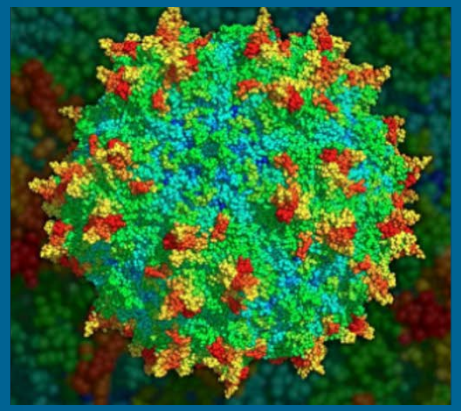
Accelerating Medicines Partnership®
Bespoke Gene Therapy Consortium (BGTC)



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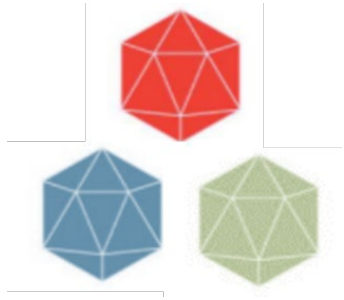
Foundation for the National Institutes of Health

Steering Committee Co-Chairs:
PJ Brooks, PhD (NCATS/NIH)
Gregory LaRosa, PhD (Pfizer)
Peter Marks, MD, PhD (CBER/FDA)

Program Management:
Courtney Silverthorn, PhD (FNIH)
Brad Garrison (FNIH)

AMP® Bespoke Gene Therapy Consortium Components

1 AAV Basic Biology Translational Implications



- Enhancing Vector Generation
- Enhancing therapeutic gene expression

Crosstalk & Learnings

Goal: Increase efficiency by orders of magnitude.

Therapies for patients

Goal: Standardized, faster, reduced $

2 Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications

Gene therapy target for rare disease

Create & Build > Capacity	Harmonize best practices	Streamline Regulatory Paths
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 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

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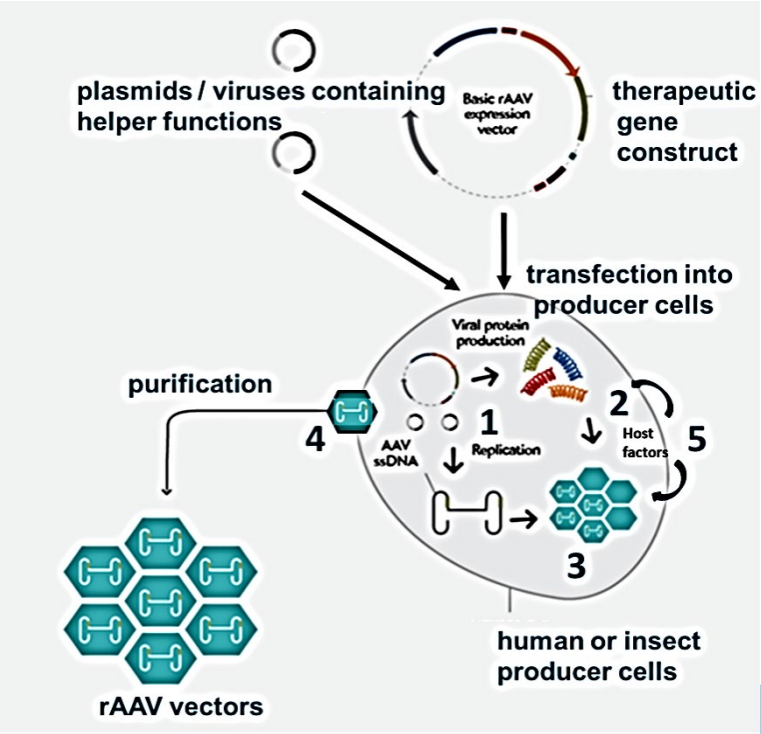
FNIH released two AMP BGTC RFP opportunities for AAV biology

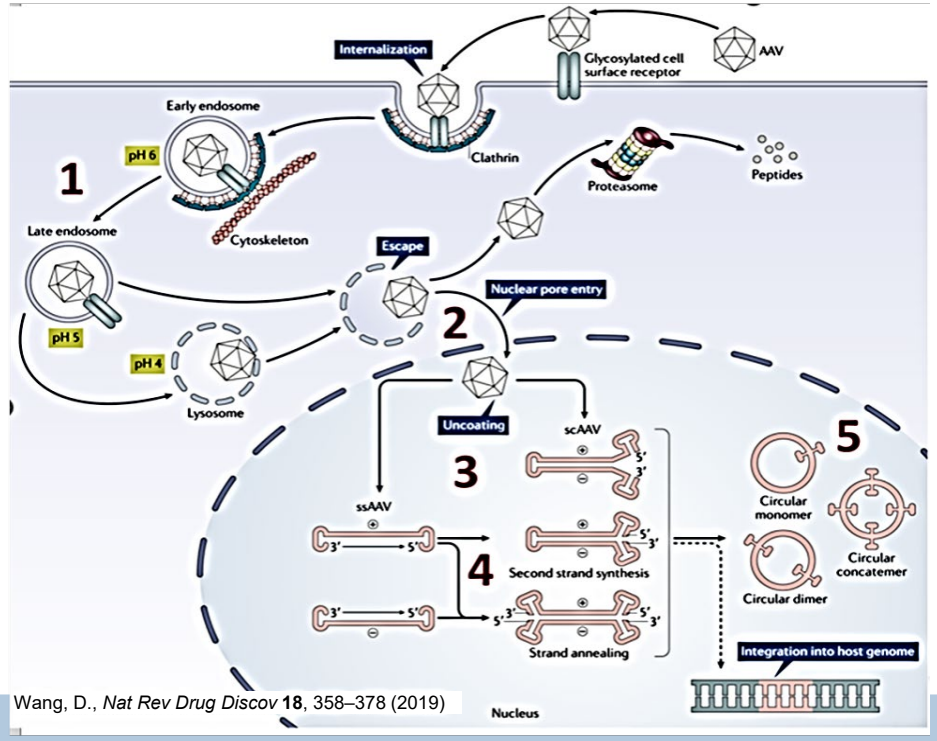
A. Enhancing Vector Generation



Results to be broadly applicable to all AAV vectors

https://fnih.org/sites/default/files/2021-12/BGTC%20RFP%20AAV%20Biology%20Vector%20Production_0.pdf

B. Enhancing Therapeutic Gene Expression



Wang, D., *Nat Rev Drug Discov* **18**, 358–378 (2019)

Results to be targeted to cell types relevant to clinical program

https://fnih.org/sites/default/files/2021-12/BGTC%20RFP%20AAV%20Biology%20Gene%20Expression.pdf

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Advancing the Understanding of AAV Biology

A. Enhancing Vector Generation

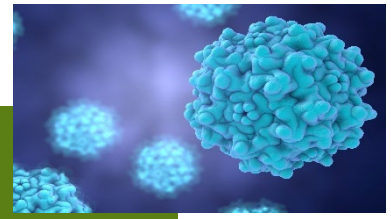
https://fnih.org/sites/default/files/2021-12/BGTC%20RFP%20AAV%20Biology%20Vector%20Production_0.pdf

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

https://fnih.org/sites/default/files/2021-12/BGTC%20RFP%20AAV%20Biology%20Gene%20Expression.pdf

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

Links to Requests For Applications posted December 2, 2021

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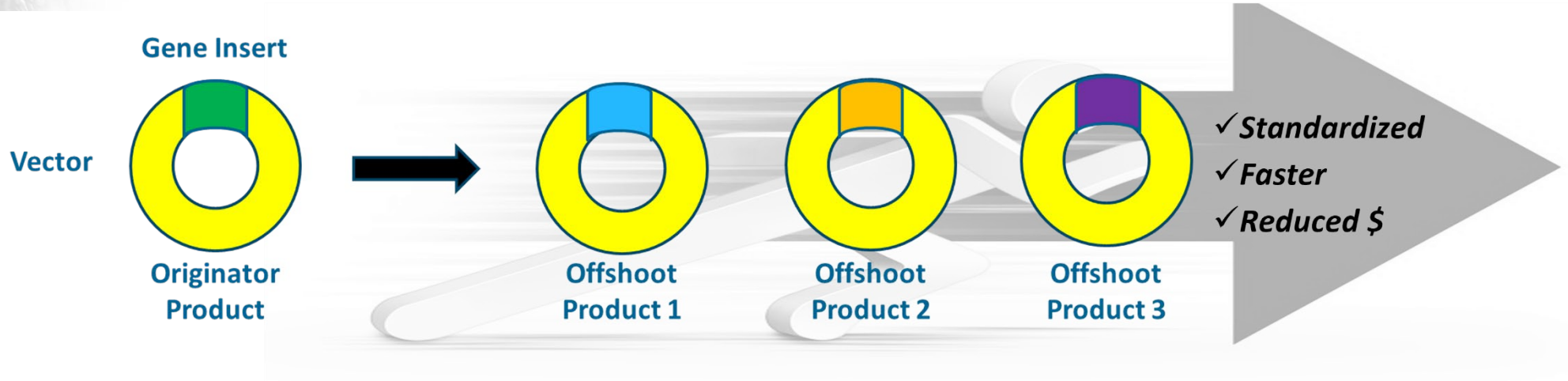
Generating a Streamlined Clinical and Regulatory Framework for Gene Therapy

- 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**



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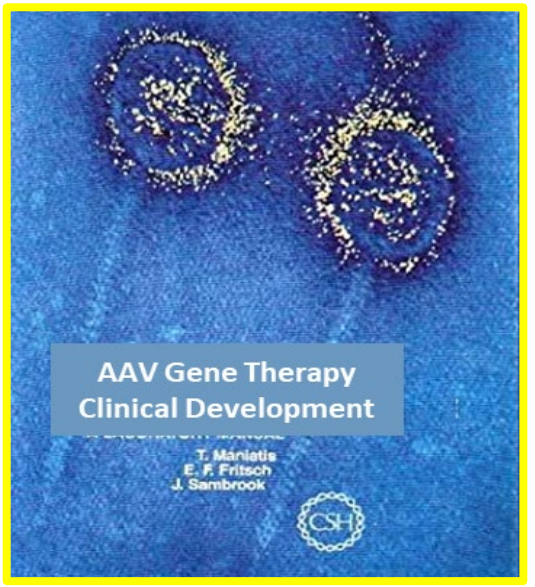
Manual for AAV Gene Therapy Clinical Development

- **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)**

Gene Therapy "Maniatis"



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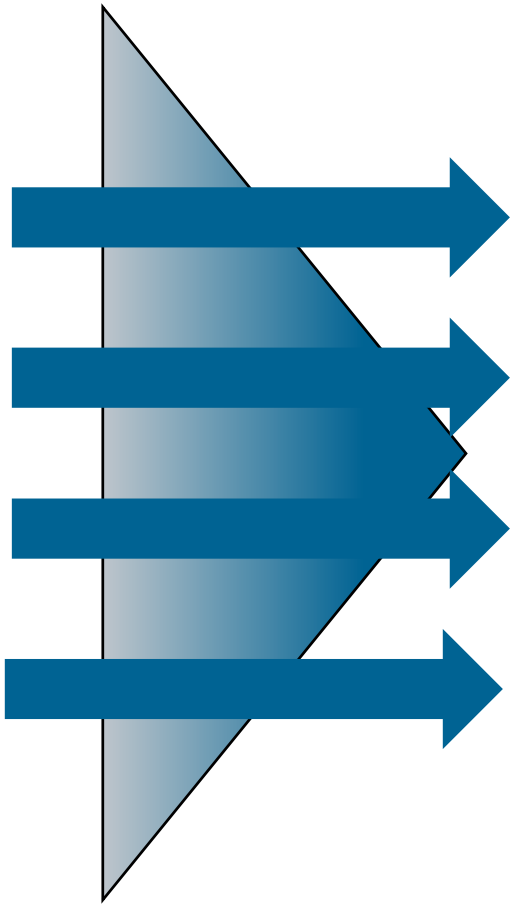
Disease Selection for the Pilots Will Provide Real Data for Streamlining the Overall Process

Thousands of Rare Diseases

Submission of potential studies by:

- Academic centers
- Government investigators
- Patient groups
- Others….



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….

Disease nomination process posted December 2, 2021

https://fnih.org/sites/default/files/2021-12/Final%20BGTC%20Disease%20Nomination%20Form%20Fillable.pdf

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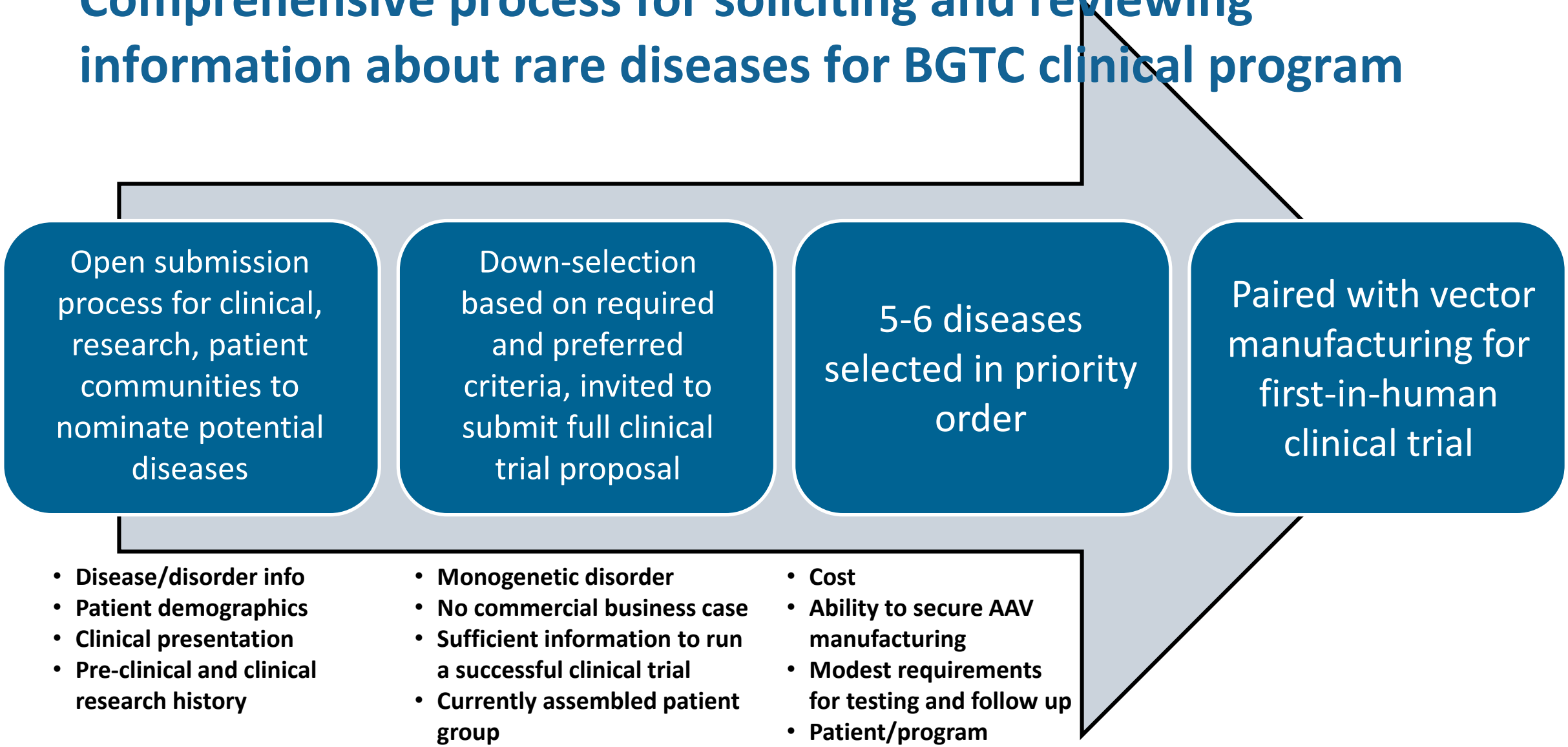
Comprehensive process for soliciting and reviewing information about rare diseases for BGTC clinical program



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Current partners (at launch)

$39.5M
Public

- National Center for Advancing Translational Sciences
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- National Eye Institute — Research Today...Vision Tomorrow
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- 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
- BRAIN INITIATIVE
- FDA

$37M
Private

- Biogen
- Janssen
- Novartis
- Pfizer
- REGENXBIO
- Spark Therapeutics
- Takeda
- TAYSHA GENE THERAPIES
- ThermoFisher SCIENTIFIC
- ultragenyx pharmaceutical
- Alliance for Regenerative Medicine
- American Society of Gene + Cell Therapy
- Cure Duchenne
- NIMBL — The National Institute for Innovation in Manufacturing Biopharmaceuticals
- NORD® National Organization for Rare Disorders

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Opportunities to augment AAV biology & MFG process improvement, & harmonized regulatory frameworks

CIRM
CALIFORNIA'S STEM CELL AGENCY

CA Institute of Regenerative Medicine

Canadian Institutes of Health Research

Health Canada

UKRI Medical Research Council

CATAPULT

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- **Continuing to pursue 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**

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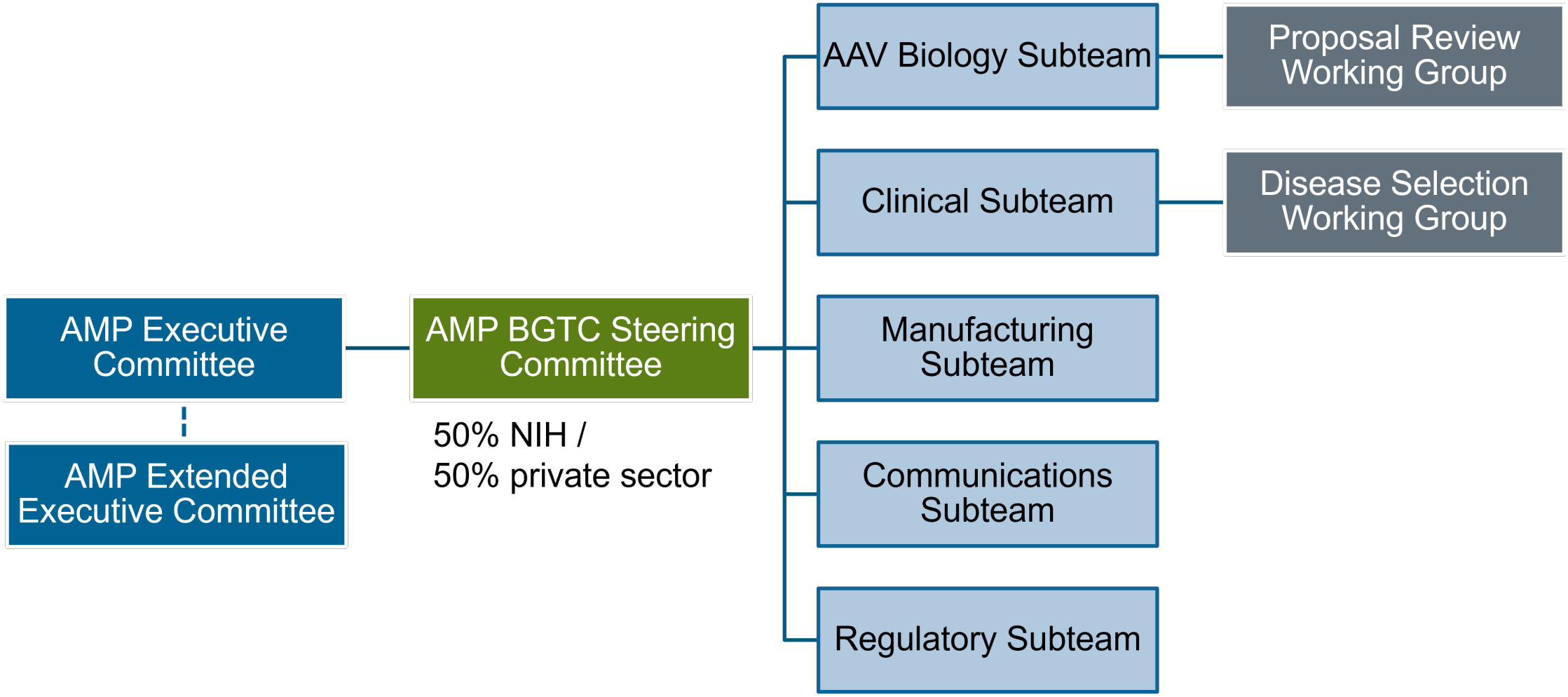
AMP® BGTC Consortium Structure



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Proposed Partner Investment

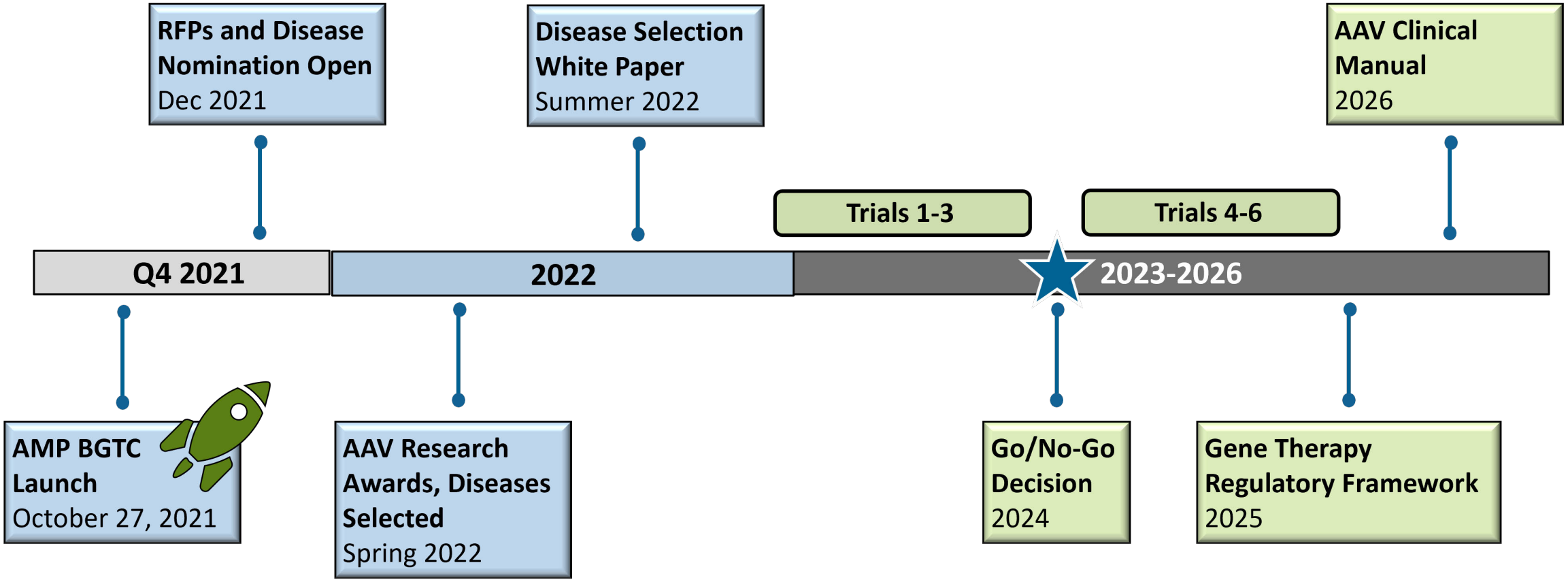
Funding Support

- Proposed full program budget ***= $89.4M over 5 years***
- Tiered levels of investment of partners based on R&D budget
  - $1B R&D budget – investment of $1M/year over 5 years
  - R&D budget < $1B (~$100K/year per $100M R&D)

Not-for-Profit, Philanthropist & Advocacy Organization Investment

- $100,000 or more annually
  - Join the Steering Committee and serve as a full voting member
- $99,999 and $25,000 annually
  - Join the Steering Committee as non-voting members

AMP BGTC short- and long-term deliverables



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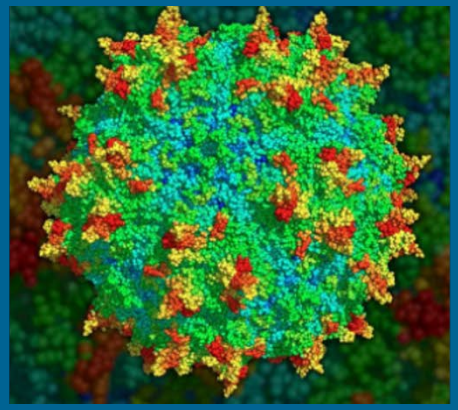


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