# ACCELERATING MEDICINES PARTNERSHIP
# NEW PROGRAM PROPOSAL FORM

Individuals or groups interested in proposing a new program area for the Accelerating Medicines Partnership (AMP), whether in an existing or new disease area, should complete this proposal form and submit it via email to the Foundation for the National Institutes of Health at AMP@FNIH.org.

The purpose of the submission is to define succinctly and clearly the proposed problem, background and rationale for the proposed program, what work is proposed, how it will be done, and how it might be funded. (**Please note that AMP does not have pre-existing funding for new programs; funds must be raised or prioritized out of public and private sector sources).** It should also be made clear why this is a good fit for AMP. Please see the attached summary of AMP and relevant policies.

| | |
|---|---|
| Proposed program name/descriptor | Accelerating Medicines Partnership for Gene Therapy (AMP-GT) |
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| Submission Date: | May 29, 2020 |
| Disease Area of Project | Gene therapy, ultra-rare disease |
| Estimated duration of the project | 5 years |
| Estimated total cost of the project | $102.5M |

## 1. Problem statement – Describe the critical scientific problem or capability gap being addressed, and the clinical/scientific significance of the problem.

Gene therapy approaches to treat, or potentially even cure, disease have been growing in interest and development activity. In some cases, the results of these treatments have been spectacular, demonstrating particular promise in Mendelian genetic disorders. Since these disorders are both numerous – over 7000 have been defined – and currently poorly treatable – fewer than 5% of the disorders have any treatment approved by the FDA – increasing numbers of companies, research clinicians and patients' families have expressed interest in accessing gene therapy for patients and family members. Unfortunately, the current environment does not provide a clear or efficient path for access to these therapies, particularly when the disease population is extremely small or the requirement is an individualized treatment and therefore of no commercial interest.

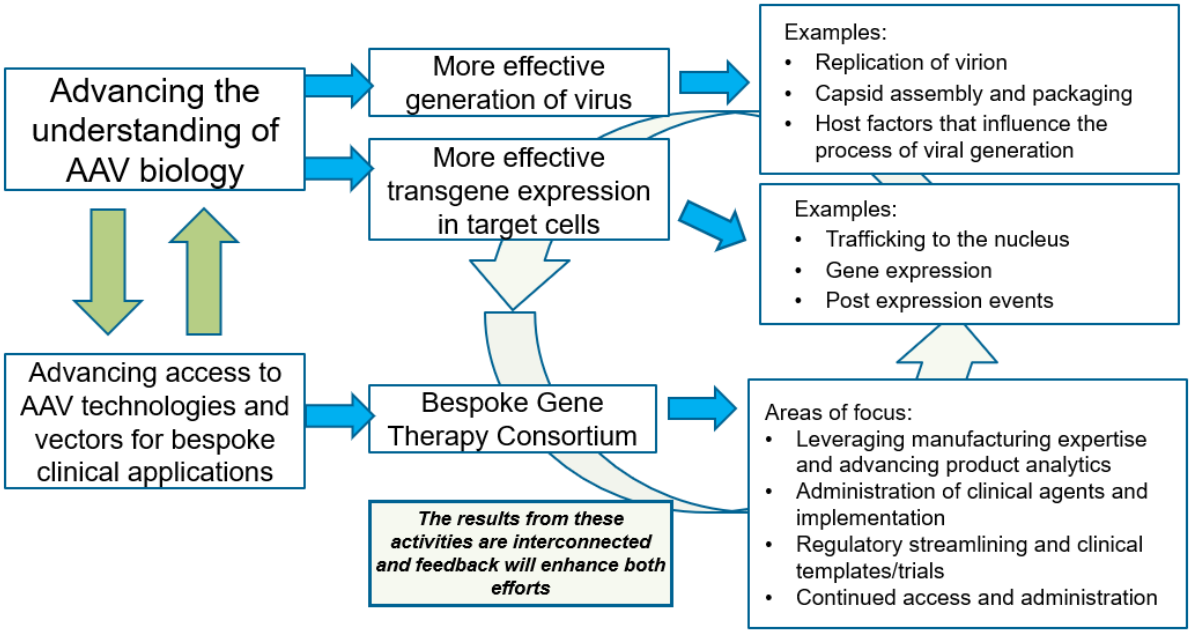
Roadblocks to broad and efficient application of gene therapy approaches to the thousands of disease populations that could potentially benefit are many. Of the approximately 7000 rare disorders, only a small fraction have a population prevalence high enough to support return-on-investment (i.e., commercial) development, even provided the current very high per-patient cost of treatment. The "long tail" prevalence distribution of rare diseases dictates that the vast majority of all currently living patients would need to be included in the clinical trials required for regulatory approval, leaving no patients to whom to market the treatment. The gene therapy approaches that are currently being employed do not allow for easy scalability, reproducibility, or regulatory generalizability. Many academic medical centers and biotech companies are using proprietary or unique processes and delivery agents to produce a given therapy. This approach requires every therapy to be treated individually and means that the regulatory process is long and difficult. Each proposed therapy needs to go through all preclinical and clinical testing, even if projects using the same or closely related vectors have come before. Equally daunting, global gene therapy manufacturing capacity has already been exceeded with current projects, leading to an average 2 year wait in the manufacturing queue. Though additional manufacturing capacity is being added in the private and public sectors, that capacity will at best double over the next several years, while demand is increasing exponentially – gene therapy IND applications to the FDA increased 10-fold in the last year alone. The increase in demand for gene therapy manufacturing, and the limitations in the development and regulatory path have led to a bottleneck in the ability to deliver these important new therapies to patients.

The limited access to gene therapy, especially to populations in the ultra-rare or bespoke[1] category has been recognized by pharmaceutical, academic, NIH, and FDA leadership. Ongoing discussions to address this issue have focused on a single delivery technology, Adeno Associated Virus (AAV), and the ability to facilitate and generalize access and processes for the development of bespoke therapies. An in depth understanding of basic AAV life cycle biology and standardization and streamlining of regulatory requirements are the areas of greatest need and largest potential impact for an Accelerating Medicines Partnership for Gene Therapy (AMP-GT).

## 2. Overview describing how you would propose that AMP address the problem, with goals and a summary of key objectives.

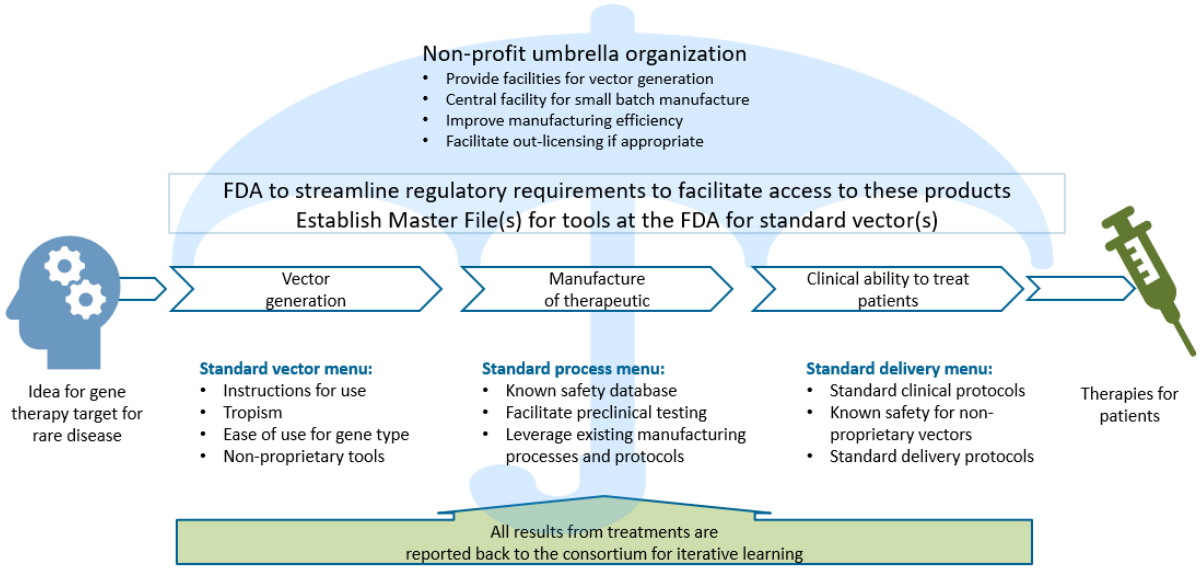
The AMP-GT initiative will address key unmet needs by establishing a precompetitive partnership to address two general areas of interest: 1) Advancing the understanding of AAV biology and 2) Advancing access to AAV technologies and vectors for bespoke clinical applications.

[1] "Bespoke" therapies are those made for a particular customer of user. As used here, the term refers to therapies for diseases where gene therapy is not currently commercially viable due to very low disease prevalence.




Advancing the understanding of AAV biology has been identified as an important area that could benefit from a focused public-private partnership. It is thought that lack of efficiency in manufacturing of AAV therapies is the result of incomplete understanding of the viral life cycle and the molecular steps associated with generation of the final product. Cross-sector expertise on the project development teams have recognized the need for a single delivery modality that could be used to develop a complete body of knowledge and allow standard vectors and protocols to be referenced for future refinement. Given the current choices, the team plans to focus on using AAV as the test case for more effective generation of virus and gene delivery to cells. The area of manufacturing science could be addressed in the precompetitive space by focusing on the basic science around AAV biology. Many areas of AAV biology remain poorly understood, such as viral genome packaging, virion assembly, virion release, post injection cell fusion and transport, and viral gene expression activation. Because of the differences in the expertise needed to address the mechanistic steps before and after injection, we plan to have two workstreams to generate a forward-looking plan to 1) elucidate the biology of the host cell to potentially increase productivity and generate a better quality gene therapy product and 2) interrogate the biology of AAV capsids and cargo in the events that follow receptor binding on the surface of the target cell.

Advancing access to AAV technologies and vectors for bespoke clinical applications has been focused on increasing the availability of AAV gene therapy approaches to populations of patients where no standard business case can be made for commercial therapeutic development. FDA has fully recognized the need for an end-to-end approach to the provision of individualized therapeutic products, particularly in the field of *in vivo* AAV gene therapy. The issues for these products include determining the quantity of supportive preclinical evidence needed prior to patient treatment, understanding the clinical information that should be captured, production of quality product fit-for-purpose – all in the context of an appropriate regulatory paradigm that facilitates safe patient treatment that has a reasonably high likelihood of being effective. Additionally, a sustainable way is needed to deliver these products if they show promise, since they are currently not considered viable from a commercial perspective. NIH, FDA and several private sector organizations are committed to proactively working with a range of federal, industrial, academic, and advocacy organizations to address the unmet medical need in this area. An outline of a framework for a public-private partnership or a consortium, which could be used to advance this field of work, is described below.




There are 4 major areas that require defined activity that can be separated and integrated later.

1) Vector manufacturing and characterization (with analytics)
2) Disease selection; construct development and supply of different AAV serotype vectors
3) Regulatory streamlining and clinical templates (central IND management)
4) Product availability (IND oversight) and data sharing by the consortium

This part of the program plan will focus on developing standard resources and protocols that would allow regulatory streamlining from concept to therapy delivery. Two established workgroups are focused on 1) enabling manufacturing and standardizing analytics (e.g., leveraging existing manufacturing experience, standardizing processes and product testing protocols, where possible) and 2) enabling clinical development (e.g. standard vectors and protocols). This part of the program and partnership, particularly workgroup 1, will include a large scientific contribution and strategic alignment with the Food and Drug Administration (FDA)[2]. These groups, along with FDA representatives, will create a set of standard reagents and approaches that will allow the generation of an "AAV gene therapy manual" that will guide the efficient generation of gene therapy products and delivery to patients using these standard approaches. It is anticipated that the results from the AAV biology investigations, which will be publicly released, will inform and enhance these procedures and increase access further.

## 3. Scientific strategy and proposed logistics

*(Outline project design, who would do what, use of novel or established technologies, timeline, key decision and funding milestones)*

The central strategy of AMP-GT is to establish a public-private partnership to provide end-to-end solutions for key issues limiting the development and application of gene therapy to ultra-rare genetic abnormalities. This concept suggests generating an umbrella organization to facilitate the development of bespoke therapies, and an increased focus on the basic biology of AAV to provide greater clarity on means to optimize vector generation and delivery. The umbrella organization (Bespoke Gene Therapy Consortium) will accelerate access by using a set of well characterized vectors and processes to generate therapeutics that the FDA could accept under a single or small number of FDA master files. The accelerating biology focus will be directed at understanding the host-virus interactions that might be altered to increase efficiency. Managing these two areas under one partnership will allow for rapid identification and testing of process modifications and feedback on their utility in the overall process. The program will focus on 4-6

[2] Marks and Witten, Toward a new framework for the development of individualized therapies (2020) Nature: Gene Therapy [https://www.nature.com/articles/s41434-020-0143-y]

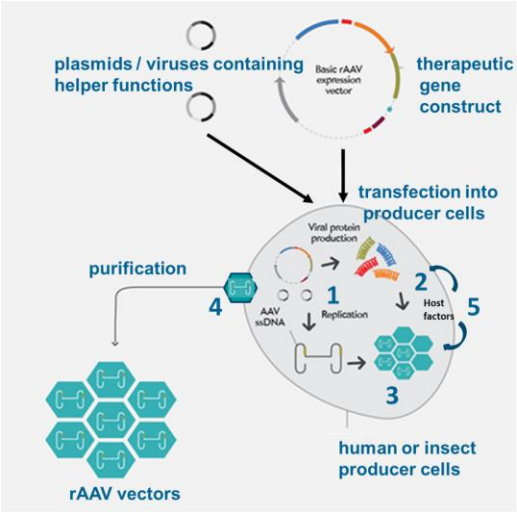
test cases from the large number of disorders of sufficiently low prevalence (~1-100 patients in the U.S.) or that, for other reasons, are unsuitable for any return-on-investment development model. It is anticipated that addressing the need for timely access to individualized gene therapies will also lead to technical developments that will advance the entire field of gene therapy.

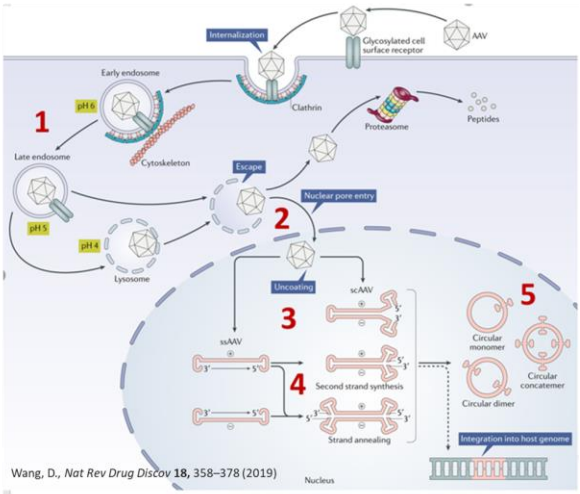
This focus will allow rapid understanding of the utility of the procedures in a pre-/non-competitive environment, and rapid feedback which, in turn, will allow faster refinement of the program processes. While initially directed at these very rare disorders, the technologies, paradigms, and information gained would be expected to be applicable to rare and common disorders with higher prevalence. Additionally, with appropriate careful scientific and technical planning, gene therapies that turn out to be applicable for modestly or significantly larger populations could potentially be seamlessly transferred from non-proprietary to proprietary systems. Such product out-licensing, in combination with licensing of any advanced production technologies that are incidentally developed, could potentially help sustain the public-private partnership financially beyond the pilot stage.

## 1. Advancing the Understanding of AAV Biology:

A lack of deep understanding of the life cycle of AAV has hampered innovation of generating more efficient AAV for use in gene therapy. A primary objective of this initiative is to focus on the events that precede and follow receptor binding on the surface of the target cell. Given differences in the major questions pre- and post-receptor binding, two subgroups have identified areas of interest and specific questions that could enhance manufacture and delivery of these therapies.

The mechanistic and functional understanding of the key steps the AAV must undergo to provide successful transcription and translation of the payload will be prioritized and plans will be suggested.




The following topics have been identified:

| Enhancing Vector Generation | Enhancing therapeutic gene expression in target cells |
|---|---|
| 1. Viral genome replication and processing for virion packaging | 1. The endosomal state of the AAV virion |
| 2. Capsid production and assembly | 2. Trafficking to the nucleus |
| 3. Packaging of viral genome to generate productive viruses | 3. Uncoating in the nucleus |
| 4. Transport and release of virus | 4. Second strand synthesis |
| 5. Host cell factors that influence the process of viral generation | 5. Concatemerization of the viral genome |

Specific research questions for each of these steps have been identified and are being discussed to assess the overall priority of each question and its likely impact on the overall efficiency on generation and delivery. During the discussions, the groups recognized that there were two potential targets of high impact research, understanding the host function and virus-specific functions. Given the number of high impact questions the group has recognized the potential utility of using whole genome and viral evolution strategies for identifying important bottlenecks in the host-virus interactions. The current discussion is focused on how best to design effective HTS approaches to these important questions.

**The proposed Advancing the Understanding of AAV Biology initiative will provide:**

- Greater understanding of how to manipulate host cells to increase the efficiency of production, which offers a huge potential for improving yield of high-quality AAV vectors.
- Increases in efficiencies will lower the cost of goods (CoG) as well as lower batch to batch variability and adverse effect related to packaging of non-vector genome sequences
- Improved understanding of the rAAV production system(s) in host cells, and assays for each key step will allow every stakeholder to optimize their production platforms independent of the underlying IP
- An enhanced understanding of the post-infection steps can optimize transgene expression and ultimately enable lower virus doses. This may lower the CoG, as well as reducing potential adverse effect related to the viral load in the patients.

These key objectives and learnings were viewed as falling within the pre-competitive space, and best tackled by a joint approach and partnership.

**The deliverables for the Advancing the Understanding of AAV Biology initiative will be:**

- Better understanding of the lifecycle of an AAV particle, which will enable rational design and optimization of AAV transduction efficiency
- Robust assays to quantitatively define interactions and viral and cellular cofactor subcellular location during multiple time points, will enable:
    - Optimization of production by selective removal or regulation of host genes
    - Optimization of sequences in the viral inverted terminal repeat to reduce non-vector packaging
    - Development and optimization of cell metabolism to maximize vector production
- Better understanding of the production host cell platforms and their interaction with components of AAV production resulting in a platform optimized for AAV production, opposed to a system that AAV can be generated in.
- Elimination of cellular inhibitors and bottlenecks to rAAV production, and inclusion of components in optimal stochiometric quantities and kinetics will maximize platform productivity and robustness
- Robust assays to quantitatively measure intracellular viral states, which can be used
    - for selection of optimized capsid variants
    - for optimization of cargo sequences
    - to screen for pharmacological tools or drugs which may increase AAV transduction efficiency in patients
    - to support development and optimization of PK/PD relationship for AAV transgene expression
- Improved transgene expression post-infection that will then allow lowering viral doses to the patient resulting in greater safety and reduced cost of goods

## 2. Advancing access to AAV vector manufacturing for bespoke clinical applications

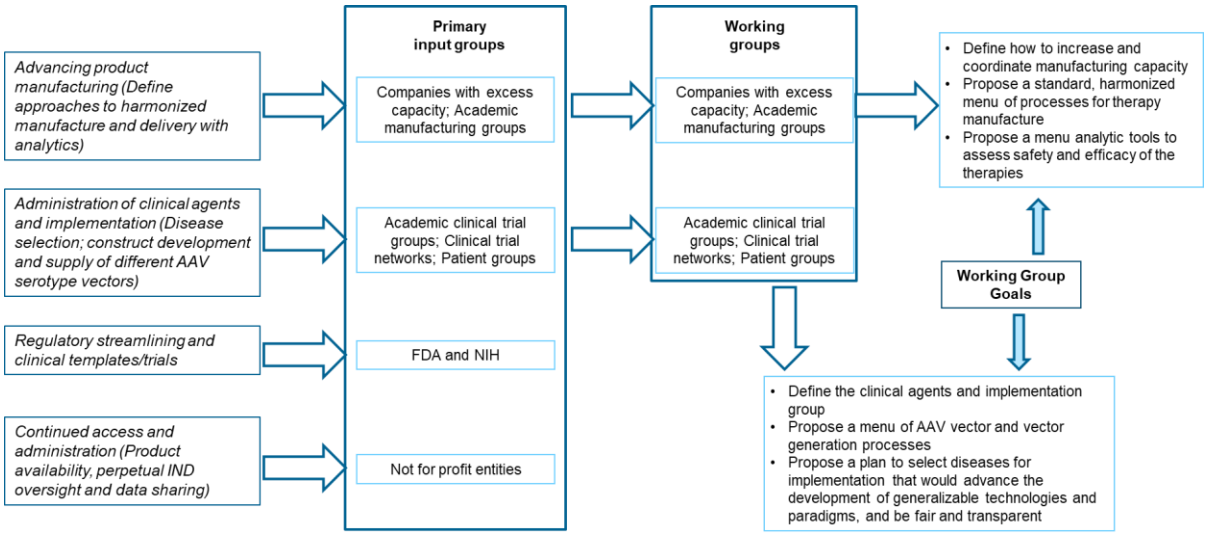
Manufacturing capacity limitations, efficiency of vector production, lack of adequate analytical/CMC assays, and human subject protection/regulatory issues pertaining to clinical studies have been identified as major roadblocks to broad and efficient use of AAV-based gene therapies for the thousands of very low prevalence human diseases whose molecular basis is understood and therefore have become candidates for bespoke gene therapy. A "Bespoke Gene Therapy Consortium", or BGTC, has been conceptualized as the second primary objective of the AMP-GT partnership to meet these needs. The BGTC will focus on the development and proof-of-principle demonstration of a standardized and efficient solution for delivering bespoke gene therapies. Given the multiple scientific challenges and operational complexity of such an effort, the BGTC team has begun by delineating the assumptions, scope, and next steps for this effort and key components of this initiative.

### Overall assumptions and steering principles

- The BGTC program is only expected to be needed until such time as efficient, scalable, and accessible paradigms for bespoke gene therapy and/or gene editing are established and available.
- The solution must address issues from end-to-end (construction of the gene therapy product to clinical administration and post-administration monitoring for safety and effectiveness)
- The BGTC effort is not attempting to deliver therapeutics for all diseases, all rare diseases, or even all very low prevalence diseases. Rather, it is intended to develop and promulgate a freely-accessible framework for clear, predictable and safe processes which could be used by anyone with the appropriate skill set to develop a bespoke therapy for their disease of interest (develop the AAV Gene Therapy Manual).

The BGTC identified four major areas that require focused discussion to define activities and deliverables:

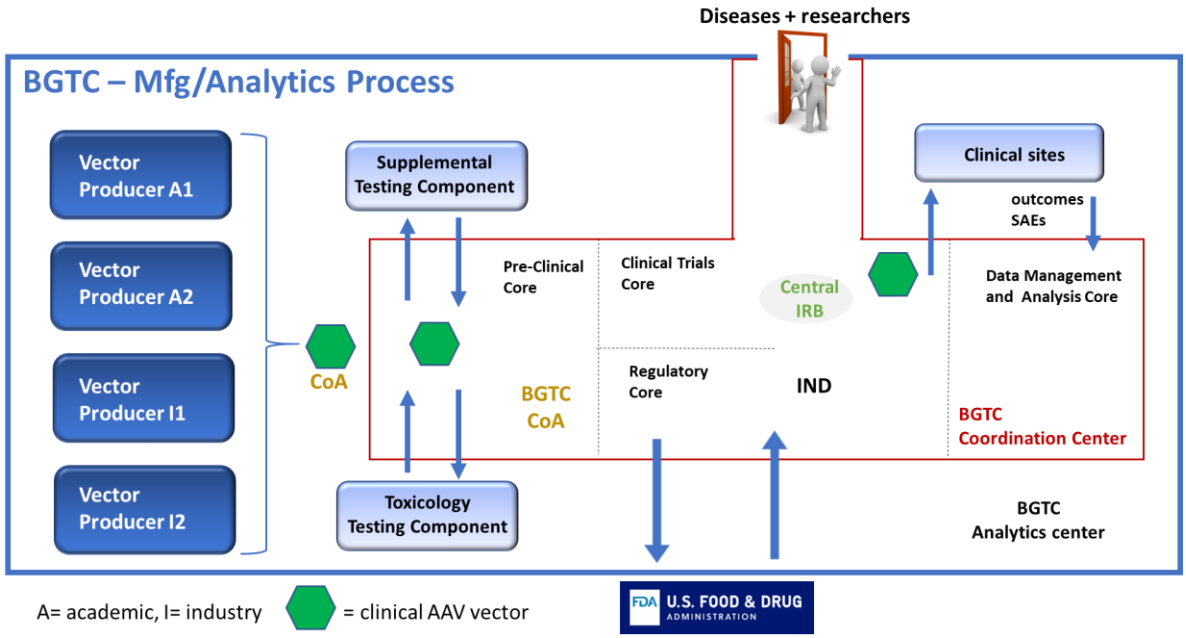
1) Advancing product manufacturing (leveraging existing manufacturing experience; standardizing processes, product testing protocols and analytics)
2) Administration of clinical agents and implementation (Disease selection; construct development and supply of different AAV serotype vectors)
3) Regulatory streamlining and clinical templates/trials
4) Continued access and administration (Product availability, perpetual IND oversight and data sharing)




The first two of these were deemed most pressing. Two sub-groups with representation from NIH, FDA, academia and industry have been assembled to address (1) and (2). Subgroup (1), the product manufacturing and analytics group, will define how to increase and coordinate manufacturing capacity, and propose a standard, harmonized menu of processes for therapy manufacture and analytic tools to

assess safety and efficacy of the therapies. Subgroup (2), the clinical agents and implementation group, will propose a menu of AAV vector and vector manufacturing processes, and a plan to select diseases for implementation that would advance the development of generalizable technologies and paradigms, and be fair and transparent. Topic (3), streamlining of regulatory process, will be addressed primarily by representatives from the FDA and clinical templates/trials by representatives from NCATS. Specifically, some of these templates will be generated from the NCATS PaVE-GT project. Likewise, topic (4), continued access, will be addressed at a later time once the program is more advanced.

These groups have identified several needs for central governing bodies that will consist of members of the partnership, NIH, FDA, industry, academia and rare disease groups, and will focus on coordinating manufacturing facilities and appropriate research and clinical sites for generation, manufacture and delivery of AAV therapies. The initial goal is to run a selected number of rare genetic diseases (5-6 total over the course of 5 years) through the process, setup standardized resources and procedures, and gather information from a spectrum of diseases (objectively and transparently chosen based on characteristics like size of population, local vs. systemic delivery, most appropriate current AAV serotype).

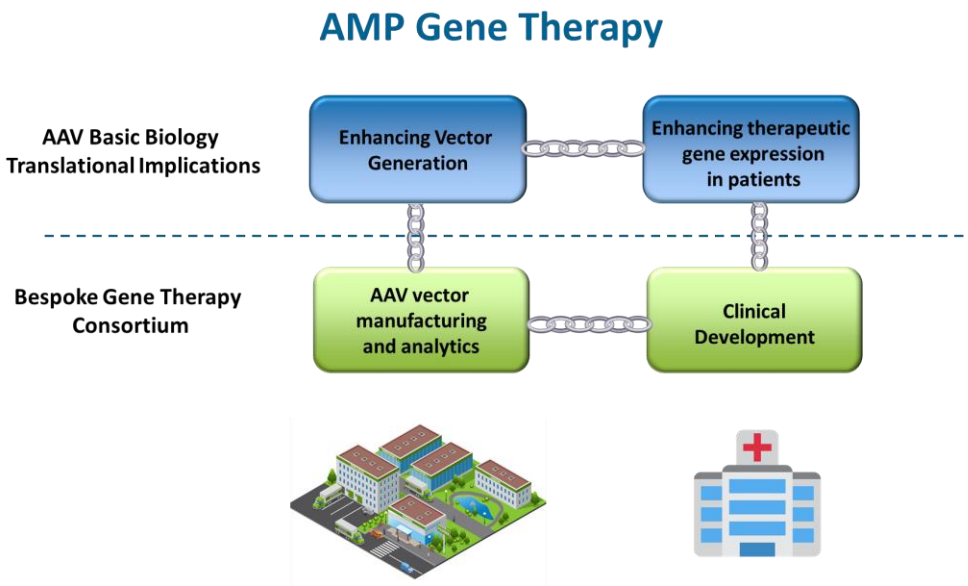



**The Bespoke Gene Therapy Consortium deliverables include:**

- Defining a menu of AAV vector and vector manufacturing ~~generation~~ processes
- A harmonized set of vector quantitation and lot release assays for all BGTC clinical vectors, which will facilitate the interpretation of adverse effects in the different trials.
- A fair and transparent algorithm to select diseases for inclusion in the trials and also facilitates BGTC goals, to be developed in consultation with patient advocacy groups and ethicists.
- A guidance manual for AAV gene therapy using the selected AAV serotype vectors.
- Organization and implementation of centralized training for a distributed model for delivery of AAV gene therapy, including visiting nurses to permit a larger geographic reach for outpatient gene therapy administration.
- The setup and implementation of a standing board of clinicians with expertise in AAV gene therapy trials to provide guidance to treatment centers and physicians who are not familiar with the common side effects of AAV gene therapy.
- A framework to manage the IND and address legal liabilities at different clinical sites, results and experiences from the execution of this multi-factorial pilot that will be valuable to the whole community and will facilitate future access to AAV gene therapies.

### 3. Crosstalk between Advancing the Understanding of AAV Biology and the BGTC

As indicated in the diagram below, there are parallels between components of the AAV biology initiative and the BGTC. Specifically, results from the Enhancing Vector Generation component could be directly translated to the AAV vector manufacturing and analytics component of the BGTC, whereas the results from the Enhancing Therapeutic Gene Expression component could be directly translated to the Clinical Development component of the BGTC. To facilitate this crosstalk, it is envisioned that the program will run experimental approaches sequentially so that learnings, from the initial wave for therapies and new information from the AAV biology group, can be incorporated into the second or third wave to enhance and refine the process.




## 4. What are the estimated costs? (Provide a rough breakdown of projected cost elements if possible).

AMP-GT costs are listed as cumulative estimates for each of the primary objectives of the partnership. Both direct and indirect costs are taken into account, noting that indirect cost rates are variable depending on the institution. NIH would provide support for the indirect costs on any of the NIH AMP-GT funded projects and awards. The AMP-GT partnership seeks co-investment of public and private sector partners: funding to supplement federal support from NIH or FDA. The program supported by the partnership and its expected deliverables will take approximately five years to complete. Total costs per private sector partner are estimated at ~$1M per year (financial and/or in-kind support; based on potential 10 partners). Discussion with interested private sector partners would be needed to build the budget for financial and in-kind support.

The process of generating this initial proposal that can be evaluated by the Accelerating Medicines Partnership leadership has taken approximately 3-4 months. If approved by the AMP leadership, the final plan refinement (with milestones and budget) will be completed in the summer of 2020. Following the completion of the final plan, funding could be complete by the end of 2020 with a program launch early in 2021.

A breakdown of the budget estimate for the initiative is below.

| AMP-GT program | Annual costs |
|---|---|
| Whole host and viral genome high throughput screening and additional targeted specific grants and contracts | $10M direct and indirect costs over a 5-year funding period |
| Cost of goods for manufacture and delivery of 5-6 gene therapies (~10 Pts/trial) | $8M direct and indirect costs over a 5-year funding period |
| FNIH Project management, meetings, and travel; includes outgoing research indirects | $2.5M direct and indirect costs in years 1-5 |
| Total Estimated Costs | $102.5M |

## 5. What prior results support the proposed program?

The goal of the ongoing PaVe-GT (Platform Vector Gene Therapy) program is to streamline and accelerate gene therapy clinical trials in rare diseases by moving from the current "one disease at a time" to a "many diseases at a time" clinical trials approach. Through the initiative, NCATS, in collaboration with other NIH institutions will use a single AAV vector as a common delivery platform for gene therapy trials in four different diseases, and all clinical vectors will be produced in the same facility using the same manufacturing and purification processes. The goal of PaVe-GT is to determine how a platform vector-based approach can increase the speed and efficiency of clinical trial start-up. Importantly, all the data generated from this project, including regulatory documents, will be placed into the public domain so that others can use it for their own clinical trials.

The BGTC component of the proposed AMP project can be seen as an expansion of the PaVe-GT concept with more diseases, more AAV vectors, more manufacturers, and multisite clinical trials, in the context of a public private partnership. Notably, portions of the regulatory documents from PaVe-GT can be utilized by the BGTC as well.

## 6. Describe why this is a good fit for AMP

### 6.1 How does the proposed research fit the mission of AMP?

This program is focused on the deeper understanding of the biological steps in the process of virus generation and delivery and how to translate these findings to patient populations. Inherently, the approach cannot be carried out by any one organization and the focus merges the interests of all stakeholders in the field.

### 6.2 Why is the research uniquely suited to being executed by AMP as opposed to other entities?

Collaboration between public and private partners is essential and will enable directed research to solve the challenges posed in this topic; provide learning opportunities for scientists in the gene therapy field; and foster open scientific interaction in the public domain. Much of the expertise in gene and cell therapy lies in academia, however, clear data important for therapeutic development regarding host responses, persistence of efficacy, redosing, and safety is lacking. Working together in this public-private partnership, combining the deep expertise and innovation in vector design, AAV biology, cell biology, and immunology

that resides in academia, with growing industry expertise and data emerging from clinical trials, as well as regulatory expertise lying in regulatory agencies, will create synergies that will enable the building of a data-driven consensus around AAV biology and bespoke gene therapy trial design and implementation.

### 6.3 Is the proposed research dependent on any existing patents or applications? How would any intellectual property that is generated be handled, consistent with AMP policies?

NIH will provide further details and be elaborated during plan development. As noted, the AMP GT program will work to adhere to the principles and policies established under AMP.

### 6.4 Is the proposed research dependent on any existing applications?

FDA to provide further details. Section will be elaborated on during plan development as this is contingent on what vector manufacturers are selected for the program, which assays may be selected for use in the core testing site(s), and potential use of the master file process for submission of information to FDA

### 6.5 How will data be shared, consistent with AMP policies?

AMP-GT will share data according to AMP policies. Summary addendum below.

## 7. Please identify known and potential funding partners.

### 7.1 Who would fund the project and why? (List likely government, company, non-profit, etc. sources)

The National Center for Advancing Translational Sciences (NCATS) mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of interventions that improve human health across a wide range of human diseases and conditions. Notably, the "innovative methods and technologies" that are NCATS focus include gene therapy, and the "wide range of human diseases" includes rare diseases, which are a special area of focus for NCATS, and for which gene therapy may have a particularly large impact. NCATS also manages the Office of Rare Diseases Research (ORDR) which guides and coordinates NIH-wide activities involving research for a broad spectrum of rare diseases including the Rare Diseases Clinical Research Network (RDCRN). RDCRN is a network of 22 consortia, each exploring 3 or more rare diseases, and are focused on longitudinal natural history studies, which can identify outcome measures that are an essential requirement for clinical trials, including gene therapy.

The FDA supports innovators developing new medical products around the world. To date, the FDA has approved four gene therapy products, which insert new genetic material into a patient's cells. The agency anticipates many more approvals in the coming years but is challenged by more than 900 investigational new drug (IND) applications for ongoing clinical studies in this area. FDA has released a number of important policy documents: six final guidances on gene therapy manufacturing and clinical development of products and a draft guidance, Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations. Dr. Peter Marks is a program lead for the AMP-GT program and author of the initial conceptualization of the core elements of the BGTC.

The National Heart, Lung, and Blood Institute (NHLBI) is the global leader in conducting and supporting research in heart, lung, and blood diseases and sleep disorders that advances scientific knowledge, improves public health, and saves lives. NHLBI supports the development of genetic therapies to treat genetic disorders such as cystic fibrosis, alpha-1 antitrypsin deficiency, thalassemia, hemophilia, and sickle cell disease.

The National Institute of Neurological Disorders and Stroke (NINDS) seeks fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS supports studies on the focal and global delivery of therapeutic genes for a wide variety of CNS disorders including ultra-rare diseases. Research focuses on stability and regulation of transgene expression and safety of both vector and expressed transgenes, similar to the objectives of AMP-GT. NINDS is also a major supporter of the Rare Diseases Clinical Research Network (RDCRN).

Representatives from the following companies have committed funds to support the concept design phase of the AMP-GT program. All have contributed expertise and experience to each of the core working groups described in this concept. Their participation and engagement portend an increased likelihood for further support for the program.

- UCB
- Eli Lilly
- Ultragenyx
- Bayer
- Roche
- Pfizer
- Sanofi
- Novartis
- Boehringer Ingelheim
- BMS

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In addition, there is strong interest in the rare disease community, both advocacy organizations and individual high worth individuals, to ensure their communities see the benefit of the results of this program.

## 7.2 Has this project been submitted elsewhere for funding; is there any potential funding overlap with other projects, ongoing or proposed?

A new NIH-based collaboration with industry will not duplicate but complement planned IMI or other pre-competitive efforts. Ideally, it will focus on new areas where progress can meaningfully speed up access to Advanced therapy medicinal products (ATMPs) through paths that will likely not be pursued with sufficient momentum by private sector players alone. The program will be designed with the opportunity to evaluate progress through the implementation of well-defined milestones.

### Existing EU IMI Initiatives

Innovative Medicines Initiative 2 (IMI 2) proposals of relevance include: (1) the ARDAT (Accelerating R&D of Advanced Therapy Medicinal Products, funded at ~$30M over five years) initiative that was submitted in April 2019 focusing on (i) generating data to understand the host response to viral vectors, persistence of expression, and re-dosing of vectors, (ii) developing improved, standardized models for predicting immunogenicity, (iii) identifying determinants of the host immune responses to gene and cell therapies and (iv) partnering with regulators to qualify methods and models that increase predictability and harmonize processes (https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview); and (2) the OPTiMize (optimizing patient access to ATMPs for rare diseases) proposal that was be submitted in September, 2019, which will focus on Improving patient access to ATMPs by enabling new value-based payment models for reimbursement, aligning the healthcare ecosystem with payer needs and bridging gaps between regulators and relevant stakeholders.

### Existing NIH Initiatives

An ongoing NIH gene editing initiative, the Somatic Cell Genome Editing program (SCGE, currently funded at ~$ 190 M over six years), is focused on improving the delivery mechanisms for targeting gene editing tools in patients, developing new and improved genome editors, developing assays for testing the safety and efficacy of the genome editing tools in animal and human cells, and assembling a genome editing

toolkit containing the resulting knowledge, methods, and tools to be shared with the scientific community (https://commonfund.nih.gov/editing). As part of this effort, a subgroup of SCGE investigators are carryout a comprehensive analysis of the tissue and cellular tropism of multiple AAV vectors, in both mice and non-human primates.

The NCATS Platform Vector Gene Therapy (PaVe-GT) Project is a collaboration among the ORDR, the NCATS Therapeutic Development Branch, the NCATS Office of Strategic Alliances, the National Human Genome Research Institute and the National Institute of Neurological Disorders and Stroke. As noted above, the goal of PaVE-GT is to of determine how this platform vector-based approach can increase the speed and efficiency of clinical trial start-up. Importantly, all the data generated from this project, including regulatory documents, will be placed into the public domain so that others can use it for their own clinical trials. These documents can also be used by the BGTC.

# SUMMARY OF THE ACCELERATING MEDICINES PARTNERSHIP (AMP)

The Accelerating Medicines Partnership (AMP) is a pre-competitive effort among government, industry, academia and non-profit organizations to harness collective capabilities, scale and resources toward improving current efforts to develop new therapies for complex, heterogeneous diseases. The focus of the partnership is on doing the research necessary to understand these diseases more fully, identifying the right targets to pursue for drug therapy, and thereby accelerating the ability to bring new medicines to patients in these diseases. To date AMP has established research programs in Alzheimer's disease, type 2 diabetes, rheumatoid arthritis, and systemic lupus erythematosus.

As AMP is designed as a precompetitive research partnership, new program proposals should be intended to observe the following AMP policies:

## Antitrust

The project participants agree that all research activities funded by the partnership fall into the pre-competitive space. There is to be no discussion of marketing activities.

## Confidentiality

The project participants agree that there is to be no sharing of confidential information as a "blanket rule." If sharing is required, a specific CDA will be established by relevant parties and FNIH.

## Solicitations

Solicitations will be open where practicable (or required by federal regulation).

## Conflict of interest

Any conflicts of interest that arise are to be documented and reviewed with FNIH and the Executive Committee, who will jointly develop a mitigation strategy.

## Publications

Projects will generally operate under a "team science" approach, and publications will have joint authorship where feasible. Specific publication strategies will be developed as part of each project plan.

## Data sharing

Findings will be shared broadly and quickly, in the interest of patients and the public health; in certain cases partnership participants may have access to findings during assessment of data quality (up to 6 months of QA/QC).

## Intellectual property

Pre-existing IP must be free to be used by the partnership. All research discoveries are intended to be released into the public domain, with no pre-emptive patenting. In rare instances when this is not possible, FNIH will determine fair strategies for distributing IP to encourage broad commercialization and balanced public health benefit and review them with the Steering Committee and Executive Committee.