Therapeutic platforms for rare monogenic diseases

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Disclosure Statement

• I have no conflicts of interest to disclose
• Any reference to off-label product use or clinical trials are made only in an educational context
• The views expressed are those of the speaker and do not necessarily reflect the policies of the National Institutes of Health or the Department of Health and Human Services
NCATS’ VISION

More treatments for all people more quickly
The Number of Disorders with Known Molecular Basis Is Rapidly Rising

But the number of diseases with approved therapies is lagging far behind (≈600)

Adapted from Online Mendelian Inheritance in Man (OMIM), https://www.omim.org/statistics/geneMap
New Strategies

• Shared molecular etiologies
  • Fewer diseases

• Platform Approaches
  • Many diseases at a time
Hypothesis: A Platform Vector Approach Will Increase Efficiency in Preclinical Testing and Clinical Trial Start-up

- **Platform Vector**
  - AAV Lead Candidates
  - Preclinical Development and Regulatory Pathway
  - Phase 1/2 Clinical Trials

- **Same**
  - Manufacturing Processes, Analytical Methods, Study Designs
  - Proof-of-Concept
  - Full IND-enabling Studies
  - INTERACT, Pre-IND, IND Filing

- **Common**
  - Clinical Protocols when Possible

**Use Common Processes and Make the Data Publicly Available**
Traditional clinical development paradigm
PaVe-GT clinical development paradigm:
Questions
PaVe-GT Status

• Lead candidate AAV9-hPCCA
• Orphan Drug designation template
• INTERACT Meeting publication in progress
  • Making documents public
• Pre-IND meeting anticipated mid-July
• Repeat for other diseases.

Rare Pediatric Disease (RPD) Designation Request for AAV9-hPCCA

This pdf file contains the RPD designation request for AAV9-hPCCA (NCATSBL-0746) and associated communications between NCATS and FDA OOPD.
Accelerating Medicines Partnership®
Bespoke Gene Therapy Consortium (BGTC)

Steering Committee Co-Chairs:
PJ Brooks, PhD (NCATS/NIH)
Tim Miller, MD (Thermo Fisher)
Peter Marks, MD, PhD (CBER/FDA)

Program Management:
Juan Esparza-Trujillo (FNIH)
Brad Garrison (FNIH)
Courtney Silverthorn, PhD (FNIH)
BGTC combines resources from a broad set of public and private partners

**Public commitments**

- **$39.5M**

**Private donations**

- **$35.7M**

**Private in-kind contributions**

- **$26.2M+**

Members:

- National Center for Advancing Translational Sciences
- Eunice Kennedy Shriver National Institute of Child Health and Human Development
- National Eye Institute
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- Biogen
- Danaher
- ELPIDA Therapeutics
- For Biologics
- Johnson & Johnson
- Novartis
- Pfizer
- Regeneron Bioscience
- Thermo Fisher Scientific
- Takeda
- American Society of Gene & Cell Therapy
- BRAIN Initiative
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Dental and Craniofacial Research
- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- National Institute on Deafness and Other Communication Disorders
- Food and Drug Administration
- California Institute for Regenerative Medicine
- Cure Duchenne
- FNIH
- Fighting Blindness
Accelerating Medicines Partnership® Bespoke Gene Therapy Consortium (AMP® BGTC)

- Make adeno-associated virus technology more accessible to a broader range of diseases

- Streamline preclinical and product testing

- Facilitate scientific and regulatory advances that will ultimately benefit the entire field
  - Standardized regulatory submission package templates

- Bring gene therapies to all affected populations sooner
  - Clinical development manual to help advance all future AAV gene therapies for rare diseases
AMP® Bespoke Gene Therapy Consortium Components

1. **AAV Basic Biology Translational Implications**
   - **Enhancing Vector Generation**
   - **Enhancing Therapeutic Gene Expression**
   - Eight research proposals selected for funding

2. **Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications**
   - **Create & Build Capacity**
   - **Harmonize Best Practices**
   - **Streamline Regulatory Paths**
   - Goal: Increase efficiency by orders of magnitude.
   - Therapies for patients
   - Gene therapy target for rare disease (62 initial submissions)
   - **CQAs (FDA Meeting held 9/29/22)**
   - **GLP/Tox (FDA Meeting June 2023)**
   - Goal: Standardized, faster, reduced $
Developing repeatable, optimized processes that can be used broadly

Submission of potential diseases to BGTC

- Single gene
- No business case
- Short follow-up
- Assembled patient group

Conduct trials of 5-6 diseases with high likelihood of clinical success selected by Steering Committee

Standardize manufacturing, pre-clinical characterization and clinical trials conducted using the same processes
BGTC clinical program aimed at creating repeatable, optimized processes that can be used broadly for Phase 1 clinical trials in rare diseases

62 disease nominations received

Open submission process for clinical, research, patient communities to nominate potential diseases

14 candidates announced July 2022

Down-selection based on required and preferred criteria, request full clinical trial proposals

Final selection announced May 16th

8 diseases selected

Paired with vector manufacturing for first-in-human clinical trial

- Disease/disorder info
- Patient demographics
- Clinical presentation
- Pre-clinical and clinical research history

- Monogenetic disorder
- No commercial business case
- Sufficient information to run a successful clinical trial
- Currently assembled patient group

- Cost
- Ability to secure AAV manufacturing
- Modest requirements for testing and follow up
- Patient/program diversity

- BGTC partners and/or RFI respondents
- Leverage prior work where possible

Disease Nomination Form
Clinical Trial RFP
Press Release
Clinical portfolio announced May 16, 2023

**Ocular**
- Congenital Hereditary Endothelial Dystrophy (CHED)
- Retinal Degeneration (NPHP5)
- Retinitis pigmentosa 45 (CNGB1)

**Neurological**
- Multiple Sulfatase Deficiency
- Charcot Marie Tooth disease type 4J
- Spastic Paraplegia type 50

**Systemic**
- Propionic Acidemia
- Morquio A syndrome (Mucopolysaccharidosis IVA)

*Elpida*
BGTC will develop and disseminate public resources for AAV gene therapy clinical development

Insights and learnings that will facilitate the success of future gene therapies for rare diseases:

- Improvements in AAV target gene expression
- Harmonized and validated sets of Critical Quality Attributes
- Guidance for pre-clinical testing requirements based on route of administration
- Standardized regulatory submission package templates
- “Vector Master Files”?
Prime editing substantially expands the scope and capabilities of genome editing, and in principle could correct up to 89% of known genetic variants associated with human diseases.
The purpose … is to provide support for applications that propose a novel genome editing clinical trial that includes at least two different diseases, using the same genome editor, route of administration, and delivery system.
SCGE Phase 2 - Accelerate the translation of *in vivo* genome editing therapies into the clinic

**Consensus needs:**

- Improved assays for assessment of quality, safety and efficacy of editing reagents
- Support for development and optimization of technologies for candidate genome editing therapeutics
- Tests of efficient regulatory pathways and *in vivo* genome editing clinical trials

**Technology development**

- SCGE Phase 2 Initiative 1
  - Assay Development

**Pre-clinical, IND-enabling studies**

- SCGE Phase 2 Initiative 2
  - IND Enabling Studies

**Clinical trials**

- SCGE Phase 2 Initiative 3
  - Clinical Trial Efficiency

**Dissemination**

- SCGE Phase 2 Initiative 4
  - Translational Dissemination Center
SCGE Phase 2 Initiative 5: TARGETTED (Targeted Genome Editor Delivery) Challenge

NIH will award up to $6M USD in prize money and provide independent testing for the most promising delivery vehicles in two Target Areas:

Research Objectives:
- **Goal**: Novel programmable delivery systems for gene editing and crossing the blood brain barrier (BBB).
  - **Programmable Target Area**: highly efficient programmable delivery system delivering genome editing machinery which targets at least 3 distinct cells, tissues or organs and be at least as efficient as the current state of the art
  - **Crossing BBB Target Area**: highly efficient nonviral delivery system capable of crossing the BBB to deliver genome editing machinery to a majority of target cell types in the central nervous system

Award: Top competitors could win up to $1M in prize money and have their solution independently tested and validated

**Submission Deadline**
October 5, 2023

[https://qrco.de/bdvZP](https://qrco.de/bdvZP)
Ultra-rare diseases
Nano-rare diseases
N-of-1, N-of-few

Therapeutic Platforms to treat monogenic disease

Many

One disease at a time