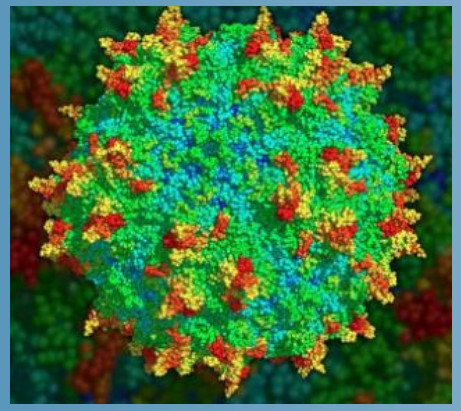
Accelerating Medicines Partnership
Bespoke Gene Therapy Consortium (BGTC)






FNIH
Foundation for the National Institutes of Health

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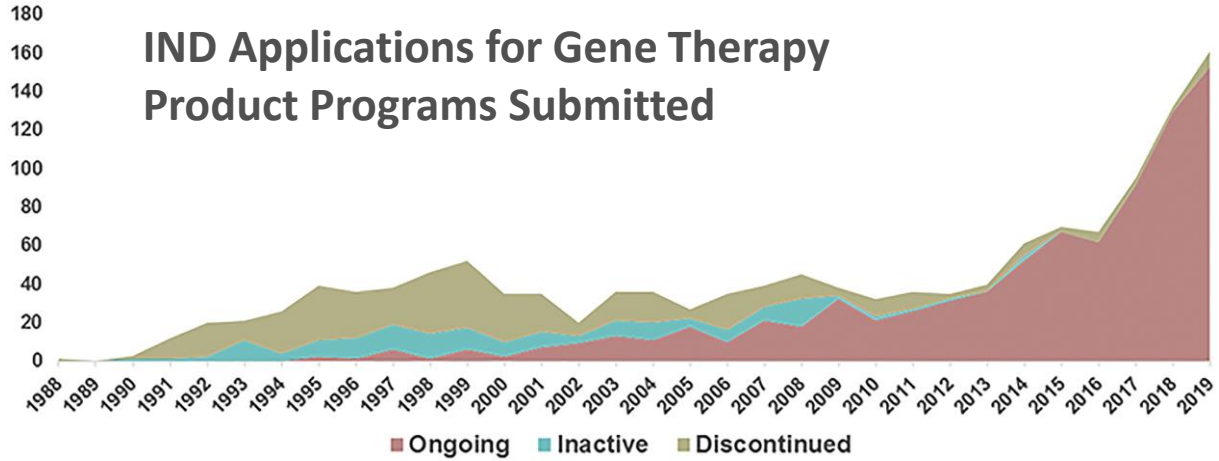
Director, Inflammation and Immunity
Foundation for the National Institutes of Health
Cell & Gene Therapy Products: Manufacturing, Quality and Regulatory Considerations
June 2021

Why the Bespoke Gene Therapy Consortium (BGTC)?

Cross-Sector Expertise Needed to Address Challenges in:

- Manufacturing
- Nonclinical development
- Clinical development
- Product access



- Medical need present in thousands of rare genetic diseases → Hundreds of diseases could potentially be addressed now

Immediate *- of the Bespoke approach to rare disease patients*

Medium-term *- to entire rare disease community → financially sustainable model for gene therapy production*

Long-term *- to larger gene therapy ecosystem through advancement of technology and the regulatory framework*

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Engaged Partnership with Key Expertise and Experience

Novartis	Sanofi	NCATS	CDMOs
BMS	Roche	NHLBI	Biotech
Pfizer	Bayer	NINDS	Advocacy
Ultragenyx	UCB	NIMH	Foundations
BI	Lilly	FDA/CBER	KOLs

Novartis	J&J	NORD
Pfizer	Spark	ASGCT
Takeda	Taysha	CureDuchenne
Ultragenyx	Thermo Fisher	ARM
REGENXBIO	Health Canada	
NIH	FDA/CBER	

Design Phase
= Concept

Construct Phase
= Project Plan

NCATS, NINDS
NIMH, Brain Initiative
3+ additional ICs

= Final Plan

Working Groups

Proposed Launch Aug 1

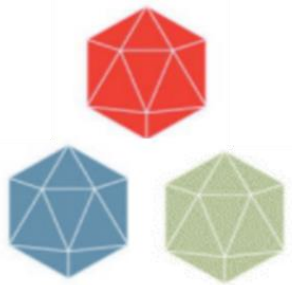
Program Development Team Identified Major Challenges to Effective Access to Gene Therapy

- **Lack of understanding of the viral life cycle and efficiency in the molecular steps associated with the generation and delivery of gene therapies**
  - **Building more manufacturing facilities is a short-sighted answer – Need to advance the science and get better!**

- **Gene therapy approaches currently employed do not allow for easy scalability, reproducibility, or regulatory generalizability and result in 'one-offs' that reinvent non-clinical and CMC processes**
  - **Developing a regulatory program that allows leveraging non-clinical and manufacturing data from one application for another can facilitate product development and access**

AMP Bespoke Gene Therapy Consortium

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

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

Goal: Standardized, faster, reduced $

Gene therapy target for rare disease

Create & Build > Capacity

Vector generation

Standard vector menu:

- Instructions for use
- Tropism
- Ease of use for gene type
- Non-proprietary tools
- **Provide facilities for vector generation**

Harmonize best practices

Manufacture of therapeutic

Standard process menu:

- Known safety database
- Facilitate preclinical testing
- **Leverage existing and novel expertise in manufacturing processes and protocols**

Streamline Regulatory Paths

Clinical ability to treat patients

Standard delivery menu:

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

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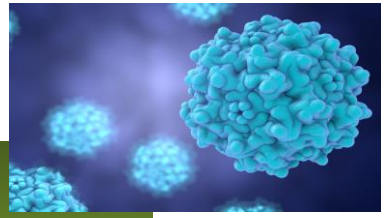
Advancing the Understanding of AAV Biology

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

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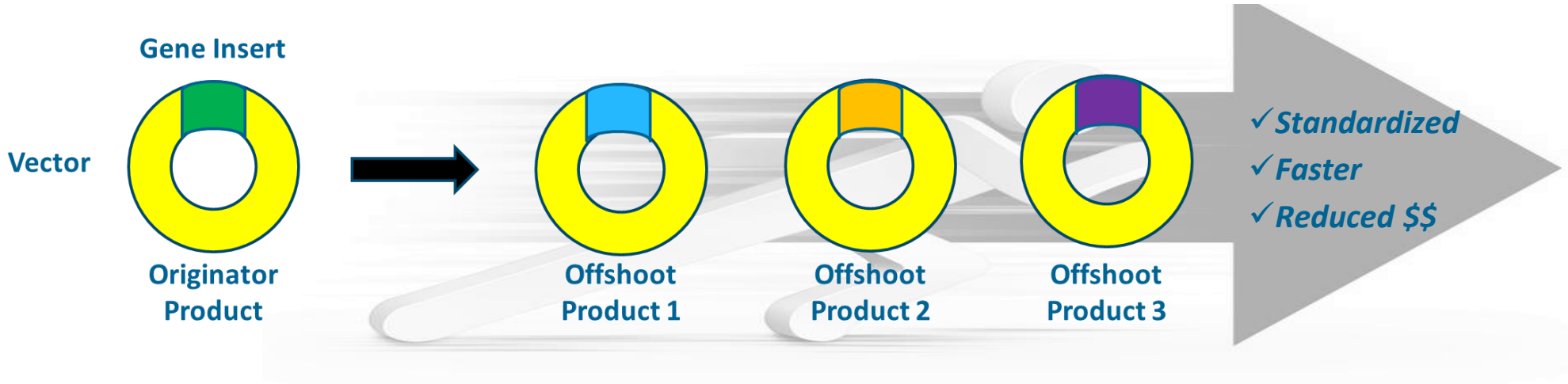
Generating a Streamlined Clinical and Regulatory Framework for Gene Therapy

- 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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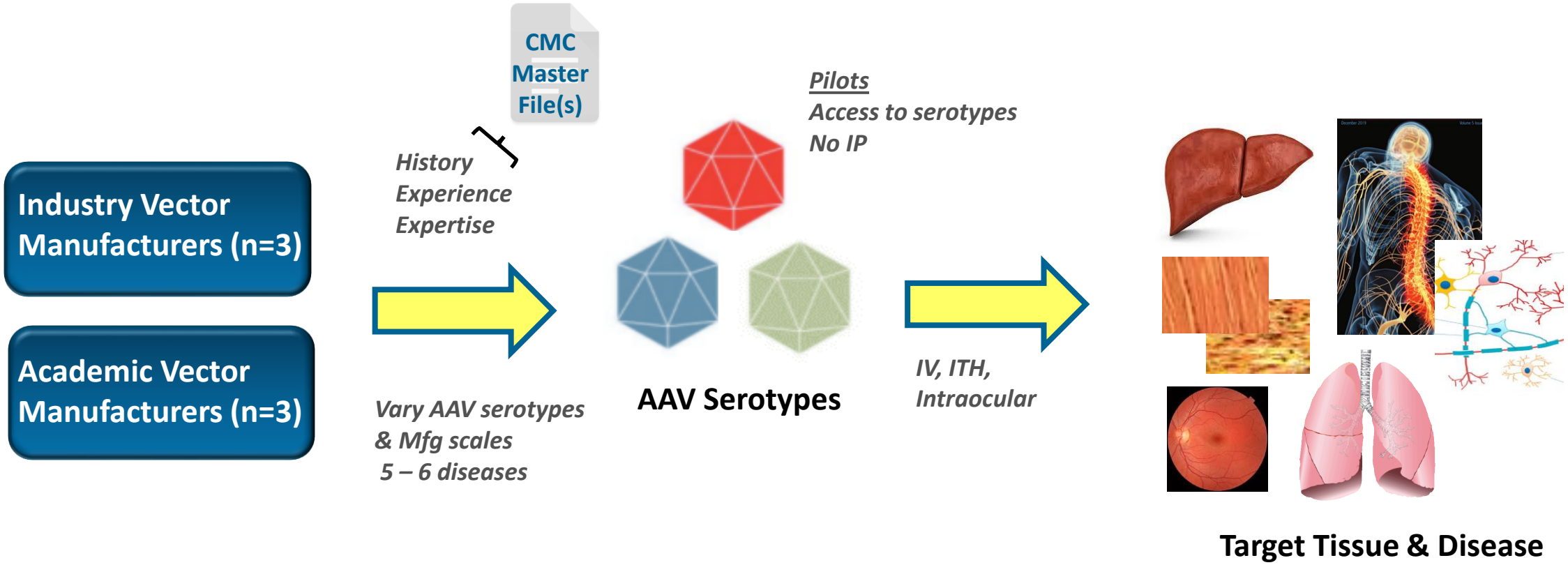
Strategy to Leverage Existing Expertise and Capacity to Manufacture Gene Therapy Product for the Pilots



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

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

Thousands of Rare Diseases

RFP submission of potential study 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….

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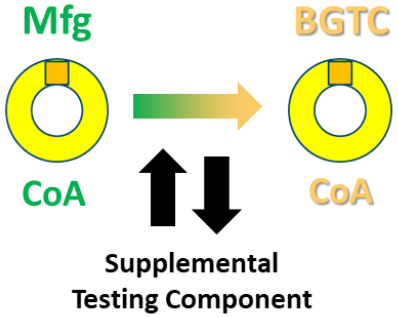
Harmonize, Standardize and Simplify CMC Testing

Identify critical attributes that must be evaluated:

- **Examples: Vg titer, purity, full:empty, potency, endotoxin & sterility → use existing Mfg processes**
- Provide scientific rationale and justification for why these tests are most critical

- Leverage manufacturer's experience with the reference product, and whether reduced testing can be scientifically justified based on iterative experience/data **→ create Master files**

- What other attributes may be reasonably assured via process history/ understanding and control **→ NIH will establish a centralized testing facility (contractor) to conduct supplemental testing** and support product-specific testing (e.g., standardized vector copy #)
- Manufacturer will supply vials (NIH to provide final labelling) and certificate of analysis (C of A) **→ NIH will be IND holder for clinical trials in BGTC pilots**



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CMC Information

Provided to Sponsor (NIH) by Manufacturer

- Full spectrum of AAV tests performed
- Highlighted tests proposed to be conducted by manufacturer **(use existing processes)**
- Other attributes may be reasonably assured via process history/ understanding and control → **NIH will establish a centralized testing facility (contractor) to conduct supplemental testing**, and also support product-specific testing (e.g., potency)
- Overall goal is to **standardize testing**, where possible - specific goal is to standardize testing for vector copy number

Quality Attribute	Test Description
Potency	Vector genome titer
	Infectious titer ($TCID_{50}$)/ ratio
	In vitro transgene expression
	In vivo potency
	In vitro potency (activity)
Identity	Capsid Identity (ELISA, Western blot, peptide map)
	Genome Identity (Sequence, qPCR, restriction map)
Physical/ Chemical	Appearance
	Osmolality
	pH
	Particulates / Light Scatter
	Extractable volume
Safety	Sterility
	Endotoxin
	rcAAV
	In vitro adventitious agents
	In vitro bovine adventitious agents
	Biodurden (DS)
Purity	Purity Proteins : (Capillary Electrophoresis (CD-SDS), SDS-PAGE and HPLC)
	% Full Capsids (particle Content)
	Aggregates
	Excipient components
	Residual affinity ligand
	Residual host cell DNA
	Residual host cell protein
	Residual helper DNA

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AMP BGTC Manufacturing and Analytics Process

- Producers contribute samples & consent to analytics on prior products on same platform (Not process info)
- FDA has access to existing animal and human data

Diseases + researchers

Vector Producers A1, A2, A3

A - Academic
I - Industry

Vector Producers I1, I2, I3

MFG CoA

Supplemental Testing Component

Toxicology Testing Component

Pre-Clinical Core

Clinical Trials Core

Central IRB

Regulatory Core

IND

BGTC CoA

Clinical sites

outcomes SAEs

Data Management and Analysis Core

BGTC Coordination Center

= clinical AAV vector, originator product(s)

= clinical AAV vector, offshoot BGTC prod.

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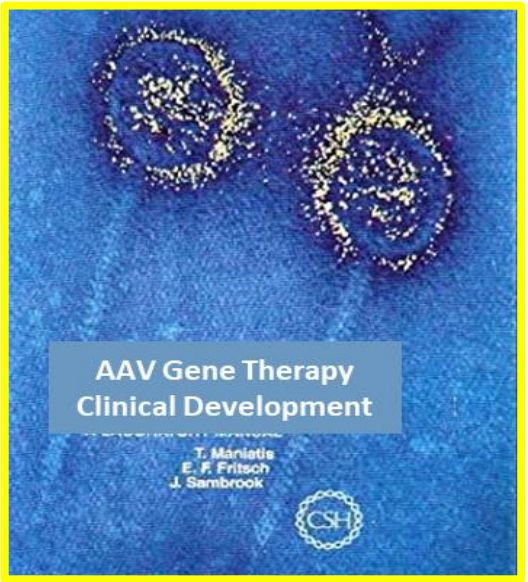
FDA U.S. FOOD & DRUG ADMINISTRATION

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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Questions?

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