple peripheral nerve sheath tumors, including cutaneous (cNF) and plexiform neurofibromas (pNF), which, although histologically benign, cause significant morbidity. Other characteristics include skin findings such as café-au-lait macules, axillary or inguinal freckling, additional tumors such as optic pathway gliomas, gastrointestinal stromal tumors, pheochromocytomas and gangliogliomas as well as bone and vascular anomalies, and a high incidence of cognitive difficulties. pNF in some NF1 patients can develop into malignant peripheral nerve sheath tumors (MPNSTs). NF1 patients are also predisposed to other malignancies, including breast cancer. The manifestations and clinical severity of NF1 are highly variable, with significant differences sometimes seen within the same family.

Loss-of-function mutations in the *NF1* gene cause this syndrome, and 50% of cases are due to new mutations without any family history. The NF1 protein product, neurofibromin, is a large protein that negatively regulates Ras signal transduction pathways. Lack of normal neurofibromin function due to *NF1* mutations constitutively activates effector pathways, leading to altered downstream functions. There are other functions of neurofibromin that are less-characterized, such as regulation of cAMP. The germline mutational spectrum of NF1 is exceptionally wide-ranging, with over 2800 mutations comprising splice site, nonsense, missense, and frame shift mutations, as well as insertions, deletions, and translocations reported. However, none has a frequency over 4%. This and NF1's variable expressivity has precluded establishing clinically relevant genotype-phenotype correlations with the exception of a small selection of mutations. Most NF1 features involve clonal expansion of a cell that

suffered somatic mutation of the other *NF1* allele (two-hit phenomenon); the somatic mutation spectrum is equally wide. For example, neurofibromas arise from Schwann cells containing an *NF1* mutation on both alleles, leading to enhanced cell proliferation and survival. *NF1* is also somatically mutated in non-syndromic cancers such as sporadic melanoma, glioblastoma, AML, lung, ovarian, breast, pancreatic, and prostate cancers.

Despite significant morbidity, an effective long-term therapy for *NF1* is an unmet medical need at this time. Although surgical debulking is still often the preferred treatment option for tumors such as pNFs, this can be extremely complicated if the tumor is intricately involved with nerve tissue, vasculature, or a vital organ. Surgery is rarely performed for *NF1* optic pathway gliomas; symptomatic gliomas are typically managed with chemotherapeutic agents, which, though effective, are not ideal for benign tumors such as in *NF1*. Although there are numerous clinical trials targeting downstream signaling, there is no approved therapy for *NF1* yet. Thus, a pressing need exists to develop effective nonsurgical treatments for *NF1*. Given the diversity of clinical expression/progression, and underlying biology, additional approaches such as gene therapy need to be considered. Genome-based therapies, being explored in other genetic conditions, are approaches that aim to target the original defect rather than a downstream effect. The Children's Tumor Foundation (CTF) is particularly interested in targeting Schwann cells for this initial study, due to the substantial morbidity from neurofibroma burden and mortality from malignant transformation of pNFs.

OBJECTIVE AND SCOPE

The objective of this RFA is to support proof of principle *in vitro* studies to investigate the feasibility of genome editing techniques, including but not limited to those based on CRISPR-Cas9, to correct pathogenic mutations in *NF1* gene. The ultimate goal of this initiative is to explore the development of genome editing as a potential therapeutic tool for *NF1*.

Projects must propose to target at least 3 *NF1* mutations, including a frameshift and a point change: c.499-502delTGTT and c.625C>T (Q209X). Rationale (in letter of intent and full proposal) should be provided regarding additional mutations selected for targeting; ideally they would be among those most recurrent in *NF1*, such as c.1466A>G or c.6789-6792delTTAC.

Experimental outcomes should include: (1) evidence indicating whether the editing reagents can correct the mutation(s) (and characterization of off-target effects), (2) degree of success in delivering the reagents to Schwann cells, and (3) a functional assay showing efficacy.

The application may also include an *in-vivo* development plan to test efficacy in animals upon *in vitro* success, which could lead to opportunities for future funding.

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 welcomed 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-NF1 researchers with expertise in gene editing are highly encouraged to apply. The non-NF expert applicant can either decide to include an NF expert in the team or will be paired up with an NF mentor through CTF.
- 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)

The Children's Tumor Foundation requires its patent policy to be signed by all awardees and recipient institutions. Since the National Institutes of Health are 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

Only two applications will be selected for funding, each for a total amount of \$240,000 for two years. The funding amount includes indirect costs, which must not exceed 10% of the total award.

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 an LOI formatted in Arial 11 point detailing –

- Project outline describing key aims/approaches of the study (1-page maximum)
- Composition of the team (1-page maximum)

LOIs will be due by 5:00 pm EST on **Friday, November 9, 2018** and must be emailed to grants@ctf.org AND vbrowder@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 2,500 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.
- **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. The two-year total must not exceed \$240,000.

- **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 (approved LOIs) will be due by 5:00 pm EST on **Wednesday, December 5, 2018** and must be emailed to grants@ctf.org AND vbrowder@ctf.org.

REVIEW PROCESS

Full applications will be evaluated by a review panel comprised of experts in NF1 and gene editing research, taking the following elements into consideration –

- Likelihood that the findings of the proposed research will have a clinical impact/implication
- 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 submit 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 the Children's Tumor Foundation.

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 U.S. 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

CTF believes in making data from all of its funded projects freely accessible irrespective of whether the findings were positive or negative. Data sharing policies will be discussed with grant recipients prior to award activation. CTF also strongly encourages researchers to voluntarily share NF drug discovery tools, such as mouse models, cell lines, candidate drugs, that are created from their funding. Terms of a material transfer agreement to facilitate this will be discussed prior to award activation.

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 submission 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 the Children's Tumor Foundation in such disclosures. CTF also requires that the awardee provide 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.