Accelerating Medicines Partnership
Gene Therapy

August 26, 2020

Co-Leads:
Peter Marks, MD, PhD (CBER/FDA)
PJ Brooks, PhD (NCATS/NIH)
Gopa Raychaudhuri, PhD (CBER/FDA)
Seng H. Cheng, PhD (Pfizer)
Accelerating Medicines Partnership in Gene Therapy (AMP GT) - Program Plan and Partnering Webinar

General Goals

• Review and understand the scope, design, impact and deliverables of the AMP GT Program
• Understand the pre-competitive partnership opportunities to address the limited access to gene therapy for populations affected by ultra-rare diseases

The webinar is being recorded for archival purposes

○ Slides will be made available following the Webinar
Zoom Housekeeping Notes

Please mute yourself when not talking to reduce background noise. (You will be muted upon entering by the host, unless you’re a speaker.) The mute/unmute button is on the task bar on the bottom to the far left.

Please submit your questions and comments using the “chat” feature. We will use these responses during the Q&A at the end of the primary program sessions. Please be sure to send your chat to “everyone.”

If you are having trouble with Zoom, please contact FNIH Events (events@fnih.org) for assistance.
Today’s Presenters

Dr. P.J. Brooks  
Program Director, Office of Rare Diseases Research

Dr. Peter Marks  
Director, Center for Biologics Evaluation and Research

Dr. Joseph Menetski  
Associate Vice-President of Research Partnerships

Steve Hoffmann  
Director, Inflammation and Immunology
<table>
<thead>
<tr>
<th>Time</th>
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<td>11:30 AM</td>
<td>Introduction and Webinar Overview</td>
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<tr>
<td>11:35 AM</td>
<td><strong>Session 1</strong>: FNIH and the Accelerating Medicines Partnership</td>
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<tr>
<td>11:45 AM</td>
<td><strong>Session 2</strong>: The AMP Gene Therapy Program</td>
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<td>12:45 PM</td>
<td>Q&amp;A</td>
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<td>1:05 PM</td>
<td><strong>Session 3</strong>: Communications and Partnering Opportunities</td>
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<td>1:15 PM</td>
<td>Q&amp;A</td>
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<tr>
<td>1:25 PM</td>
<td><strong>Ongoing Actions, Timelines and Next Steps</strong></td>
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Session 1

FNIH and the Accelerating Medicines Partnership

FNIH
Who are we?
What do we do?
How we achieve it?

AMP
What is AMP?
How did we get here?
About the FNIH

The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people’s lives.

Founded by Congress

The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

Why Collaborate?

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity
By the Numbers

$1.2B raised to date

$0.90 of every dollar spent directly supports programs

600+ programs supported since inception

124 active research partnerships, scientific education/training, conferences/events, capital programs

17 years of “exceeds or meets industry standards” rating by Charity Navigator
Select FNIH Partnerships

- **Accelerating Medicines Partnership**
  NIH (OD), NIA, NIAMS, NIDDK, NINDS, 12 companies, 10 not-for-profit organizations
  - $302 million

- **Partnership for Accelerating Cancer Therapies**
  NCI, PhRMA, 12 pharmaceutical companies
  - $220 million

- **Grand Challenges in Global Health (GCGH)**
  Bill & Melinda Gates Foundation
  - $201 million

- **Alzheimer’s Disease Neuroimaging Initiative (ADNI)**
  NIA, NIBIB, 25+ companies, 3 not-for-profit organizations
  - $148 million

- **The Biomarkers Consortium**
  FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations
  - $95 million

- **LungMAP: Master Lung Protocol Trial**
  NCI (SWOG), FDA, Friends of Cancer Research, 10 companies to date
  - $40 million

- **Helping End Addiction Long-Term (HEAL) Partnership Committee**
  NIH contract
  - $0.4 million

Coordination and Programmatic Leadership

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)**
- **GeneConvene Global Collaborative**
The Accelerating Medicines Partnership
AMP Overview and Scope

• NIH partnered with FNIH, FDA, 10 biopharmaceutical firms, multiple non-profits (including patient advocacy groups), to:
  o Increase the number of new diagnostics, therapies
  o Reduce time, cost of developing them

• Investing >$350M in four projects (5-year initial commitment):
  o Alzheimer’s disease (launched in 2014)
  o Type 2 diabetes (2014)
  o Rheumatoid arthritis/Lupus (2014)
  o Parkinson’s Disease (2018)
  o Schizophrenia (Sept 2020)

• Project management provided by FNIH

Developing continuing (2.0) programs:
• AD
• Common Metabolic Disease (CMD) and
• Autoimmune and Immune-Mediated Diseases (AIM)

New program:
• Gene Therapy
<table>
<thead>
<tr>
<th>Disease</th>
<th>Industry Members</th>
<th>Government Members</th>
<th>Non-profit Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease</td>
<td>AbbVie, Biogen, GSK, Lilly</td>
<td>NIH, National Institute on Aging</td>
<td>Alzheimer's Association, U.S. Against Alzheimer's</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>Janssen, Lilly, MERCK, Pfizer</td>
<td>NIH, National Institute of Neurological Disorders and Stroke</td>
<td>American Diabetes Association, JDRF</td>
</tr>
<tr>
<td>Autoimmune Diseases</td>
<td>AbbVie, Bristol-Myers Squibb, Pfizer, SANOFI</td>
<td>NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases</td>
<td>Lupus Research Alliance, Arthritis Foundation</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td>Celgene, verily, GSK, Pfizer</td>
<td>NIH, National Institute of Neurological Disorders and Stroke</td>
<td>THE Michael J. Fox Foundation, PRMA</td>
</tr>
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</table>
Operating Principles of AMP

• **Simple governance:** Steering Committees under an overall Executive Committee
  o Steering Committee leadership by nominated co-chairs – one industry, one NIH or Academic
  o Firm rules on funding equity, in-kind contributions
  o Project management by FNIH to minimize overhead

• **Tight management of deliverables and timelines:** Concrete interim deliverables with go/no go on next phases based on interim findings

• **Industry engagement:** Participants ensure focus is on relevant, translatable research and provide contributions in-kind (e.g., relevant data)

• **Patient advocacy groups and foundations:** Ensure perspectives and needs of the disease patient populations contribute to project design and ongoing execution

• **Data Sharing:** Findings shared broadly and quickly, in the interest of patients and the public health

• **Pre-Competitive:** No pre-emptive patenting; broadest possible opportunity for commercialization
AMP Gene Therapy: Origins

Advanced Therapy Medicinal Products (ATMPs) development regarding host responses, persistence of efficacy, redosing, and safety.

HEVER Sr. Pharma Leadership

IMI Innovative Medicines Initiative

EFPIA

ARDAT
Accelerating Research and Innovation for ATMPs

Today

2019

- Q3 Workshop & Calls

2020

- Q2/Q3
- Q1/Q2
- June

Stakeholder Survey

F2F Mtg

Working Groups

Concept Approval

AMP Gene Therapy
Engaged Partnership with Strong Potential for Support

- Strong involvement and leadership from multiple NIH ICs, FDA & leading academic KOLs and Institutions

<table>
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<tr>
<th>NCATS</th>
<th>NINDS</th>
<th>NHLBI</th>
<th>NIMH</th>
<th>FDA/CBER</th>
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</table>

- Several pharma committed funds to support the design phase of the AMP-GT program
- Multiple representatives contributed expertise and experience to the core working groups

AveXis / Novartis  BMS  Eli Lilly  Roche  UCB
Bayer  Boehringer-Ingelheim  Pfizer  Sanofi  Ultragenyx
AMP GT Program Development Process

- “50/50” Public/Private Funding Split
- Broad, prompt access to data and results
- No preemptive patenting of IP

FNIH: LOAs with Private Sector Partners

PROGRAM LAUNCH

NIH Grants Solicitation and Awards Processes (FAR)

Detailed Research Plan
- NIH, FDA
- Private Sector Partners

Funding Agreements

Preliminary Support Commitments
- Govt
- Companies
- Non-Profits

Initial Research Outline ("White Paper")
- NIH, FDA
- Companies
- Academic KOLs
- Non-Profits
- Approved Concept May 29, 2020

AMP Executive Committee

Concept Evaluation

NIH Project Management and Support

FNIH
Session 2

The AMP Gene Therapy Program (AMP GT)

Variation on a Theme
Increased Activity in Gene Therapy

Number of IND applications to FDA is increasing noticeably and there are over 900 active INDs as of Dec 31, 2019.

Correlates with prediction of 40 to 60 product launches and more than 500,000 treated by 2030.
Approved Gene Therapies

**United States**
- Tisagenlecleucel (2017)
- Axicabtagene ciloleucel (2017)
- Voretigene neparvovec-rzyl (2017)
- Onasemnogene abeparvovec-xioi (2019)

**European Union**
- Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (2016)
- Tisagenlecleucel (2018)
- Axicabtagene ciloleucel (2018)
- Voretigene neparvovec-rzyl (2018)
- Autologous CD34+ cells encoding βA-T87Q-globin gene (2019)

Alipogene tiparvovec  
(approved 2012, withdrawn 2017)
Challenges of Individualized Therapies

• Manufacturing
• Nonclinical development
• Clinical development
• Product access

Current manufacturing platforms limit gene therapy production

Viability? (Cost) 1-100
Sweet Spot >100-10,000
Viability? (Technology) >10,000

Can leveraging validated processes facilitate the development of new products?
Benefits of AMP GT Partnership

• Makes adeno-associated virus (AAV) technology more accessible to a broader range of diseases

• Potential to streamline preclinical and product testing

• Facilitates scientific advances that will ultimately benefit entire field

• Bring therapies to all individuals in need sooner
Accelerating Medicine Partnership – Gene Therapy

AAV Basic Biology
Translational Implications

Enhancing Vector Generation

Enhancing therapeutic gene expression in patients

AAV vector manufacturing and analytics

Clinical Development

Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications

Bespoke Gene Therapy Consortium
AAV Basic Biology Working Groups

Vector Generation

Chris Frye  
P. J. Brooks*  
Deanna Portero  
Chris Boshoff  
Dimitris Papanicolaou  
Otmame Boussif  
Samih Yagmour  
Tim Charlebois*  
Markus Haindl  
Karen Vincent  
Marrah Lachowicz-Scroggins  
Emmanuel Adu-Gyamfi  
Bettina Buhring  
Enrique Michelotti  
Ingo Gorr  
Onur Kas  
Tal Kramer

Eli Lilly
NIH/NCATS
NIH/NCATS
NIH/NINDS
Novartis
Novartis
Novartis
Pfizer
Roche
Sanofi
NIH/NHLBI
FDA/CBER
NIH/NIMH
NIH/NIMH
Boehringer-Ingelheim
UCB
UCB

Gene Expression

Udo Maier*  
Feng Pan  
Zhao Cheng  
P. J. Brooks*  
Deanna Portero  
Jill Morris  
Dimitris Papanicolaou  
Otmame Boussif  
Samih Yagmour  
Suryanarayan Somanathan  
Joseph Rabinowitz*  
Andreas Schaubmar  
Catherine O-Riordan  
Pankaj Qasba  
Bettina Buhring  
Enrique Michelotti  
Onur Kas  
Tal Kramer

Boehringer-Ingelheim
Eli Lilly
Eli Lilly
NIH/NCATS
NIH/NCATS
NIH/NINDS
Novartis
Novartis
Novartis
Pfizer
Pfizer
Roche
Sanofi
NIH/NHLBI
NIH/NIMH
NIH/NIMH
NIH/NIMH
UCB
UCB

* WG Co-Chairs
Advancing the Understanding of AAV Biology

A. Enhancing Vector Generation

1. Viral genome replication and processing for virion packaging
2. Capsid production and assembly
3. Packaging of viral genome to generate productive viruses
4. Transport and release of virus
5. Host factors that influence the process of viral generation

B. Enhancing Therapeutic Gene Expression in Target Cells

1. The endosomal state of the AAV virion
2. Trafficking to the nucleus
3. Uncoating in the nucleus
4. Second strand synthesis
5. Concatemerization of the viral genome
6. Post expression events
Proposed Approach to Advancing AAV Biology

Strategy:
• **Support high throughput functional genomic approaches and targeted funding opportunities:**
  o Assays for each step in AAV vector production and gene expression in target cells amenable to high-throughput screening (HTS)
    ▪ Whole genome screening using siRNA, CRISPR
    ▪ Library of approved drugs
    ▪ Possibly using NCATS facility as a central testing site
  o Focused funding on specific questions that may not be covered by HTS approaches
Key Role of Gene Therapy Partners in AAV Biology

- Prioritize and weight questions and primary focus
- Shape the format and process for sharing results
- Continuous guidance of the research through periodic review of project(s)
- Suggest innovation to BGTC pilot program
Focus on the Bespoke Gene Therapy Pilot Program

Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications

AAV vector manufacturing and analytics

Clinical Development

Bespoke Gene Therapy Consortium
All results from treatments are reported back to the consortium for iterative learning.

Bespoke Gene Therapy Consortium (BGTC)

Non-profit umbrella organization
- Provide facilities for vector generation
- Central facility for small batch manufacture
- Improve manufacturing efficiency
- Facilitate out-licensing if appropriate

FDA to streamline regulatory requirements to facilitate access to these products
Establish Master File(s) for tools at the FDA for standard vector(s)

Vector generation
Manufacture of therapeutic
Clinical ability to treat patients

Standard vector menu:
- Instructions for use
- Tropism
- Ease of use for gene type
- Non-proprietary tools

Standard process menu:
- Known safety database
- Facilitate preclinical testing
- Leverage existing manufacturing processes and protocols

Standard delivery menu:
- Standard clinical protocols
- Known safety for non-proprietary vectors
- Standard delivery protocols

Therapies for patients

Idea for gene therapy target for rare disease
Non-profit umbrella organization

Instructions for use
Tropism
Ease of use for gene type
Non-proprietary tools

Known safety database
Facilitate preclinical testing
Leverage existing manufacturing processes and protocols

Standard clinical protocols
Known safety for non-proprietary vectors
Standard delivery protocols

Standard vector menu:

Standard process menu:

Standard delivery menu:

All results from treatments are reported back to the consortium for iterative learning.
Proposed Approach to Advancing Access by the Bespoke Gene Therapy Consortium

Strategy:

• Address the needs of getting a simple AAV generation/production manual (*Maniatis for Gene Therapy*) by coordinating and harmonizing the production of a set of vectors and processes that will allow rapid timelines and cost-effective delivery for the future:
  o Run 5-6 pilot projects for diseases with different prevalence, vector dose requirements, routes of administration (iv, it, subretinal)
  o Limited number (± 3) different AAV vector serotypes in the pilot
  o An algorithmic approach to identify appropriate target diseases by analysis of existing (and future) databases
  o Define and standardize vector quantitation, toxicity testing and lot release assays, in coordination with industry and academic manufacturers
BGTC Working Groups

Mfg & Analytics

- Peter Marks* FDA/CBER
- P. J. Brooks* NIH/NCATS
- Gopa Raychaudhuri* FDA/CBER
- Jude Samulski University of North Carolina
- Tim Charlebois Pfizer
- Samih Yaghmour Novartis/Avexis
- Kelvin Lee NIIMBL
- Barry Byrne University of Florida
- Bettina Buhring NIH/NIMH
- Enrique Michelotti NIH/NIMH
- Deanna Portero NIH/NCATS
- Richard Synder Thermo Fisher
- Sandy MacCrae Sangamo Therapeutics
- Chris Boshoff NIH/NINDS
- Jill Morris NIH/NINDS
- Laetitia Malphettes UCB
- Stefanos Grammatikos UCB
- Onur Kas UCB
- Maen Qadan Eli Lilly
- Chris Frye Eli Lilly
- Scott May Eli Lilly

Clinical Development

- P. J. Brooks* NIH/NCATS
- Beverly Davidson* CHOP
- Cheryl McDonald NIH/NHLBI
- Deanna Portero NIH/NCATS
- Kevin A. Strauss Clinic for Special Children
- Yael Weiss Ultragenyx
- Steven Gray UT Southwestern
- Enrique Michelotti NIH/NIMH
- Bettina Buhring NIH/NIMH
- Peter Marks FDA/CBER
- Gopa Raychaudhuri FDA/CBER
- Rachel Sher NORD
- Vanessa Boulanger NORD
- Chris Boshoff NIH/NINDS
- Jill Morris NIH/NINDS
- Khara Ramos NIH/NINDS
- Johannes Streffer UCB
- Marina Braun UCB
- Marcel Brink UCB
- Maen Qadan Eli Lilly
- Chris Frye Eli Lilly
- Scott May Eli Lilly

* WG Co-Chairs
Strategy to Leverage Existing Expertise and Capacity to Manufacture Gene Therapy Product for the Pilots

Industry Vector Manufacturers (n=3)

Academic Vector Manufacturers (n=3)

3 AAV serotypes
3 Mfg scales
5 – 6 diseases

GOAL: Transgene sequence is the only difference being introduced into an established manufacturing paradigm
Vector Manufacturing

• Manufacturer would prepare and test vector supplies for both preclinical/tox and clinical use

• Provide sufficient quantity of vector to supply treatment for clinical trial
  o Clinical indication matched and agreed upon in advance
  o Considerations: capacity, timelines, dose/patient, # of patients, storage stability → vector requirements met by one or two successful batches at the specified scale
    ➢ 0-100 doses for intravenous administration ($10^{15}$ vg/dose)
    ➢ 0-100 doses for intrathecal administration ($10^{14}$ vg/dose)
    ➢ 0-100 doses for intraocular injection ($10^{13}$ vg/dose)

• Manufacturer will supply vials (NIH to provide final labelling) and certificate of analysis (C of A)
  o No drug substance supply to be maintained (for simplicity)

Ongoing discussions with potential partners

Exploring Partner ability and willingness to manufacture and supply clinical vector as in-kind support for the pilot project
Release Testing and Specifications

• Identify critical attributes that must be evaluated
  o Examples: Vg titer, purity, capsid identity and concentration, full:empty, potency, endotoxin & sterility
  o Provide scientific rationale and justification for why these tests are most critical
  o Consider what may be leveraged from the manufacturer’s experience with the reference product, and whether reduced testing can be considered (scientifically justified) based on past experience/data

• Provide description of tests to be performed by the manufacturer (or Supplemental Testing Component, where applicable)
Assay Standardization and Harmonization

- Overall goal is to standardize testing, where possible
  - One specific goal is to standardize testing for vector copy number

- Current Perspectives
  - Manufacturers will test vector using their existing processes
  - Industry and academic manufacturing partners may need additional support to fulfil the testing requirements
  - NIH will establish a centralized testing facility to conduct supplemental testing, and also support product-specific testing (e.g., potency)

As the IND holder, NIH will be responsible for the CoA that is submitted to FDA to support the clinical trial
Engagement with FDA

• Consider establishing Master Files
• Early engagement with FDA staff for feedback on specific issues e.g., testing requirements for AAV-based gene therapy products
  o Focus on principles so feedback is generally applicable (not product-specific)
• Explore streamlining regulatory requirements – examples:
  o Leveraging pre-clinical and CMC data based on past experience with vector or similar GT product, if scientifically justified, to reduce testing of future iterations of a similar product
  o Innovative clinical trial design for bespoke products
• Full spectrum of formal FDA meetings available to support product development
  o e.g., CATT, INTERACT, pre-IND meetings etc.
• Pathway to licensure?
How to Prioritize Rare Diseases in the BGTC?
Evidentiary and Ethics Criteria for Disease Selection

- Draft criteria were developed and revised by representatives from gov’t, industry, academia, bioethics and patient advocacy
- Goal of establishing a complementary set of diseases, to allow maximum generalizability and potential benefit to the field
- Partners will have direct input and role in the final disease selection
- Highlight → this is a PILOT
  - Learning through the program
  - Improve as it matures
## BGTC Pilot Disease Selection Criteria

### Pre-Clinical Screening Template

<table>
<thead>
<tr>
<th>Invariant Criteria</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>U.S. prevalence &lt;1 per 100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established genotype-phenotype association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Amenable to AAV-mediated gene replacement (i.e. AR, X-linked)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Therapeutically relevant protein product &lt;666 amino acids</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variant Criteria</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robust clinical trial endpoints (patient-centered outcomes, biomarkers)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Valid animal model (e.g. mouse, swine, domestic, etc.)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Proof-of-concept data in animal model (i.e. efficacy)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Safety and/or overexpression data in animal model (toxicology)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No known commercial interest</td>
<td>Yes</td>
<td>No</td>
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</table>

**Extra Queries for BGTC Pilot Only**

### BGTC Pilot Study: Additional Screening Considerations

<table>
<thead>
<tr>
<th>Expected Magnitude of Benefit</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected benefit represents substantial improvement over current therapies</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected benefit substantially improves event-free survival</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected benefit substantially reduces psychomotor disability</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected benefit restores primary sensory modality (e.g., vision, hearing)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected benefit prevents end-stage organ failure (e.g., heart, liver, kidney)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Probability of Success</th>
<th>Yes</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>Established network of key opinion leaders to facilitate trial design</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Established patient advocacy and/or support group</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Existing patient registry</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Concentrated regional subject representation(s); e.g. ethnic groups</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected meaningful change of functional endpoint (e.g., gait) within ≤1 year</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expected meaningful change of biomarker (e.g., analyte) within ≤1 year</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Appropriate study power: expected benefit significant with N treated subjects</td>
<td>Yes</td>
<td>No</td>
</tr>
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<tr>
<th>Disadvantaged Populations</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Impacts newborns, infants, or young children</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Impacts non-Caucasian individuals</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Impacts socioeconomically disadvantaged populations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Impacts medically uninsured individuals</td>
<td>Yes</td>
<td>No</td>
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Getting to Final Selections

- Continued input and expertise from members of the Clinical Development WG
- Engagement and vetting of criteria and process with NIH Division of Ethics
- Transparency, clarity of process and program education will be an essential piece of the associated Communications efforts for AMP GT

*Core Ethical Values for Clinical Research Priority-Setting*

<table>
<thead>
<tr>
<th>Social Value</th>
<th>Acceptable Risk-Benefit Ratio for Individual Participants</th>
<th>Procedural Fairness</th>
<th>Complexities in implementing a “Selection Algorithm”</th>
</tr>
</thead>
</table>
| • Magnitude of benefits  
  • Probability of success  
  • Disadvantages | • Diseases/Trials - acceptable risk (AAV exposure) vs. benefit calculus  
  • Consider multiple levels: high risk/high reward; low risk/low reward selections | • selection be logical and transparent  
  • Impartial and not conflict of interest by decision-makers | • Multiple criteria may not work well for (Y/N)  
  • e.g. items within social value |
Clinical Trial Design and Development

• Wherever possible, leverage already existing NIH funded clinical trial programs
  o Rare Diseases Clinical Research Network (RDCRN) [https://www.rarediseasesnetwork.org/](https://www.rarediseasesnetwork.org/)
  o NINDS NeuroNext [https://neuronext.org/](https://neuronext.org/)
  o CTSA Program [https://ncats.nih.gov/ctsa](https://ncats.nih.gov/ctsa)
  o Other

• A single BGTC IRB

• Include board of expert clinicians in AAV GT trials to guide treatment and learning

• Pilot testing of visiting research nurses to allow administration of gene therapy in areas outside of major academic medical centers
Key Deliverables of the BGTC

• A menu of AAV vector and vector generation processes
• A harmonized set of vector quantitation and lot release assays
• A process for disease selection for trials
• Manual for AAV gene therapy using select AAV serotype vectors
• Establish board of expert clinicians in AAV GT trials to guide treatment and learning
• Framework to manage IND & legal liabilities; pilot studies for shared learning and future processes
• Implementation of results from Advancing the Understanding of AAV Biology component
Key Role of Gene Therapy Partners in BGTC Pilot

- Participate in the BGTC: learn first-hand and guide the pilot as program moves forward
- Engage on subteam(s) that are directly involved in the development and standardization and harmonization of testing processes, assays and regulatory interactions
- Continuous guidance of BGTC progress through periodic review of project
- Incorporate the innovations and understanding from the AAV biology research
The AMP-GT partnership seeks co-investment (50:50) of public and private sector partners: funding to supplement federal support from NIH and FDA.

<table>
<thead>
<tr>
<th>AMP-GT program</th>
<th>Annual costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole host and viral genome high throughput screening and additional targeted specific grants and contracts</td>
<td>$10M direct and indirect costs</td>
</tr>
<tr>
<td>Cost of goods for manufacture and delivery of 5-6 gene therapies (~10 Pts/trial)</td>
<td>$8M direct and indirect costs</td>
</tr>
<tr>
<td>FNIH Project management, meetings, and travel; includes outgoing research indrects</td>
<td>$2.5M direct and indirect costs</td>
</tr>
<tr>
<td>Total Estimated Costs</td>
<td>$102.5M</td>
</tr>
</tbody>
</table>
Decisions, Support and Partner Engagement

- Project Plan will expand on these key questions and how they interrelate → RFPs
- Proposals may be supported through multiple funding mechanisms (grants, contracts, collaborative and in-kind agreements); managed by NIH, FDA or FNIH
- AMP GT stakeholder representatives will have a meaningful role (e.g., subteam, decisions) to review, prioritize, select best proposals and outline the appropriate levels of support
Session 3

Communications and Partnering Opportunities
Communications

Help advance education and engagement strategies relating to gene therapy

1. **Fund and help develop special outreach to external stakeholders:**
   - Patient and research communities, regulatory authorities, industry, academia and other nonprofits
   - Dissemination of materials about the science of Gene Therapy
     - Infographics, FAQs, announcements, project results
     - Symposia (regional or national conferences), publications, commentaries, workshops, webinar(s), print and/or web materials or videos

2. **Fund and help develop materials to support internal stakeholders (project partners) in communicating about AMP-GT**
   - e.g., talking points, internal Q&A, preparation notes for speaking with media

3. **Support development of internal and external communications activities through an AMP-GT Outreach Working Group**
   - Share patient/family perspective(s) with scientific project team/SC

4. **Help with patient recruitment as necessary**
Development of AMP GT Webpage(s)

Good model in NCATS PaVe-GT
https://pave-gt.ncats.nih.gov/

Goal: Complement and link resources and information from multiple sources
Alignment and Scientific Sharing with Other Consortia

• Many pharma partners are also investing in complementary efforts
  o ARDAT – Accelerating Research and Innovation of ATMPs
    ▪ Advanced Therapy Medicinal Products (ATMPs) development regarding host responses, persistence of efficacy, redosing, and safety

• AMP GT will work with ARDAT and IMI leads to coordinate regular exchanges between the two programs (e.g., at conferences, F2F mtgs)

• Opportunity to bring greater visibility, involvement and expertise across programs
Proposed Industry Investment

Funding Support

• Proposed budget for AMP GT scientific program = $102.5M
• NIH/FDA anticipated support for 50% of budget
• Private sector desired support = the other 50% (~$50M)
• Seeking a minimum of 10 large Pharma partners: ~$1M / year over 5 years
• Tiered levels of investment of additional partners based on R&D budget

Representation

• R&D Stakeholders may appoint one representative as a full voting member of the SC
• Opportunities to nominate representatives with specific expertise and experience for subteams or special purpose groups are expected to be necessary in the program
  o Regulatory manufacturing, communications, etc.
Proposed Not-for-Profit, Philanthropist & Advocacy Organization Investment

Funding Support

- Key contributors: nonprofit, advocacy leaders, and philanthropists
- Join the Steering Committee as a Stakeholder and serve as a full voting member with a financial commitment of $100,000 or more per year
- Organizations and individuals donating between $99,999 and $25,000 annually may join the Steering Committee as non-voting members

Representation

- Stakeholders may appoint one representative as a full voting member of the SC
- Opportunities to nominate representatives with required expertise and experience for subteams or special purpose groups may emerge
AMP GT Steering Committee: Voting

- NIH, FDA, and not-for-profit organizations will have votes that will not exceed 50% of total
- Industry Partners will have the other 50% of the votes
- Academic investigators, whether provided funding by the project or not, may be added at the Steering Committee's discretion. To avoid potential conflicts of interest, such academic members would not be voting members
Time Commitments and Meetings

• Monthly SC teleconferences
• 1 – 2 face-to-face meetings of the SC per year
• The SC may elect to form Working Groups to advise the full Steering Committee on scientific, operational or technical issues
Timelines and Next Steps
AMP GT Program Development Process

- “50/50” Public/Private Funding Split
- Broad, prompt access to data and results
- No preemptive patenting of IP

**NIH Grants Solicitation and Awards Processes (FAR)**

**Detailed Research Plan**
- NIH, FDA
- Private Sector Partners

- **Initial Research Outline (“White Paper”)**
  - NIH, FDA
  - Companies
  - Academic KOLs
  - Non-Profits
  - Approved Concept May 29, 2020

- **Preliminary Support Commitments**
  - Govt
  - Companies
  - Non-Profits

- **FNIH Project Management and Support**
- NIH, FDA
- Private Sector Partners

**FNIH: LOAs with Private Sector Partners**
Ongoing Actions & Next Steps

• Collate questions and comments from Webinar (chat, follow-up emails, direct conversations) → send additional questions to FNIH

• Finalize the Project Plan (Q3 2020)
  o White paper and outline of pilot manufacturing process and engagement with BGTC Coordinating Center & FDA
  o Refinement of disease selection criteria
  o Continued development of a strategic plan for Communication efforts

• Formal Letters of Agreement sent to potential partners (Q4 2020)
Contact Information

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THANKS FOR YOUR ATTENTION
Back-up Slides
## AMP GT: Complementing and Expanding on NCATS PaVe-GT

### PaVe-GT and FDA-NCATS-FNIH Public-Private Partnership

<table>
<thead>
<tr>
<th></th>
<th>PaVe-GT</th>
<th>FDA-NCATS-FNIH Public-Private Partnership</th>
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<tbody>
<tr>
<td><strong>Diseases</strong></td>
<td>Four rare diseases selected</td>
<td>TBD # of diseases</td>
</tr>
<tr>
<td><strong>AAV Source</strong></td>
<td>Single manufacturer</td>
<td>Consortium ?</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>Make public all FDA communications and submissions</td>
<td>Adapt PaVe-GT templates ?</td>
</tr>
<tr>
<td><strong>Clinical Sites</strong></td>
<td>NIH Clinical Center</td>
<td>Multiple clinical sites ?</td>
</tr>
<tr>
<td><strong>AAV Serotypes</strong></td>
<td>Single serotype</td>
<td>Multiple serotypes ?</td>
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