# Request for Proposals (RFP) on enhancing therapeutic gene expression in human gene therapy for the Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC)

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|---|---|---|
| **A. FNIH RFP NUMBER:** 2022-BGTC003 | **B. DATE ISSUED:** June 9, 2022 | |
| **C. ISSUED BY:** | **D. ADDRESS OFFERS TO:** | |
| FNIH<br>11400 Rockville Pike<br>Suite 600<br>Bethesda, MD 20852 | **D.1. HARD COPIES (if required):**<br><br>Electronic Submissions Only | **D.2. ELECTRONIC COPIES:**<br><br>BGTC@fnih.org |
| **E. FOR INFORMATION REGARDING THIS SOLICITATION CONTACT:** | | |
| **E.1. NAME:** Brad Garrison | **E.2. EMAIL:** bgarrison@fnih.org | |
| **IMPORTANT:**<br><br>**F.** To be considered for award, Offers must be received at the location specified in Block D.2. above by 11:59PM Eastern Time August 28, 2022. Offers must be clearly identified with the solicitation number provided in Block A above. | | |

The Foundation for the National Institutes of Health, a non-profit, 501(c)(3) charitable organization that supports the National Institutes of Health (NIH) in its mission to improve health by forming and facilitating public-private partnerships for biomedical research, is issuing a Request for Proposals (RFP) to support the Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC). The BGTC is executed by FNIH as a public-private partnership involving the NIH, the U.S. Food and Drug Administration (FDA), multiple pharmaceutical companies, non-profits and patient advocates and is dedicated to making gene therapy a reality for people with rare genetic diseases affecting populations too small to be viable from the current commercial perspective. Given its precompetitive research focus, any publications and/or Intellectual Property (IP) generated from the efforts of the BGTC must adopt a "team science" approach and are intended to fall within the public domain, consistent with the AMP principles outlined herein.

Despite the potential for substantial therapeutic impact, the limited access to bespoke, or tailor-made, gene therapy for ultra-rare diseases has been recognized by pharmaceutical, academic, NIH and FDA leadership. Ongoing discussions to address this issue have focused on using well-established adeno-associated virus (AAV) vectors as the single delivery technology, and the ability to facilitate and generalize access and processes for the development of bespoke gene therapies. In order to accelerate and advance the scalability, reproducibility, and regulatory ability to deliver individualized, or bespoke gene therapies to ultra-rare patient populations, the BGTC will combine studies focused on AAV biology as related to human gene therapy with a pilot clinical trial program manufacturing and testing AAV vectors in a more standardized fashion. The BGTC expects to use the research and clinical data to produce an operational playbook that invokes the use of streamlined templates, master regulatory files, and uniform production processes to inform and streamline future gene therapies. This model program provides a tremendous opportunity to

impact patients with very rare diseases and offers hope for a pathway toward the commercial viability of these treatments.

## Purpose

The overall goal of this RFP is to solicit proposals that will advance our understanding of how AAV transduces tissues and cells of clinical importance and/or develop approaches to significantly improve transduction efficiencies in such tissues and cells. The proposals can focus on any of the key mechanistic steps involved in transduction, either extracellular or intracellular events. Examples of transduction steps include extracellular transport across the blood-brain-barrier (BBB), extracellular transport through tissues, cellular receptor binding, cellular internalization and intracellular trafficking, escape from vesicles, nuclear entry, evasion of intracellular host cell innate immune responses, and viral genome processing and conversion to episomes. The ultimate goal is to enhance the therapeutic impact of AAV gene therapy in humans.

## Background

Advancing the understanding of AAV biology as related to human gene therapy has been identified as an important pre-competitive area that could benefit from a focused public-private partnership. Many areas of AAV biology, such as extracellular transport, cell entry, intracellular transport, and nuclear processing of the AAV capsid and genome, remain incompletely understood. Therapeutic efficacy in patients could be substantially improved by a better understanding of AAV biology, and optimization of key mechanistic steps. This RFP (2021-BGTC003) is focused on interrogating the biology of AAV in clinically important target tissues and cells to enhance therapeutic gene expression in patients.

## Specific Research Objectives

The overarching technical objectives for this RFP are to increase fundamental knowledge about AAV transduction biology and to develop solutions which improve one or more steps in the recombinant AAV transduction process. The topic area of investigation targeted by this RFP is improvement of therapeutic gene expression from recombinant AAV vectors in human gene therapy, which may include, but is not limited to, methods for research on and optimization of the following mechanistic steps:

- crossing extracellular biological barriers such as the blood-brain-barrier,
- internalization of the vector,
- endosomal state of the vector;
- trafficking to the nucleus;
- uncoating in the nucleus;
- second strand synthesis;
- concatemerization of the viral genome;
- regulation of therapeutic gene expression events,
- appropriate post-translational modification
- and trafficking of gene products.

Proposals must address a problem of relevance to clinical human gene therapy, such as mitigating off-target delivery, optimizing transduction in target tissues/cell types of clinical importance, addressing tissue- or cell-type specific toxicity, overcoming intracellular innate immune responses, etc.

Applications that propose novel, high impact approaches for investigating and/or improving AAV transduction, with or without HTS-compatible assays, will be considered. Submissions proposing the development of high-throughput screening (HTS)-compatible assays must be applicable to any human cell type and preferentially be designed such that assay(s) developed could be incorporated into existing NCATS screening capabilities by the conclusion of the term of the award. For further details, see Assay Development & Screening | National Center for Advancing Translational Sciences (nih.gov).

Topics listed below would be considered non-responsive to this RFP:

- Efforts to improve hepatocyte transduction efficiency
- Efforts to increase AAV replication and recombinant AAV production (see 2022-BGTC004, Request for Proposals (RFP) on enhancing AAV vector production for human gene therapy for the Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC))
- Research limited to treating a specific disease
- Research focused on the host adaptive immune response (i.e., B- or T-cell mediated responses) would be considered out of scope for this initiative (please see the Accelerating Research and Development for Advanced Therapies (ARDAT) project being conducted by the Innovative Medicines Initiative for more information on research efforts in host adaptive immune responses).
- Research focused on gene editing would also be considered out of scope (please see the PaVe-GT project being conducted by the NCATS for more information on research efforts in gene editing).

In addition to overall scientific merit and rigor, review criteria will include the following considerations:

- Is the work proposed focused on investigating and/or improving mechanistic steps in AAV transduction, either extracellular or intracellular in nature?
- Is the work likely to result in a clinically relevant enhancement of therapeutic gene expression in patients? Importantly, the use of relevant human cell models over exclusively mouse models will be taken into consideration.
- Is the work addressing a high value clinical question for human gene therapy? (e.g., optimization of hepatocyte gene transfer is not considered clinically critical compared to other pertinent questions)
- Will the research outcomes or technologies developed be broadly applicable for human gene therapy across disease indications and cell types?
- If the project proposes using NCATS HTS capabilities, are the assays compatible with the NCATS screening platform?
- Is the proposed work likely to result in tangible deliverables within the project period?

Additional funding considerations include:

- Availability of funds
- Current state of knowledge in the field at the time of funding
- Overall BGTC program balance and complementarity with other projects
- Innovation and the use of novel technology
- Impact in advancing knowledge of the defined subject matter
- Applicability to the specific aims noted in this RFP
- Grantsmanship and high quality of presentation of the materials

## Award Information

### I. Funds Available and Anticipated Number of Awards

The number of awards and the amount per award is contingent upon the submission of a sufficient number of meritorious submissions and proper budget justification within the proposal.

### II. Award Budget

Proposal budgets are limited to an amount up to $250,000 of direct costs per year for up to two (2) years and need to reflect the actual needs of the development of the proposed assay. Indirect costs (F&A) must be 15% or less, in addition to the proposed direct costs. Proper scientific and budget justification will need to be provided for evaluation. The proposal review working group reserves the right to award at a lower amount than requested.

### III. Award Project Period

The scope of the proposed assay work should determine the award project period. The request may be for up to two (2) years of funding. The earliest anticipated start date is November 1, 2022.

## Eligibility Information

Organizations eligible to apply are:

- Private or public sector
- US-based or international
- Able to comply with the necessary AMP BGTC intellectual property, data sharing, and publication guidelines (AMP BGTC Principles are described in Section II, Data, Publications and Intellectual Property).

## Proposal and Submission Instructions

### I. Submission Deliverables

Complete proposals will include:

- Proposal research plan, which should describe the information below, but more details can be provided in the proposal response template (Appendix 1):
  - Background, specific aims, preliminary studies (if applicable), research methods, other relevant supporting documents (optional)
  - Justification of the broader applicability of the targeted biology and rationale for why improved knowledge and/or improvements to the particular transduction step could benefit the AAV field beyond a specified disorder
  - If proposing NCATS-compatible HTS screening assays, proposals must address compatibility with NCATS HTS- assay guidance criteria (see: https://ncats.nih.gov/preclinical/drugdev/assay#criteria ) .
- Detailed budget that delineates:
  - Personnel
  - Reagents, materials, equipment, sample acquisition (if necessary)
  - Other requirements for work proposed

An example budget table can be found in Appendix 1

- Detailed budget justification
- Proposed project timeline
- One Biosketch for the Principal Investigator and no more than two Biosketches of co-Investigators, collaborators, or other contributors.
- Completed BGTC Proposal Submission Form (Appendix 1)

## II. Data, Publications and Intellectual Property

All applicants will be expected to comply with the AMP BGTC Principles as outlined below.

**Publications**
This project will operate under a "team science" approach, and publications generated by the Steering Committee will have joint authorship. Specific publication strategies will be developed by the Steering Committee prior to project start, including proposal for lead authors and co-authors. All publications and data resources generated by recipients of BGTC funding must acknowledge BGTC investigators and/or funder(s) and be made publicly accessible within 6 months of publication. Specific publication strategies will be discussed with the BGTC Steering Committee as needed.

**Intellectual property (IP)**
Given its precompetitive research focus and commitment to making results of that research available as broadly and promptly as possible, it is not expected that BGTC will generate novel IP. BGTC research partners may use pre-existing IP of the other BGTC research partners for work done under the partnership. BGTC research partners agree not to file patent applications on research discoveries made under the partnership, except in the rare instance when a consensus of FNIH and the BGTC agree that it is in the best interests of the partnership and public health to do so. IP developed under NIH awards are subject to applicable Federal law, regulation, and policies.

## III. Page Limit & Margins

Please limit your response to 10 pages or less (single spaced, 11-point Arial or Times New Roman font), including figures and legends, excluding cover page and attachments (Biosketches, detailed budget, budget justification, letters of support, etc.).
Each Biosketch should not exceed 3 pages.
Further section length suggestions are provided in Appendix 1.
Please use standard one-inch margins throughout

## IV. Award Reporting

For those proposals selected for award, the Principal Investigators on the award should expect to submit progress updates for the project every 6 months in a format that will be described in the award agreements.

## V. Additional Information Required

Please provide any existing IP or patent information relevant to the assay that may affect its use in the partnership, or the banking of any resulting data funded by this effort in a public controlled access database for use after initial publication of the findings. Further guidance is available upon request.

## VI. Submission Instructions

Send responses via e-mail to BGTC@fnih.org with a copy to Mr. Brad Garrison, Senior Project Manager (bgarrison@fnih.org).

## Key Dates

**Submission Due Date:** August 28, 2022, 11:59 PM Eastern Time

**Targeted Submission Review Period:** August 29, 2022 – October 28, 2022

**Potential Oral Presentations from Finalists (*If Needed*):** Date TBD
*Applicants will be informed after initial review of proposals whether they will need to provide an oral presentation with the ability for Q&A to the BGTC Proposal Review Working Group*

**Award Announcement:** *Anticipated* Q4 2022

**About the Foundation for the NIH**
*Established by the United States Congress to support the mission of the NIH – improving health through scientific discovery in the search for cure – the Foundation for the NIH is a leader in identifying and addressing complex scientific and health issues. The Foundation is a non-profit, 501(c)(3) charitable organization that raises private-sector funds for and manages a broad portfolio of unique programs that complement and enhance NIH priorities and activities. For additional information about the Foundation for the NIH, visit www.fnih.org.*

Appendix 1


# BGTC Proposal Submission Form and Response Template

| | | |
|---|---|---|
| **Title of Project** | | |
| ***Principal Investigator(s) (submitter)***<br>Name:<br>Title:<br>Submitting Organization:<br>Address:<br>e-mail:<br>Tel:<br><br>***Co-investigator(s) (add more as needed)***<br>Name:<br>Title:<br>Submitting Organization:<br>Address:<br>e-mail:<br>Tel: | | |
| **Submission Date:** | | |
| **Time Period of Project:** | | |
| **Project Total Budget:** | | |
| ***Internal Use Only*** | | |
| WG Decision, Date: | | |
| Steering Committee Decision, Date: *(if needed)* | | |
| Executive Committee Decision, Date: *(if needed)* | | |

## Section 1: Project Overview *(500 words maximum)*

Describe the assay to be developed, the clinical/scientific need for the assay, and the capability gap being addressed.

***1.1 Specific Aims and Objectives***

***1.2 Project Deliverables/Outputs***

***1.3 Applicability*** *- Describe why this project is appropriate for the BGTC RFP, the pre-competitive nature of the project, and how the project is novel.*

- Include a brief description of other efforts known to the applicant to ensure non-duplication.
- Does the work proposed have scientific merit?
- Is the work proposed focused on investigating and/or improving mechanistic steps in AAV transduction, either extracellular or intracellular in nature?
- Is the work likely to result in a clinically relevant enhancement of therapeutic gene expression in patients? Importantly, the use of relevant human cell models over exclusively mouse models will be taken into consideration.
- Is the work addressing a high value clinical question for human gene therapy? (e.g., optimization of hepatocyte gene transfer is not considered clinically critical compared to other pertinent questions)
- Will the research outcomes or technologies developed be broadly applicable for human gene therapy across disease indications and cell types?
- If the project proposes using NCATS HTS capabilities, are the assays compatible with the NCATS screening platform?
- Is the proposed work likely to result in tangible deliverables within the project period?
- Provide an estimate and calculation for the % improvement that can be expected in efficacy or other metric, as a result of this work.

## Section 2: Scientific Design *(2000 words maximum)*

***2.1 Background and Supporting Data***

- Including Precision, reproducibility, target tissue

**2.2** ***Experimental Plan***

- Describe in detail the scientific strategy, design and logistics. Include how the study design will address the project goals and objectives.
- Describe in detail the experiments to be conducted
- Describe the type of data to be analyzed (retrospective and/or prospective)

**2.3** ***Analytical Methods***

- Describe in detail analytical methods that will be used.
- Provide a statistical analysis plan, including power calculations.
- If any studies are designed to replicate preliminary data or findings from prior studies, please describe those clearly.

**2.4** ***Technologies and Assays***

- Describe the current technologies or assays to be used in the project.
- Provide analytical validation data for the assay(s) to be used.

**2.5** ***Human/Animal Subjects***

- Will human or animal subjects be involved in this Project? If so, how?

## Section 3: Data Sharing and Intellectual Property Management Plan *(1000 words maximum)*

*Please note: Use of pre-existing IP and sharing of newly generated IP must comply with AMP BGTC Principles described in Section II, Data, Publications and Intellectual Property.*

***3.1 Describe pre-existing intellectual property (IP) that could have a bearing on the project.***

***3.2 List any relevant existing patents and patent applications held by key participants in the project (include patent number, title, submission date).***

***3.3 Describe any new IP that may be generated.***

***3.4 Describe plans for risk management concerning:***

- Data use
- Data security
- Legal compliance

***3.5 Describe plans for depositing data in the BGTC Data Portal or a similarly approved public database prior to initial publication.***

*Please note: Data sharing plans must comply with AMP BGTC Principles described in Section II, Data, Publications and Intellectual Property.*

## Section 4: Timeline, Milestones, Deliverables and Budget *(1000 words maximum)*

***4.1 Provide a timeline for deliverables, and an end date for the project.***

***4.2 Describe the milestones and how will progress on achieving them will be assessed.***

- Describe any opportunities for interim feasibility assessment(s) based on Project progress.

***4.3 Project Budget***

- Please complete the high-level budget table (see next page) *in addition to* attaching a detailed budget justification explaining the need for the costs requested with detailed breakdown of costs. Submission will not be reviewed if both of these items are not included.

| Category | % FTE | Year 1 | Year 2 | Total |
|---|---|---|---|---|
| **Personnel** | | | | |
| List each FTE individually with their percentage | | | | |
| | | | | |
| | | | | |
| **Supplies** | | | | |
| | | | | |
| **Equipment** | | | | |
| **Subcontracts** | | | | |
| List each individually | | | | |
| **Total Direct Cost** | | | | |
| **Overhead** (15% of direct costs in lines above) | | | | |
| **Total Project Costs** | | | | |

***4.4 Detail any existing funding relationships.***

## Section 5: Program Support *(500 words maximum)*

***5.1 List key personnel, including names, titles and role in the Project.***

- List collaborators, advisors, and/or hired consultants outside the consortium. Include letters of support.

## Section 6: Legal Agreements

***6.1 Legal Agreements***

- List any contracts, memoranda of understanding, grants, data or material transfer agreements that are likely to be necessary to execute the project plan.

## Attachments

- Detailed budget and budget justification
- Biosketches (*max three Biosketches not to exceed three pages each)*
- Letters of support