NCATS

COLLABORATE. INNOVATE. ACCELERATE.

Therapeutic platforms for rare monogenic diseases

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Disclosure Statement

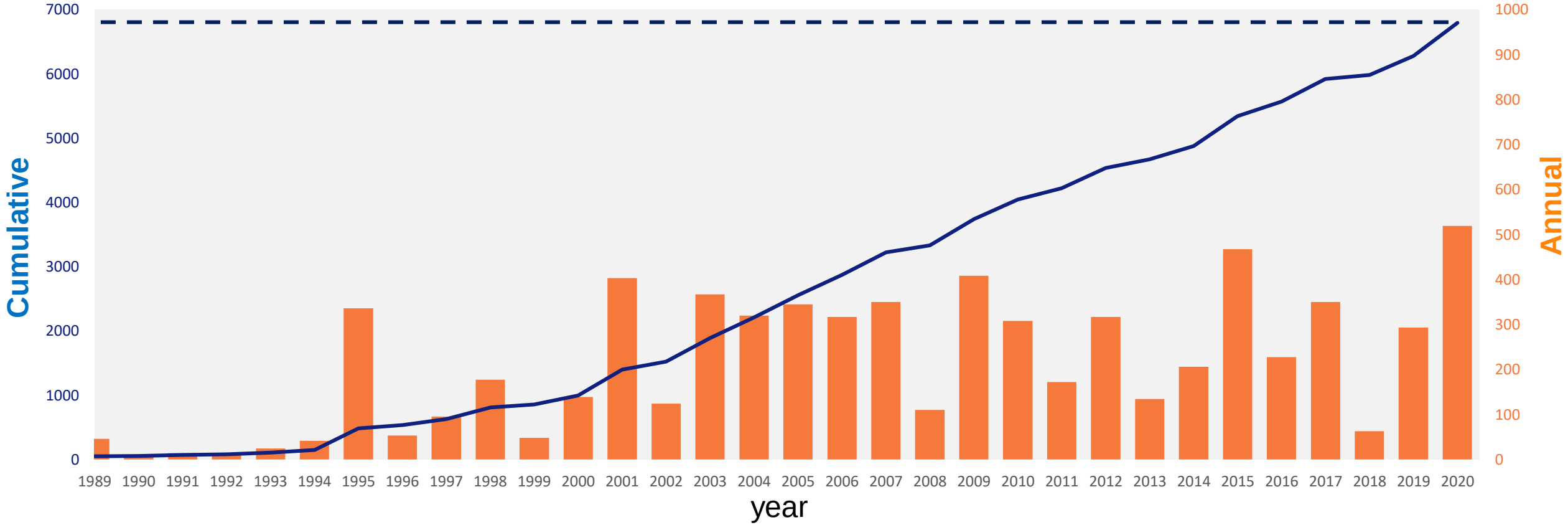
- I have no conflicts of interest to disclose
- Any reference to off-label product use or clinical trials are made only in an educational context
- The views expressed are those of the speaker and do not necessarily reflect the policies of the National Institutes of Health or the Department of Health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

NCATS' VISION

More treatments for all people more quickly

The Number of Disorders with Known Molecular Basis Is Rapidly Rising

>10000



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

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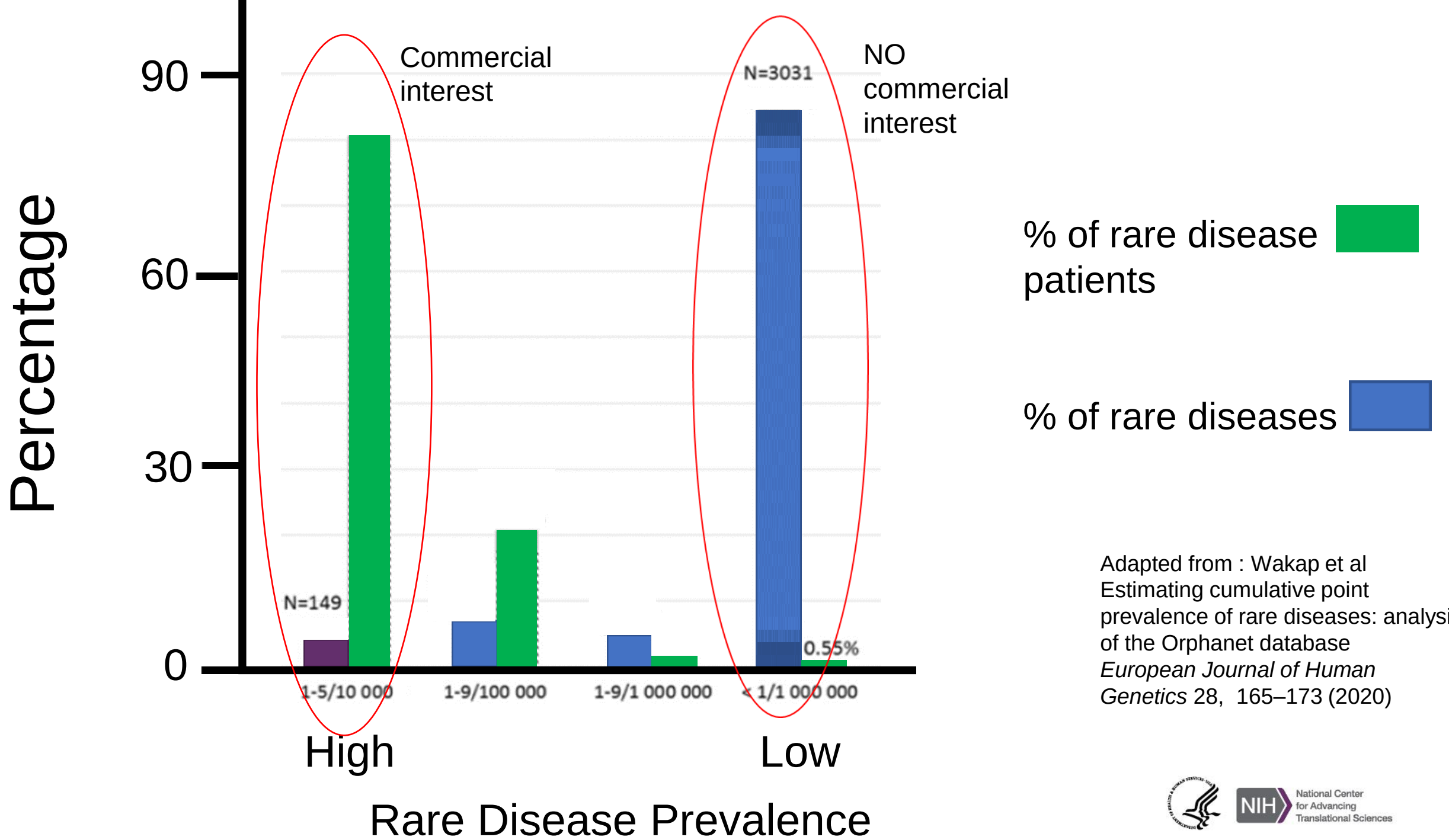

Adapted from : Wakap et al Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database *European Journal of Human Genetics* 28, 165–173 (2020)

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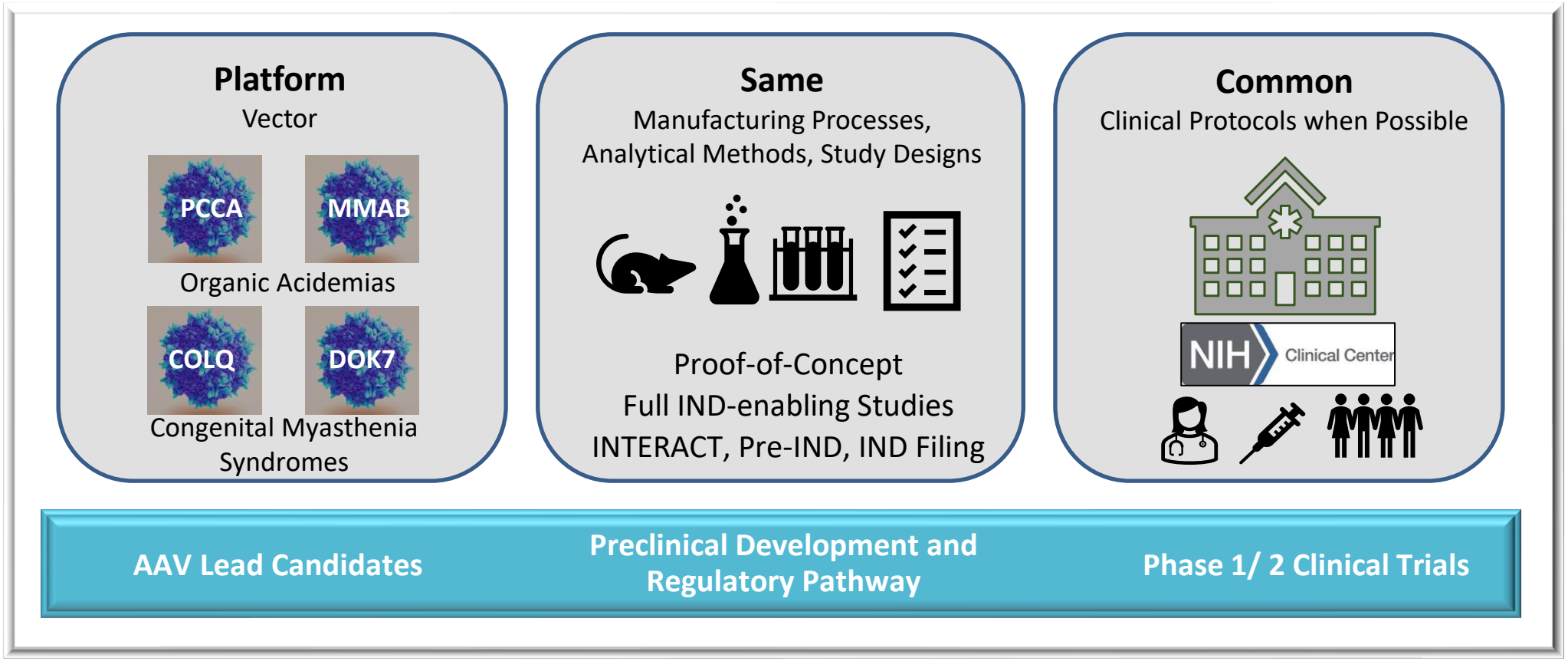
New Strategies

- Shared molecular etiologies
  - Fewer diseases
- Platform Approaches
  - Many diseases at a time

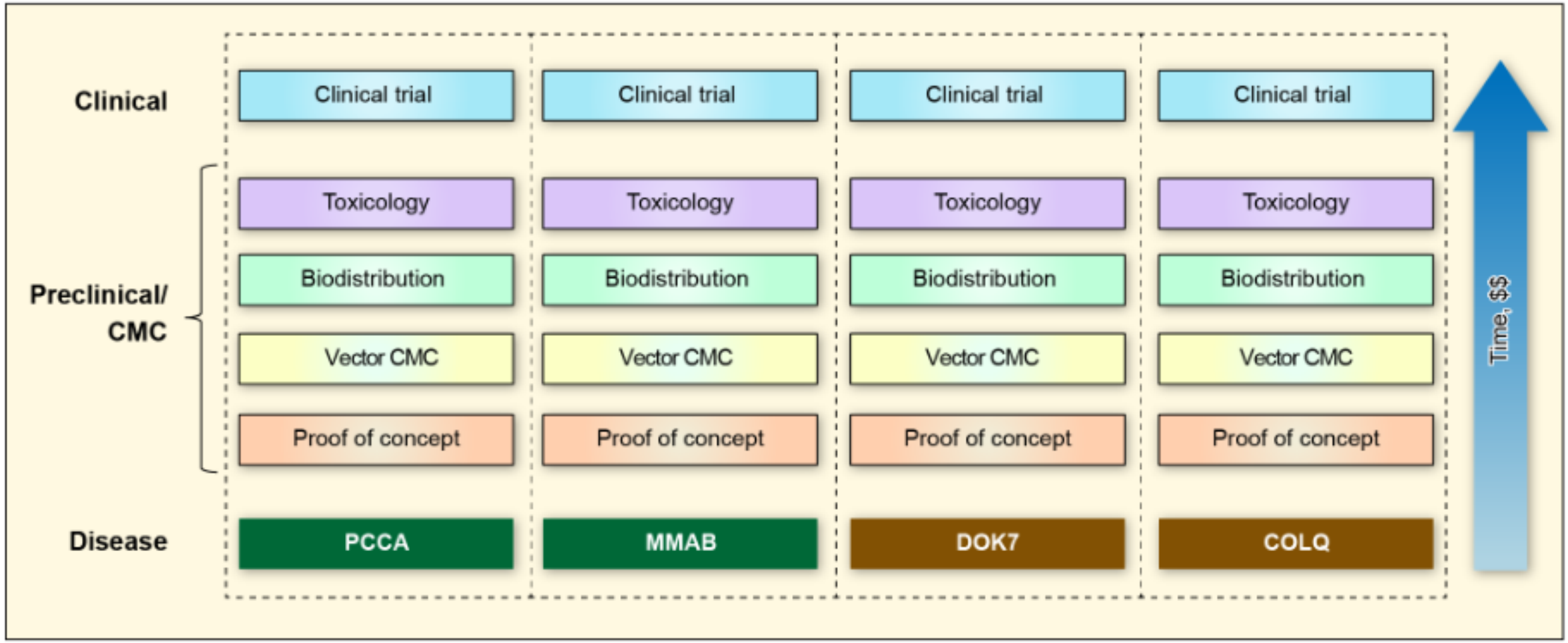
Platform Vector Gene Therapy (PaVe-GT)

RARE DISEASE DAY at NIH

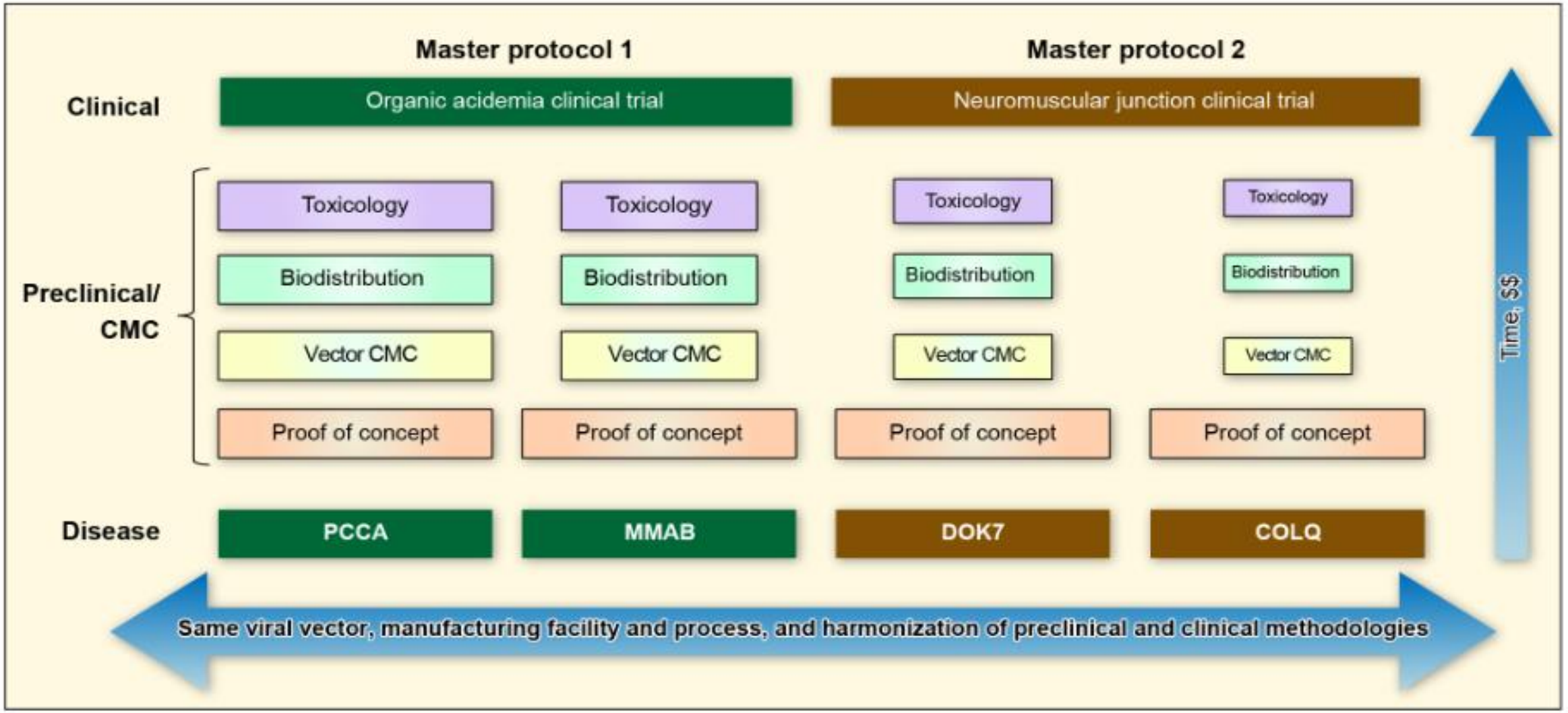
Hypothesis: A Platform Vector Approach Will Increase Efficiency in Preclinical Testing and Clinical Trial Start-up



Use Common Processes and Make the Data Publicly Available



Traditional clinical development paradigm



PaVe-GT clinical development paradigm: Questions

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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..

Past members: Don Lo, PhD; Lili Portilla, MPA; Anne Pariser, MD; Jean Dehdashti, RAC; Asaf Alimardanov, PhD; Janelle Hauserman, PhD; Eric Esposito; Dimah Saade, MD; Claire Driscoll, MS

SUBSCRIBE

Sign-up for PaVe-GT updates.

Subscribe

PAVE-GT RESOURCES

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.

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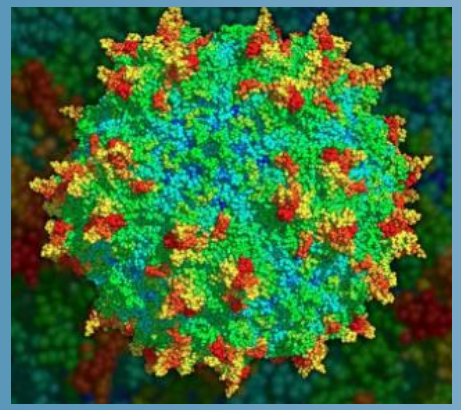
Accelerating Medicines Partnership®
Bespoke Gene Therapy Consortium (BGTC)






FNIH
Foundation for the National Institutes of Health

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

- 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

$39.5M *Public commitments*

$35.7M *Private donations*

$26.2M+ *Private in-kind contributions*

Biogen · DANAHER · ELPIDA THERAPEUTICS · FORGE BIOLOGICS · janssen · NOVARTIS · Ovid Therapeutics · Pfizer · REGENXBIO · Spark THERAPEUTICS · Takeda · ThermoFisher SCIENTIFIC · ultragenyx pharmaceutical · Alliance for Regenerative Medicine · ASGCT American Society of Gene + Cell Therapy · CIRM CALIFORNIA'S STEM CELL AGENCY · Cure Duchenne · FOUNDATION FIGHTING BLINDNESS · GENETHON CURE THROUGH INNOVATION · NIMBL The National Institute for Innovation in Manufacturing Biopharmaceuticals · NORD National Organization for Rare Disorders · rett syndrome research trust Making Rett History · RTW Charitable Foundation

FNIH

Accelerating Medicines Partnership® Bespoke Gene Therapy Consortium (AMP® BGTC)

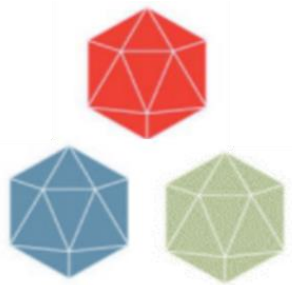
- Make adeno-associated virus technology more accessible to a broader range of diseases

- 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

Goal: Increase efficiency by orders of magnitude.

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

Gene therapy target for rare disease (62 initial submissions)

- Create & Build Capacity
- Harmonize best practices
- Streamline Regulatory Paths

Manufacture of therapeutic → Pre-clinical testing → Clinical ability to treat patients

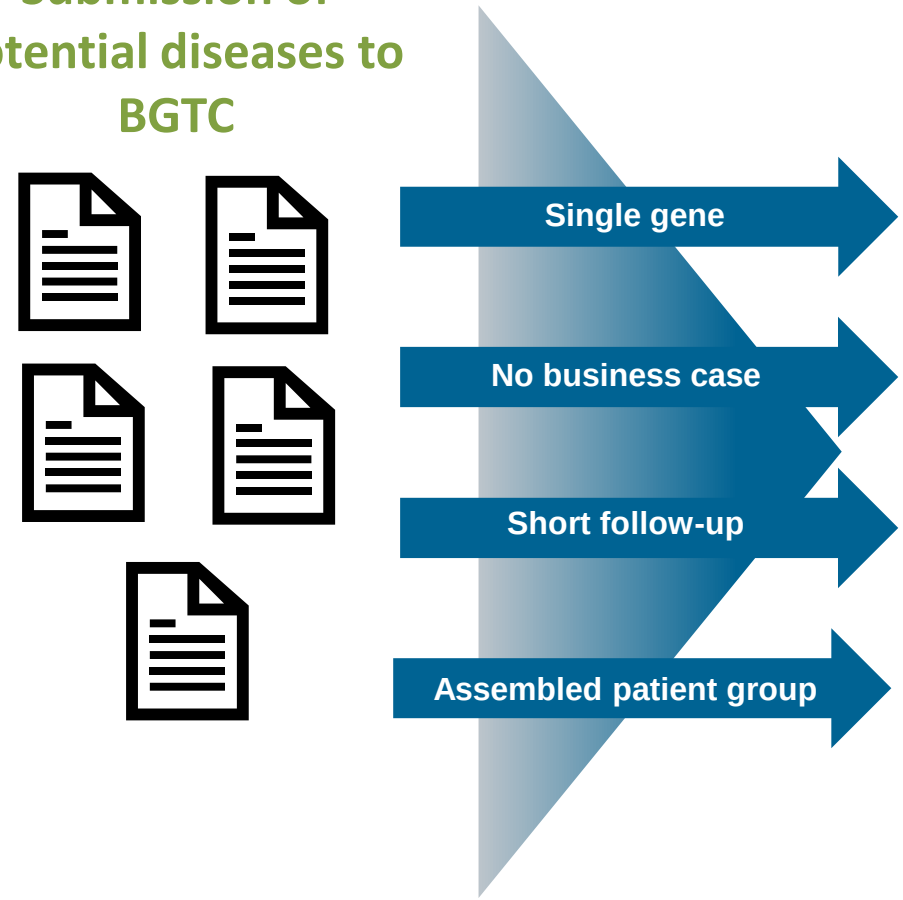
- CQAs (FDA Meeting held 9/29/22)
- GLP/Tox (FDA meeting June 2023)

Therapies for patients

Goal: Standardized, faster, reduced $

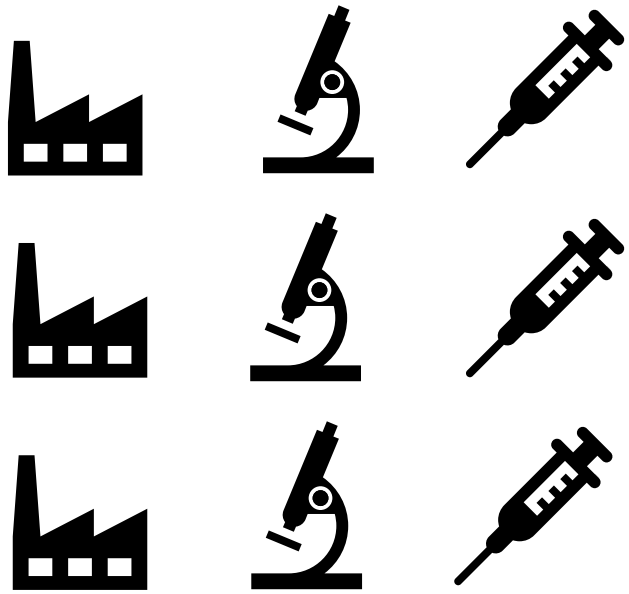
Developing repeatable, optimized processes that can be used broadly

Submission of potential diseases to BGTC



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



FNIH

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

Disease Nomination Form

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

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

14 candidates announced July 2022

Clinical Trial RFP

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

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

Final selection announced May 16th

Press Release

8 diseases selected

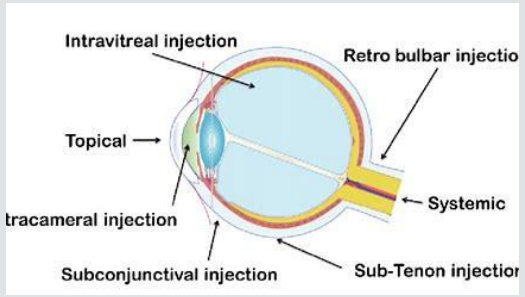
- Cost
- Ability to secure AAV manufacturing
- Modest requirements for testing and follow up
- Patient/program diversity

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

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

FNIH

Clinical portfolio announced May 16, 2023



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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

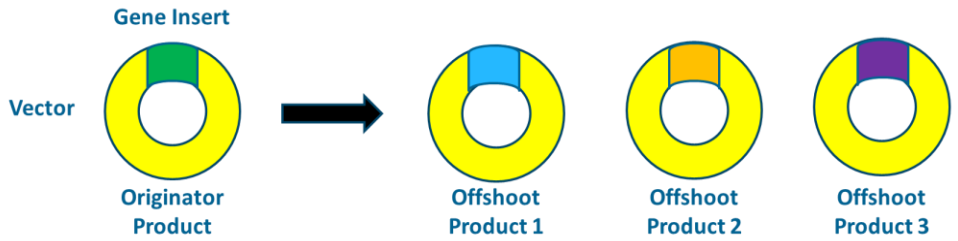
- Propionic Acidemia
- Morquio A syndrome (Mucopolysaccharidosis IVA)

Elpida CIRM *
CALIFORNIA'S STEM CELL AGENCY

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”?**

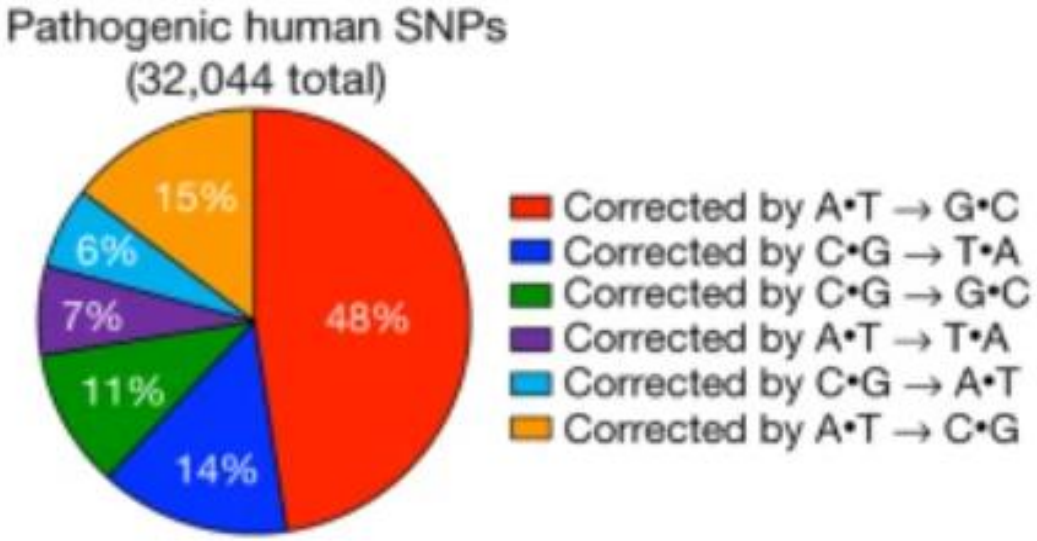


Published: 20 April 2016

Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage

Alexis C. Komor, Yongjoo B. Kim, Michael S. Packer, John A. Zuris & David R. Liu

Nature **533**, 420–424 (2016) | Cite this article



nature

Article | Published: 21 October 2019

Search-and-replace genome editing without double-strand breaks or donor DNA

Andrew V. Anzalone, Peyton B. Randolph, Jessie R. Davis, Alexander A. Sousa, Luke W. Koblan, Jonathan M. Levy, Peter J. Chen, Christopher Wilson, Gregory A. Newby, Aditya Raguram & David R. Liu

Nature **576**, 149–157(2019) | Cite this article

“ 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.”

Supported in part by the NIH SCGE program

NIH National Center for Advancing Translational Sciences

https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-22-016.html

Department of Health and Human Services

Part 1. Overview Information

RFA-RM-22-016

Participating Organization(s) National Institutes of Health (NIH)

Platform Clinical Trials of Genome Editors in Multiple Diseases (UG3/UH3, Clinical Trial Required)

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.

NIH National Center for Advancing Translational Sciences

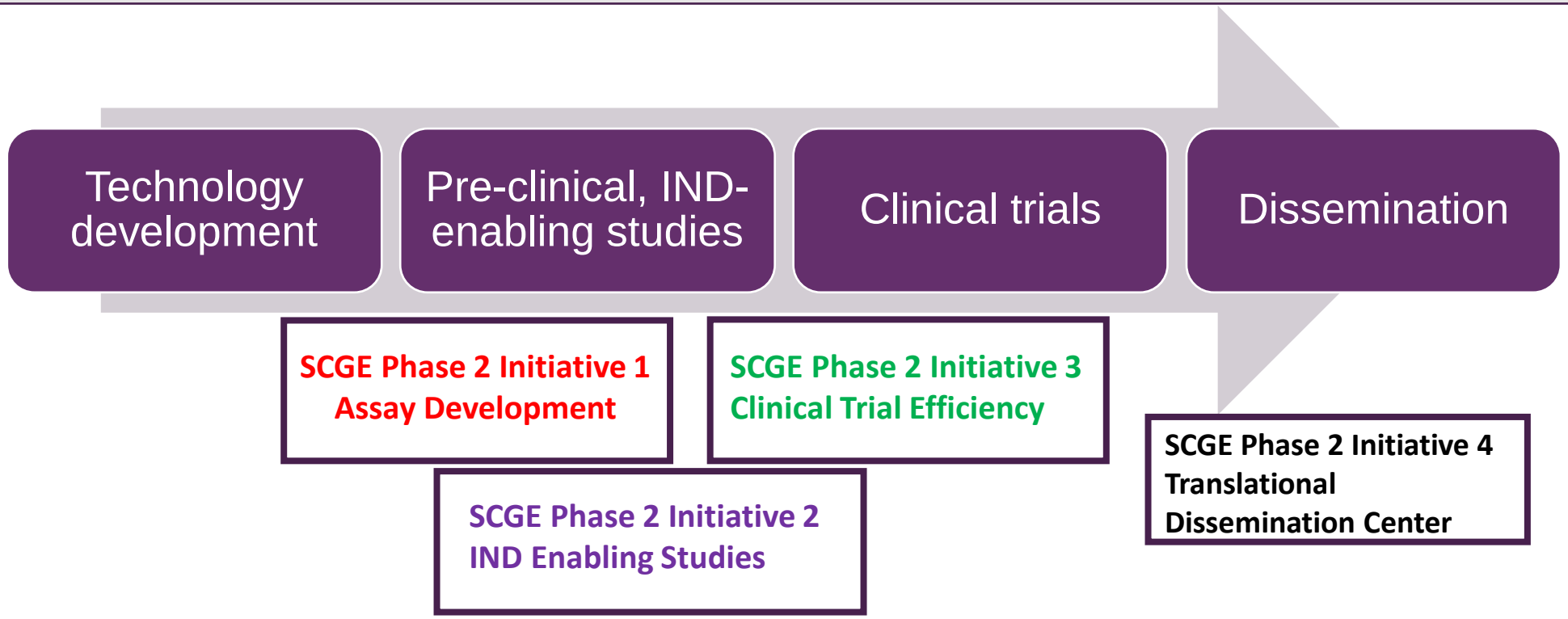
SCGE Phase 2 - Accelerate the translation of *in vivo* genome editing therapies into the clinic

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



SCGE Phase 2 Initiative 5: TARGETED (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/bdveZP

Many

~~One~~ diseases at a time

~~Ultra-rare diseases~~
~~Nano-rare diseases~~
~~N-of-1, N-of-few~~

Therapeutic Platforms to treat monogenic disease

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