

## REQUEST FOR PROPOSALS

# GENE-TARGETING STRATEGIES FOR NEUROFIBROMATOSIS TYPE 1

September 1, 2017

The **Gilbert Family Foundation (GFF)** is pleased to announce a Request for Proposals (RFP) for high-impact translational research in **gene-targeting strategies** that address the underlying genetic abnormalities in neurofibromatosis type 1 (NF1) and have the potential to eradicate the disease. Proposals will be accepted for **Team Science Awards** defined as collaborative research amongst investigators with experience in gene-targeting strategies in or outside the field of NF1. Through research that may be funded based on responses to this RFP, GFF plans to fund at least \$7 million among multiple research institutions over three years.

### INTRODUCTION

**Neurofibromatosis type 1 (NF1)** is an autosomal dominant, monogenic disorder that affects 1 in every 3,000 individuals throughout the world. Hallmark features of NF1 include multiple café au lait (light brown) skin spots, neurofibromas (small benign growths) on or under the skin, and tumors on nerves that can lead to disfigurement, blindness, and cancer. NF1 can also result in cognitive disability, skeletal deformity, and cardiovascular malfunction. The course of the disease is both unpredictable and variable among individuals. Even within the same family, patients may experience vastly different symptoms with varying degrees of severity.

NF1 results from mutations or deletion of the [neurofibromin 1 \(NF1\) gene](#), which encodes a negative regulator of the Ras signal transduction pathway called [neurofibromin](#). To date, drug development has primarily focused on addressing the molecular abnormalities that arise downstream of the *NF1* gene mutation/deletion. There are no therapies that address the underlying issue of this genetic disease; present therapies do not cure the disease.

GFF is a 501(c)3 nonprofit organization founded by philanthropists Dan and Jennifer Gilbert to address their two priorities and passions: accelerating a cure for NF1 and transforming the city of Detroit, Michigan. To begin its NF1 focus, GFF will embark on two bold research initiatives: (1) the Gilbert Vision Restoration Initiative, inspired by their son's loss of vision from NF1 and with a goal of advancing vision enhancement and restoration therapies (which is not the subject of this RFP), and (2) the **Gilbert Gene Therapy Initiative (GGTI)**, to develop innovative therapies that address the underlying genetic abnormalities in NF1 patients. In its first phase, GGTI will explore the feasibility of multiple gene-targeting therapeutic strategies for NF1 as well as novel or enhanced *in vivo* gene delivery systems.

### OBJECTIVE AND AREAS OF INTEREST

In November 2016, GFF and the Milken Institute Center for Strategic Philanthropy convened 14 NF1 and gene therapy experts to identify high-impact opportunities to accelerate the development of promising gene-targeting strategies for NF1. In particular, the meeting participants discussed four therapeutic approaches that should be explored for NF1 and form the grant topics for this RFP. In addition, the experts described the need for novel or enhanced systems for delivering the therapeutic payloads.

The objective of this RFP is to identify promising gene-targeting strategies that address the underlying causes of NF1, have the potential to eradicate the disease, and prepare them for subsequent preclinical and clinical development. A responsive proposal must establish the feasibility of one of the following gene-targeting approaches for NF1 and/or develop an enhanced or novel gene delivery system. Proposals that articulate a clear path to NF1 clinical application will be strongly favored.

- **Gene Replacement**

Clinical manifestations of NF1 result from loss-of-function of neurofibromin protein, which is coded by the *NF1* gene. Inserting the full-length, wild-type *NF1* gene to replace mutant alleles may restore neurofibromin levels and function. However, the *NF1* cDNA (8.5kb) is larger than the cargo capacity of present commercially-available vectors. Therefore, delivering a truncated version of the *NF1* gene that retains an appropriate level of gene/protein function could be explored as an option as well.

- **Gene Editing**

Gene editing is a recent therapeutic strategy that could circumvent the challenges of delivering new full-length or truncated *NF1* genes. However, because there are thousands of unique *NF1* gene mutations, a more economic gene-editing therapy may fix certain regions along the gene that are associated with a higher incidence of mutations, or mutation hotspots.

- **Exon Skipping**

*NF1* gene mutations that are isolated to a particular exon are attractive targets for the exon skipping approach as functional neurofibromin expression may be achieved if the problematic areas are skipped over. Likewise, exon skipping could be used to recapitulate the milder phenotype that is associated with a 3-base pair in-frame deletion in exon 17.

- **Mutation Suppression**

At least 20% of *NF1* gene mutations are nonsense mutations. Although an individual patient may only have one nonsense mutation (that is, the other allele is normal or has a different type of *NF1* mutation), rescuing the neurofibromin expression from this mutant allele may have therapeutic significance.

- **Gene Delivery Systems**

Targeted and efficient delivery of therapeutic payloads remains a major challenge for human gene therapy treatments. Considerations for effective gene delivery systems in NF1 include:

- Because the full-length *NF1* cDNA is 8.5kb, a full gene replacement approach would require engineering of present vectors to increase their cargo capacities or novel delivery systems.
- NF1 patients are born with a germline *NF1 mutation* and incur somatic mutations on the second allele throughout their lives. A cure for NF1 may entail addressing the somatic mutations and the germline mutation, which would require maximal *in vivo* systemic transduction efficiency.
- Therapeutic strategies that do not alter the genome may require long-term administration to NF1 patients, which include infants and children; thus, safety is of particular concern.

**GFF will not consider funding:**

- Research whose *ultimate* goal is to treat existing manifestations of NF1, e.g., dermal neurofibromas, rather than address the underlying genetic abnormalities in NF1.
- Research that does not have a potential to eradicate NF1 as a disease.

## KEY SELECTION CRITERIA

- **Innovative and transformative research:** Novel approaches with strong scientific rationale that could advance the development of a gene therapy-based strategy to address the underlying genetic abnormalities in NF1.
- **Potential for rapid progression to clinical testing:** Proposals that articulate a clear path to NF1 clinical application will be strongly favored.
- **Scientific merit:** Outstanding and rigorous proposals as determined by peer review.

## TEAM SCIENCE AWARD

Awards for team science are designed to foster a collaborative research process amongst researchers with complementary expertise and capabilities, who will work together to advance new therapeutic solutions for NF1. GFF expects to provide **at least \$7 million over three years** among **multidisciplinary teams of two or more established Principal Investigators (PIs)**, providing at least **\$1.2 million per team** to undertake projects with a clear potential to lead to novel gene therapy for NF1 patients.

Teams may consist of investigators from the same institution, different institutions, and may be international. The designated Administrative PI is responsible for administrative leadership. All PIs on the team share authority for scientific leadership.

Team Science Awards have a collaborative and multidisciplinary emphasis, involving meaningful collaboration between participants. **Applications therefore must include a description of the nature of and rationale for the proposed collaboration, the specific role of all PIs, and synergistic opportunities.** Evidence of prior productive collaborations between members of the team is also useful.

## APPLICANT ELIGIBILITY

**PIs must hold a full-time faculty or industry appointment at the level of Assistant Professor (or equivalent) or above at an academic, non-profit research institution, or industry organization whose primary mission is medical research within or outside the United States.** PIs must be able to show clear evidence of an independent research program. Fellows or those in other training or research support positions are not eligible. Investigators need not be specifically trained in the field of NF1 or have any documented experience with NF1 research. However, researchers who are new to NF1 are strongly advised to work closely with an NF1 research expert and to consult existing literature on the disease during the formative stages of the research plan. If there are any questions about eligibility, please contact GFF before submitting an application. Contact information appears at the end of this RFP. Applications from PIs who do not meet the eligibility criteria will not be reviewed.

**An investigator may serve as PI on only one proposal submitted to GFF.** Multiple applications will be accepted from a single institution, provided that each application has a different PI and represents a distinct hypothesis.

## APPLICATION INSTRUCTIONS

There will be a two-stage peer-review application process:

1. Letters of Intent (LOIs) are due by 5:00 PM Eastern Time on September 29, 2017.
2. GFF will select one or more LOIs to advance to full review. For those applications selected to advance during review, full-length proposals are due by 5:00 PM Eastern Time on December 8, 2017.

**All applications are due by 5:00 PM Eastern Time on the dates specified above. LOIs and proposals received after the applicable deadline will not be considered.**

GFF utilizes the [proposalCENTRAL online application tool](#) and the document templates and requirements therein. Please carefully follow the instructions in [proposalCENTRAL](#) and below. Applications include the following steps and components.

### **Letter of Intent**

All applicants must submit a one-page LOI to GFF prior to submission of a full proposal. Please carefully follow the instructions in [proposalCENTRAL](#). The LOI application consists of the following components:

1. **Title Page:** Enter the project title.
2. **Applicant/PI Information:** Team Science applications must identify one PI for administrative purposes (the Administrative PI for the proposal). This is the Applicant.
3. **Organization/Institution Information:** This is the Administrative PI's institution.
4. **Key Personnel Information:** Identify other PIs on the team. All PIs share authority for project leadership.
5. **LOI: *1-page maximum*** that includes (a) a description of the scientific aims and translational potential and (b) the nature of and rationale for the proposed collaboration, the specific role of each participant, and synergistic opportunities. Letters exceeding the 1-page limit will not be considered.

### **Full-length Application**

Full-length applications will be invited from meritorious LOIs selected by GFF. Please carefully follow the instructions in [proposalCENTRAL](#) and below. Applications include the following steps and components.

1. **Title Page:** Enter the project title. For proposals involving multiple institutions, please include a total amount requested for each institution in the designated spaces provided.
2. **Templates and Instructions:** Download RFP and templates.
3. **Enable Other Users to Access this Proposal:** Allow others (e.g., institutional administrators or collaborators) to view, edit, or submit your proposal.
4. **Applicant/PI:** Key information about the applicant PI. This ***must*** be the Administrative PI on team science applications.
5. **Organization/Institution:** Key information about the Applicant/PI's institution, including name and email address of the signing official who, in addition to the PI, will be contacted if the award is selected for funding.
6. **Key Personnel:** List and provide contact information for key persons. Include all PIs on the proposal as well as any additional key personnel.

7. **Abstracts and Keywords:** Provide a lay audience friendly abstract and a technical abstract (2,000 characters maximum each) and key words. Please note: the lay abstract will become public if the award is selected for funding; therefore, it should not contain any proprietary information.
8. **Budget Period Detail:** Enter budget detail for each award period requested. GFF will not support indirect costs, overhead costs, or other similar institutional levies in excess of 5% of the total award amount. Fringe benefits for personnel salaries are allowable.
9. **Budget Summary and Justification:** A summary of the budget detail will be shown. In addition, the budget will provide sufficient detail for the evaluation of the major portions of the budget that are being requested. If more space is required than is provided in the proposalCENTRAL forms (2,000 characters), applicants may upload the budget justification in document form in step # 11. For proposals involving more than one institution: Do not include partner institution costs under contract costs but rather make it clear in your application which costs are appropriated to which collaborator. The contract cost category should only be used for contracts with outside facilities for performance of services.
10. **Organizational Assurances:** IRB and IACUC approvals, if applicable.
11. **Upload Attachments:** Upload the following:
  - a. **Curriculum vitae for PIs and other key personnel:** Applicants may use the template provided or the NIH biosketch format.
  - b. **Current and pending research support for the PIs:** Use the template provided in proposalCENTRAL, which includes a statement of overlap. Any overlap of current or pending support with the GFF proposal must be described and explained.
  - c. **Project description:** Must be formatted in Arial 11 point or Times New Roman 12 point font with no less than ½ inch margins. **5 pages maximum**, inclusive of the following: Background and specific aims, preliminary data, **timeline, milestones**, experimental design and methods, figures (which may be embedded within the above sections), and rationale/fit with key criteria, including the potential for clinical impact. Descriptions exceeding the 5-page limit will not be considered.
  - d. **Literature references:** A list of up to 20 references (maximum) supporting the project description is allowed, in addition to the 5-page project description.
  - e. **For multi-institutional proposals:** Attach a letter from the Administrative PI's institution confirming that if the award is made, the institution will execute the necessary sub-award agreements within 30 days of execution of the award agreement between GFF and the applicant institution and will transfer funds from their institution to the collaborating institution(s).
12. **Validate:** Check for any missing required information.
13. **Signature pages:** Print the signature page, which must be signed by the PI and the institution's signing official, and uploaded as part of the application package.
14. **Submit:** Please note that no proposals will be able to be submitted past the deadline. Technical support for the on-line application system is not available after 5:00 PM Eastern Time.

## TIMELINE

- **September 29, 2017:** Letters of Intent are due by 5:00 PM Eastern Time
- **Early November:** Teams from meritorious LOIs are invited to submit full length proposals
- **December 8, 2017:** Full-length proposals are due by 5:00 PM Eastern Time
- **December 2017/January 2018:** peer and organizational review
- **Late January 2018/Early February 2018:** Awardees notified (GFF may adjust the notification date without notice to applicants)
- **April 2018:** Projects commence

## REVIEW MECHANISM

All proposals will undergo rigorous peer review by GFF, comprised of experts in NF1 and diverse areas of gene therapy research. Applications will be scored according to the Key Selection Criteria (above). GFF will provide reviewer critiques or evaluations to applicants through proposalCENTRAL. Depending on peer review and GFF program priorities, GFF may work with applicants to modify the submitted work plan and/or budget.

## AWARD ADMINISTRATION

### AWARD LETTER

Upon acceptance of an award, the PI and his/her employing Institution will be required to sign an Award Letter indicating acceptance of GFF's Award Terms and Conditions within 30 days. GFF must be notified in advance and approve of any significant changes in research objectives, key personnel, or budget both at the time of the award and throughout the term of the award. This includes moves of key personnel between institutions.

### APPROVALS

GFF requires certification through proposalCENTRAL of compliance with Human Subjects and Animal Care Assurance as applicable. In cases where ethical/regulatory approval is required to perform the work, such approvals will be required before initial payments are made.

### MULTI-INSTITUTIONAL PROJECTS

For projects including key personnel at other institutions, the PI must verify in advance that funds can be transferred from his/her institution to the collaborating institution. This requirement can be met by attaching a letter from the PI's sponsored programs office stating a commitment to comply with this requirement. Sub-award agreements between collaborating institutions must be executed within 30 days of GFF's execution of the award agreement with the applicant institution, and will be subject to GFF's Award Terms and Conditions.

### FUNDING

For all proposals, the level and duration of funding may be adjusted by GFF as appropriate for the scope of the proposal and the funds available. Partial funding will also be considered to obtain proof-of-principle data in support of innovative ideas with transformative potential. GFF will not provide more than 5% of the total award amount for indirect costs, overhead costs, or other similar institutional charges. Full-term funding will be contingent upon review of annual progress reports and other oversight activities conducted by GFF. Multi-year support is not automatic for any GFF award and is

conditioned on submission of complete and accurate progress reports and demonstrated progress on the funded proposal.

### **ANNUAL MEETING**

PIs whose projects are selected for funding are expected to attend the annual GGTI meeting, at which they will present research findings made under their awards. GFF will cover reasonable travel costs related to participation in these meetings.

## **FREQUENTLY ASKED QUESTIONS**

### **Eligibility**

**Q: Must PIs have an academic faculty appointment? Is this a hard-and-fast rule?**

A: PIs must have a full-time appointment at an academic, non-profit research institution or biomedical-focused industry organization at the level of Assistant Professor (or equivalent) or above; however, while a tenure-track is preferred, it is not required. Evidence of independent investigator status and an environment conducive and supportive of translational research is required. If there is any doubt or question about a PI's eligibility, please contact GFF (contacts provided below) before an application is submitted. Applications from PIs who do not fit the eligibility criteria will not be reviewed.

**Q: Does GFF fund investigators and institutions outside of the United States?**

A: Yes, investigators at institutions outside of the United States are eligible. PIs must be at the level of Assistant Professor or equivalent. Academic appointments of institutions outside of the US can differ from those traditionally found in the US. Contact GFF if there are any questions about eligibility prior to submitting a proposal.

### **Application Components**

**Q: How are proposals submitted? Do I need to send a hard copy?**

A: All proposals must be submitted electronically via [proposalCENTRAL](#). The signature page should be signed and a scanned PDF copy be uploaded as part of the application in proposalCENTRAL. Hard copies will not be accepted.

**Q: Does GFF require the NIH salary cap to be used when calculating salary and fringe benefit requests for the budget?**

A: No, but applicants may use it at their discretion.

**Q: What needs to be included in the "current and pending support" section?**

A: Please submit a listing of all sponsored research support for the effort of the PI that is active or pending (submitted or awarded by a research sponsor but not yet started). Include the name of the title of the project, research sponsor, total annual funding, start and end dates, and percent of committed time. For each project, you must include a statement of overlap or non-overlap with the GFF proposal. A template is provided in proposalCENTRAL.

**Q: Is the NIH biosketch CV format acceptable for submission to GFF?**

A: Yes, you may use your NIH biosketch or the template provided in proposalCENTRAL.

## **ADDITIONAL INFORMATION AND CONTACTS**

For questions regarding this RFP and eligibility, please email Kathy Russell, Advisor to GFF, at [klrussell411@gmail.com](mailto:klrussell411@gmail.com).

For all other questions regarding GFF or its awards, please contact YooRi Kim, Scientific Officer of GFF, at [YooRiKim@gilbertfamilyfoundation.org](mailto:YooRiKim@gilbertfamilyfoundation.org).

Technical questions about the proposalCENTRAL submission system should be directed to their customer support at 800-875-2562 (Toll-free US and Canada), +1 703-964-5840 (Direct Dial International), or by email at [pcsupport@altum.com](mailto:pcsupport@altum.com).