RARE DISEASES + ORPHAN PRODUCTS
BREAKTHROUGH SUMMIT

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Together We Are Strong: Best Practices and Case Studies for Successful Partnerships

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AMP Bespoke Gene Therapy Consortium

1. **AAV Basic Biology Translational Implications**
   - Vector generation
   - Enhancing vector generation
   - Enhancing therapeutic gene expression
   - Crosstalk & Learnings

2. **Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications**
   - Create & Build > Capacity
   - Harmonize best practices
   - Streamline regulatory paths

   **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 and novel expertise in manufacturing processes and protocols

   **Standard delivery menu:**
   - Standard clinical and delivery protocols
   - Establish Master File(s) for std vectors & facilitate out-licensing if appropriate

Gene therapy target for rare disease

Therapies for patients

Goal: Increase efficiency by orders of magnitude.
Goal: Standardized, faster, reduced $89.4M PROGRAM
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**

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

- Opportunity for a greater understanding of the viral life cycle and enable the field to overcome the limitations of AAV-based vectors
- Knowledge of AAV interactions with the host at the cellular level remains undefined. A more thorough understanding of AAV interactions with the host is key to efficient transduction
Disease Selection for the Pilots Will Provide Real Data for Streamlining the Overall Process

Thousands of Rare Diseases

5-6 Diseases Selected

Characteristics:
• Clear monogenetic cause that is amenable to AAV
• No commercial business case
• Sufficient information to run a successful clinical trial
• Low trial requirements for testing and follow up (i.e., short trial)
• Currently assembled patient group
• Others....

RFP(s) submission of potential study by:
• Academic centers
• Government investigators
• Patient groups
• Others....
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)**

**AAV Serotypes**

- **CMC Master File(s)**
- **History Experience Expertise**
- **Pilots Access to serotypes No IP**
- **IV, ITH, Intraocular**

**Target Tissue & Disease**

- **Vary AAV serotypes & Mfg scales 5 – 6 diseases**
Generating a Streamlined Clinical and Regulatory Framework for Gene Therapy

• Currently, many gene therapies for rare disorders are produced as “one-offs”

➢ Transformative approach developing regulatory innovations is needed to bridge the gap between science and technology

➢ Platforms and processes that leverage successful gene therapy products and knowledge in the setting of bespoke therapies

- Standardized
- Faster
- Reduced $$
Manual for AAV Gene Therapy Clinical Development

- Insights and learnings that facilitate success of future gene therapy
- Optimized lot release methods and assays
  - Harmonized and validated sets of vector quality tests
- An objective method and core criteria for disease selection
  - Bespoke and rare diseases trials
- Standardized regulatory submission package(s)
Potential Partners in AMP BGTC

Public

NCATS  NICHD  BRAIN Initiative
NINDS  NEI  NIAMS
NIMH  NIDCD  NIDCR
NHLBI  NHGRI  FDA

Private

Novartis  Biogen  ASGCT  NORD  REGENXBIO
Pfizer  Ultragenyx  ARM  Taysha  J&J  CureDuchenne
Takeda  Spark  Thermo Fisher  Genetic Alliance
Health Canada

Proposal to Initiate Program

$58M
- AAV Biology Awards
- CMC, Trial Core & Analytics
- 3 Pilots (2 at NIH, 1 ext)
- Program Mgmt

Full Program Proposal

$89.4M
- AAV Biology Awards
- CMC, Trial Core & Analytics
- 6 Clinical Trial Pilots
- Program Mgmt

Potential for additional in-kind support

Proposed Launch
Oct 2021
Opportunities to augment AAV biology & MFG process improvement, & harmonized regulatory frameworks

• Pursuing multiple opportunities to partner with domestic and international organizations to support research awards and sponsor investigators and infrastructure for pilot trials

• Canadian National Research Council (NRC) and UK MRC have constructed Govt-supported vector mfg facilities – potential use for selected clinical trials

• Strong Health Canada interest in BGTC partnering to augment and coordinate development of regulatory processes and framework aligned with FDA
Data/Knowledge Portal: Outreach and Education

• Raise awareness among key audiences.
• Highlight the launch and accomplishments of the initiative among the research and patient advocacy communities.

• Provide messaging tools.
• Give partners the useful, well-prepared internal messaging materials they need to address questions that may arise from media or elsewhere.

Enable partners’ efforts.
Provide partners with easily tailored, customizable materials to allow for the dissemination of key messages of the Bespoke Gene Therapy Consortium in the partners’ own words and with their own branding.
Outreach and Education: The proposed PLANS

Year 1: promoting the LAUNCH
Sample tactics: Social media engagement tools, launch materials, video

Year 2: promoting the DRUMBEAT
Sample tactics: Explainer videos, infographics, meeting materials

Year 3: promoting the PUBLICATIONS
Sample tactics: branded emails, ads & speaking placements at conferences

Year 4: promoting the MANUAL
Sample tactics: digital outreach tools, eg, blog posts and social media toolkits

Year 5: promoting the IMPACT
Sample tactics: webinar overview series, symposium
AMP BGTC: Initial launch action items

- **Program Launch**
  - Publish RFA(s)
  - Disease Proposal Deadline
  - AAV Bio Deadline

**Disease Selection**
- September: Notice of Intent to Publish
- October: Finalize RFA(s)
- November: Webinars and Information Sessions
- December: Secure, contract MFG for Pilots 1-3

**AAV Biology**
- September: Notice of Intent to Publish
- October: Finalize RFA(s)
- November: Webinars and Information Sessions
- December: Review proposals, select Pilot Diseases, Match MFGs
- Q1 2022: Review applications and select awardees

Initiate & establish CMC, Regulatory, & Communications subteams
AMP BGTC Project Timeline *(estimated launch in Q4 2021)*

- **2021**: AAV Bio RFA(s)
- **2022**: Vector Gen/ Delivery Development
- **2023**: HTS Assay Testing & Analytics, Vector Manufacturing Pilots 1 - 3
- **2024**: HTS Assay Testing & Analytics, Vector Manufacturing Pilots 4 - 6, Pilot Bespoke Clinical Trials (1 – 3)
- **2025**: Pilot Bespoke Clinical Trials (3 – 6)
- **2026**: CMC Testing & Analytics Subteam, Regulatory Streamline Subteam, Comms & Patient Edu Program & Continuous updates of web & portal

Key Milestones:
- 1: Launch
- 2: Disease Selection
- 3: Draft Reg Framework
- 4: Draft Manual
- 5: Go/No Go Milestone
- Final Deliverables
BUILDING THE CONGENITAL HYPERINSULINISM COLLABORATIVE RESEARCH NETWORK

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CONGENITAL HYPERINSULINISM

• Most common cause of persistent hypoglycemia in infants and children:
  ▪ ¾ cases of persistent hypoglycemia in neonates
  ▪ Estimated incidence 1:20,000 live births

• Molecular genetics:
  ▪ 12+ different loci associated with hyperinsulinism
  ▪ Mutation analysis negative in ~ 40-50%

• Current therapies:
  ▪ Diazoxide ~ up to 60% of cases are unresponsive*

➤ Outcomes:
  ▪ 48% of affected children have neurodevelopmental deficits

Rosenfeld, Ganguly & De Leon. Am J Med Gen C, 2019
COLLABORATIVE RESEARCH NETWORK APPROACH

Vision and Goals

CHI Foundational Programs (Partner programs to be added)

- Natural History Studies and Registries
- Centers of Excellence Program
- Awareness and Education
- Research
- Community Connection

Workstreams

- Diagnostics
- Medical and surgical treatments
- Care guidelines/Centers of Excellence
- Glucose monitoring
- Clinical trials/Industry Engagement
- Genetics
- What is HI? Nomenclature, Inclusion/Exclusion

Prioritized research agenda

- Scientific and medical breakthroughs
- Increased patient-level support to access care
- Review community needs, goals and objectives
KEY TAKEAWAYS AND PARTNERSHIP BENEFITS

Clinician/ Researcher Perspective

- Patient community perspective informs clinical and research program development
- Engaged patient community facilitates research progress:
  - Research participation
  - Funding
- Tri-partnership collaboration between patient community, academic researchers and industry:
  - Improves research strategy
  - Accelerates progress

Patient Organization Perspective

- Research collaboration
- Puts patients at the center of a strategy that leads to faster diagnosis and new treatments
- Global perspective for identifying and implementing research needs
- Improved infrastructure for communication, research partnerships, and funding opportunities
- On-going continuing education
Thank you!

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3-WAY COLLABORATIONS
THE SECRET SAUCE

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Travere Therapeutics

Roberta Smith
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"OLD SCHOOL" COLLABORATION STRUCTURE

Company

Academic lab

Project Genesis & Funding

Specific Expertise

Disease Foundation

Consulted on occasion
“NEW SCHOOL” COLLABORATION STRUCTURE

THE SECRET SAUCE

**NIH**
National Center for Advancing Translational Sciences

- Drug discovery expertise
- Assay development
- High-throughput screening
- Cell models
- Hit to drug candidate
- Infrastructure/funding

**NCATS**

- Patient/Lay Person perspective to research
- Promotion and access to research community and tools
- Education and access to patients
- Advocacy

**Travere**
- Drug discovery expertise
- Pre-clinical, clinical, commercial
- Funding

**Disease Foundation**
Thank you!

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