Common Fund Concept Clearance: Somatic Cell Genome Editing Program – Phase 2 (Vote)

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National Center for Advancing Translational Sciences

Common Fund Proposal for Translating *in vivo* Genome Editing Therapies to the Clinic

The Common Fund

Concept Clearance: Phase 2 Common Fund Program

TITLE: Somatic Cell Genome Editing Program (SCGE), Phase 2

Objective: To accelerate the development of genome-editing therapeutic agents by facilitating IND-enabling studies, establishing pathways to regulatory approval, and disseminating successful strategies for initiating first in human clinical trials.

1. Improve assays to determine quality, safety and efficacy of editing reagents
2. Optimize in vivo candidate genome editing therapeutic candidates toward IND applications
3. Demonstrate first in human basket trials for *in vivo* genome editing therapeutics
4. Foster collaboration and disseminate new technologies and protocols to the community

Funds Available ~$45M per year for 16 awards

Program Duration: 5 years, FY23-27 (Phase 2)

Council Action: Vote on support of Program

SCGE Phase 2 Concept Clearance - Background

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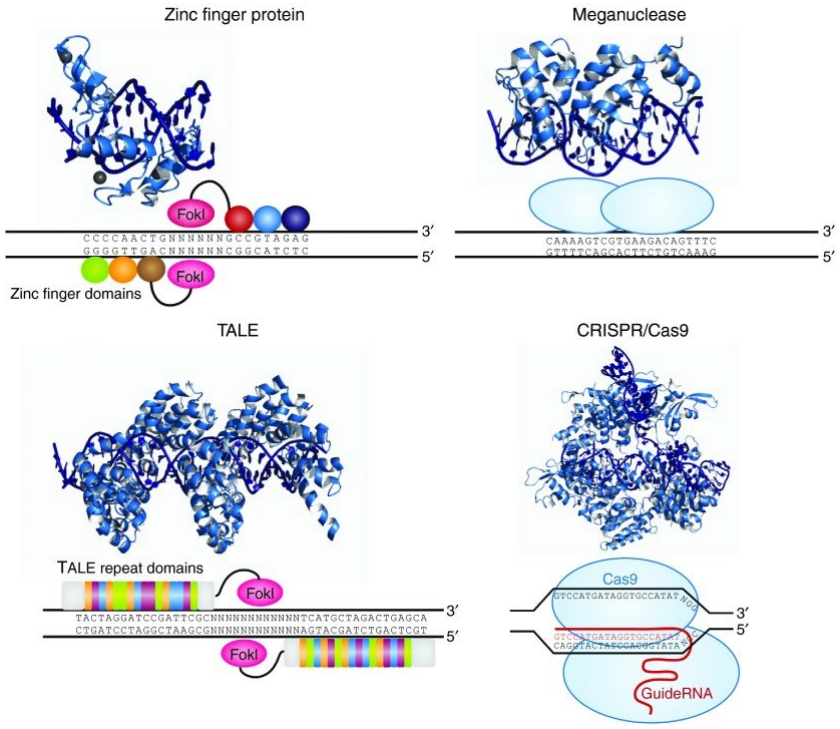
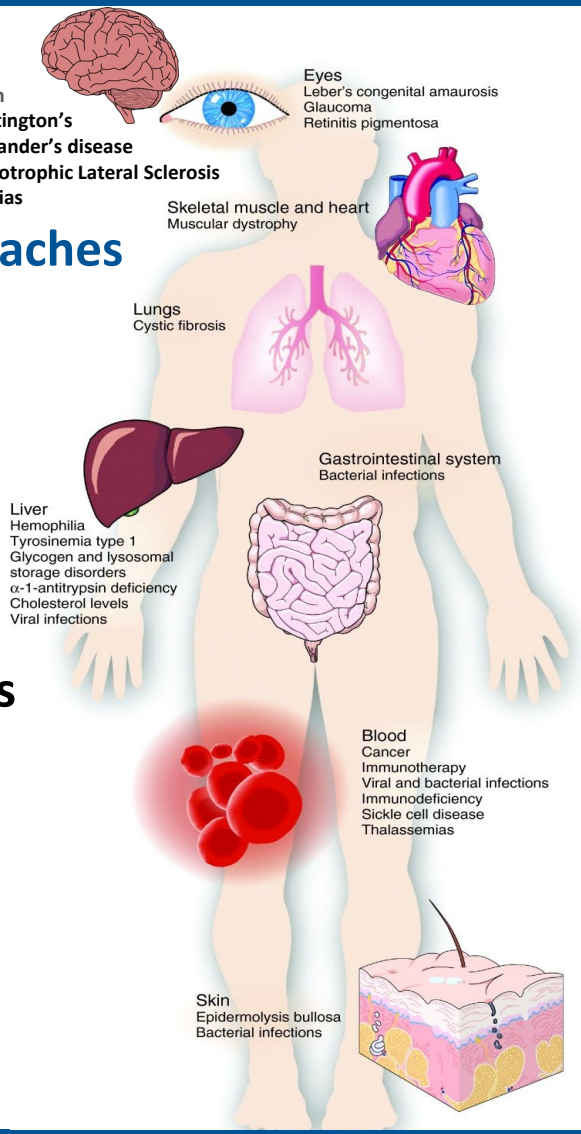
Genome editing allows precise corrections to made in patients' DNA and RNA
CRISPR-cas9 catalyzed development of experimental genome editing therapeutics
Thousands of genetic diseases are amenable to targeted *in vivo* genome editing approaches



Gaps and Opportunities from
2017 Common Fund Planning Workshop

Improved animal models to detect editing
Human cell systems for measuring adverse events
Delivery systems for *in vivo* targeting
Methods to track edited cells *in vivo*
Safer and more effective editors

SCGE Phase 1 addressed these gaps



Images from Maeder and Gersbach, Mol Therapy 2016

Science Contents News Careers Journals

A new way to modify DNA, "prime editor" couples two enzymes, Cas9 (blue) and reverse transcriptase (r
guide RNA (green) that takes the complex to a specific place on DNA's double helix (yellow and purple) a
holds the code for an insertion of new DNA at that spot. PEYTON RANDOLPH

26

New 'prime' genome editor could surpass CRISPR

By Jon Cohen | Oct. 21, 2019 ,

nature biotechnology

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Article | Published: 15 June 2020

CHANGE-seq reveals genetic and epigenetic effects on CRISPR–Cas9 genome-wide activity

Cicera R. Lazzarotto, Nikolay L. Malinin, Yichao Li, Ruochi Zhang, Yang Yang, GaHyun Lee, Eleanor Cowley, Yanghua He, Xin Lan, Kasey Jividen, Varun Katta, Natalia G. Kolmakova, Christopher T. Petersen, Qian Qi, Evgheni Strelcov, Samantha Maragh, Giedre Krenciute, Jian Ma, Yong Cheng & Shengdar Q. Tsai

nature nanotechnology

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nature › nature nanotechnology › letters › article

Letter | Published: 09 September 2019

A biodegradable nanocapsule delivers a Cas9 ribonucleoprotein complex for in vivo genome editing

Guojun Chen, Amr A. Abdeen, Yuyuan Wang, Pawan K. Shahi, Samantha Robertson, Ruosen Xie, Masatoshi Suzuki, Bikash R. Pattnaik, Krishanu Saha & Shaoqin Gong

Nature Nanotechnology **14**, 974–980(2019) | Cite this article

15k Accesses | **65** Citations | **156** Altmetric | Metrics

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REPORT

CRISPR-CasΦ from huge phages is a hypercompact genome editor

Patrick Pausch[1,2,*], Basem Al-Shayeb[1,3,*], Ezra Bisom-Rapp[4], Connor A. Tsuchida[1,5], Zheng Li[6], Brady F. Cress[1,2], Gavin J. Knott[1,2,7], Steven E. Jacobsen[6,8], Jillian F. Banfield[1,9], Jennifer A. Doudna[1,2,8,10,11,12,†]

nature communications

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Article | Open Access | Published: 28 October 2019

Engineered amphiphilic peptides enable delivery of proteins and CRISPR-associated nucleases to airway epithelia

Sateesh Krishnamurthy, Christine Wohlford-Lenane, Suhas Kandimalla, Gilles Sartre, David K. Meyerholz, Vanessa Théberge, Stéphanie Hallée, Anne-Marie Duperré, Thomas Del'Guidice, Jean-Pascal Lepetit-Stoffaes, Xavier Barbeau, David Guay & Paul B. McCray Jr.

Nature Communications **10**, Article number: 4906 (2019) | Cite this article

8996 Accesses | **19** Citations | **61** Altmetric | Metrics

SCGE Phase 2 Planning Activities

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Workshop with:
20 subject matter experts from academic, government and industry - April 20, 2021 -
https://commonfund.nih.gov/editing/meetings

- Session 1: Clinical Trial and Regulatory Innovation
- Session 2: Prospects for Advancing *In Utero* SCGE
- Session 3: Gaps and Opportunities in Basic Development and Discovery
- Session 4: IND-Enabling Preclinical Tools
- Session 5: Issues in Immunogenicity

Consultations with:

SCGE Phase 1 Program Consultants (Drs. Paula Cannon, Kathy High, Vic Myers and Fyodor Urnov)
FDA Center for Biologics Evaluation and Research staff (Drs. Ying Huang, Anna Kwilas, and Peter Marks)
NIH Leaders of translational programs for genome-based therapies (Drs. Chris Boshoff, NINDS's CREATE-Bio and URGenT; Mike Pieck, NHLBI's Catalyze)
DARPA Program Manager for PREPARE (Dr. Amy Jenkins)

Environmental scan of:

In vivo genome editing therapeutics in clinical trials
Industry genome editing pipelines
NIH genome editing therapeutics portfolio

The Future of *in vivo* Genome Editing is Here

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Biotech

With first-in-human trial results, Intellia shows the world that gene editing has arrived

by Annalee Armstrong | Jun 26, 2021 11:15am

NTLA-2001 for ATTR

editas MEDICINE

Editas Medicine Announces Enrollment of the First Pediatric Cohort in the BRILLIANCE Clinical Trial of EDIT-101 for the Treatment of LCA10 Following IDMC Endorsement

June 23, 2021 07:00 ET | Source: Editas Medicine, Inc.

SCGE Phase 2: Translating *in vivo* Genome Editing Therapies into the Clinic More Broadly & Efficiently

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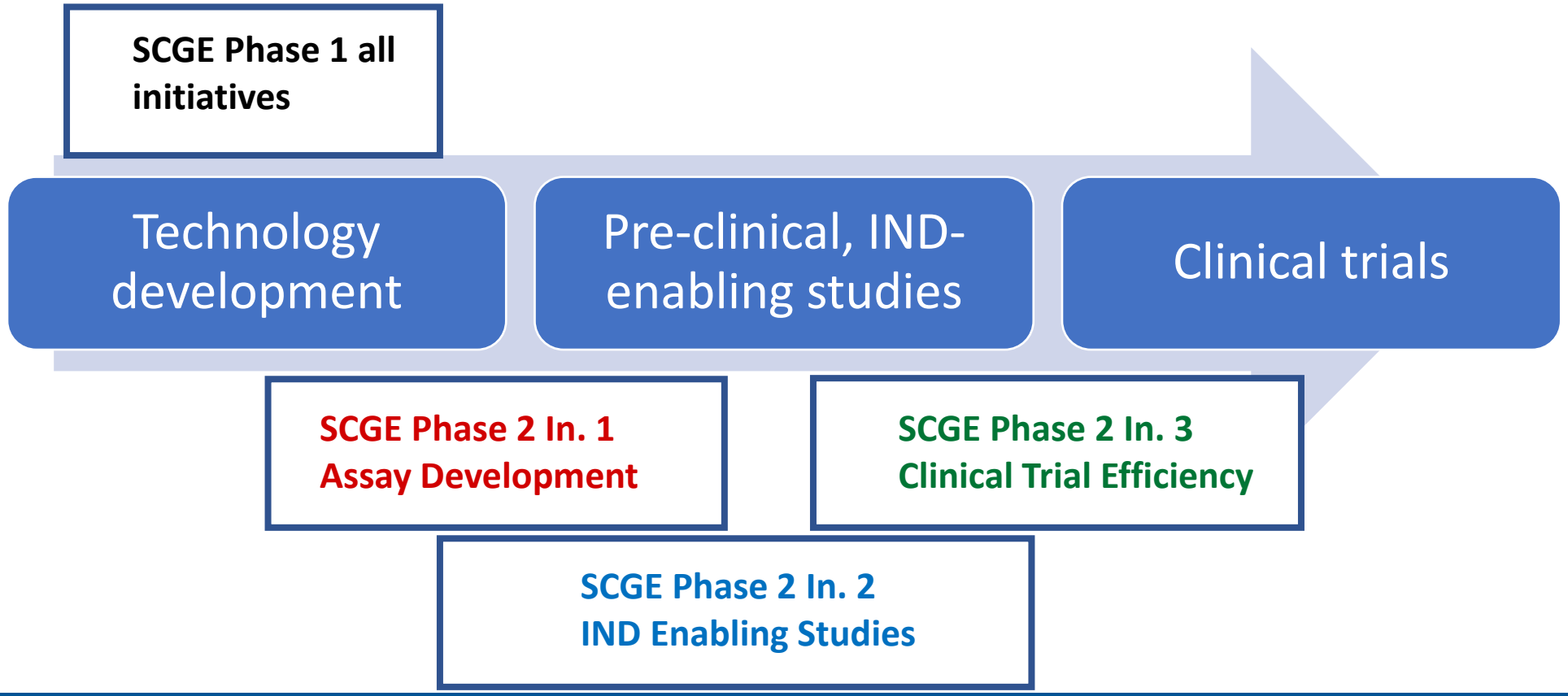
Consensus needs:

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 Proposed In. 1

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Technology development

Pre-clinical, IND-enabling studies

Clinical trials

SCGE Phase 2 In. 1
Assay Development

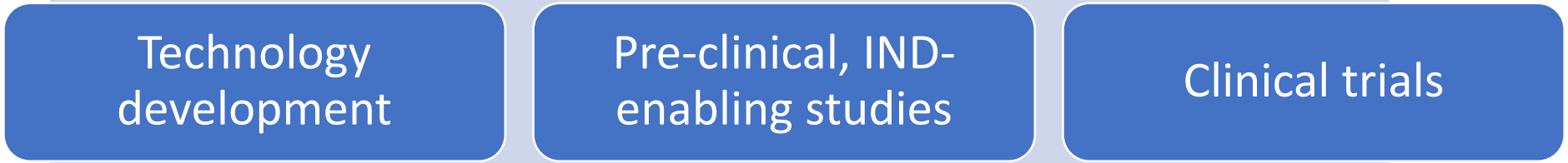
Initiative 1. (U01) Genome Editing Assay Development
Deliverable: Multiple improved assays for preclinical studies
Impact: Facilitate IND submissions for genome editing

Will support optimization and validation of broadly applicable, IND-enabling assays for experimental genome editing therapeutics

- **3-year technology development phase (U01)**
- **Includes:**
  - **Assays for pharm/tox, CMC, on/off-target effects, immune response, cell tracking, etc.**

SCGE Phase 2 Proposed In. 2

The Common Fund



SCGE Phase 2 In. 2
IND Enabling Studies

Initiative 2. (U19) Research Programs for Genome Editing Therapeutic Development
Deliverable: Multiple approaches to developing genome editing therapeutics for different disease scenarios
Impact: IND packages ready for future gene editing clinical trials

Will support the optimization and characterization of experimental in vivo genome editing therapeutics though IND-enabling studies

- **5-year awards**
- **Broad-based, multidisciplinary approach to genome editing therapy development**
- **Each research program targeting multiple diseases in same tissue or cell type**
- **Activities to support IND submissions of multiple projects as needed, e.g., pharm tox, CMC, off-target assays**

SCGE Phase 2 Proposed In. 3

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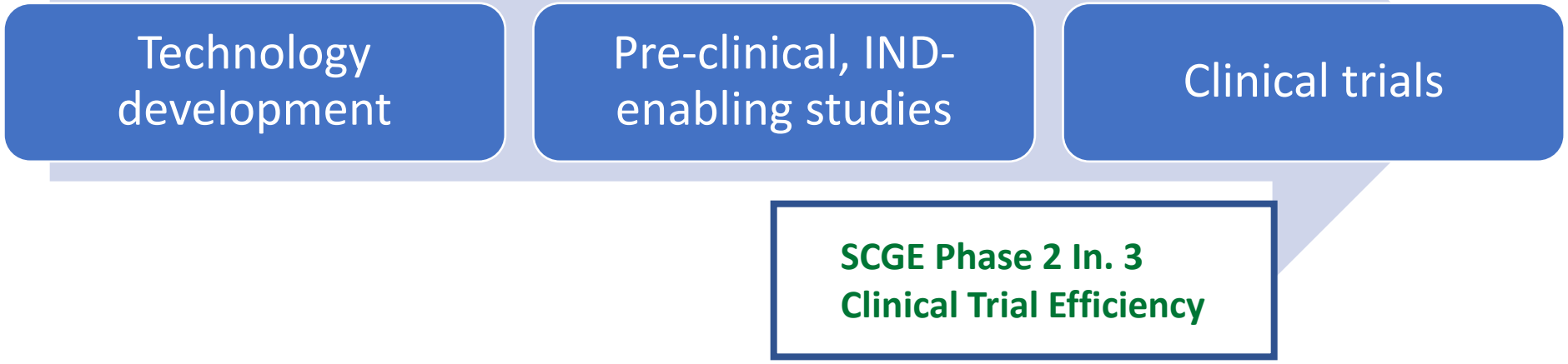


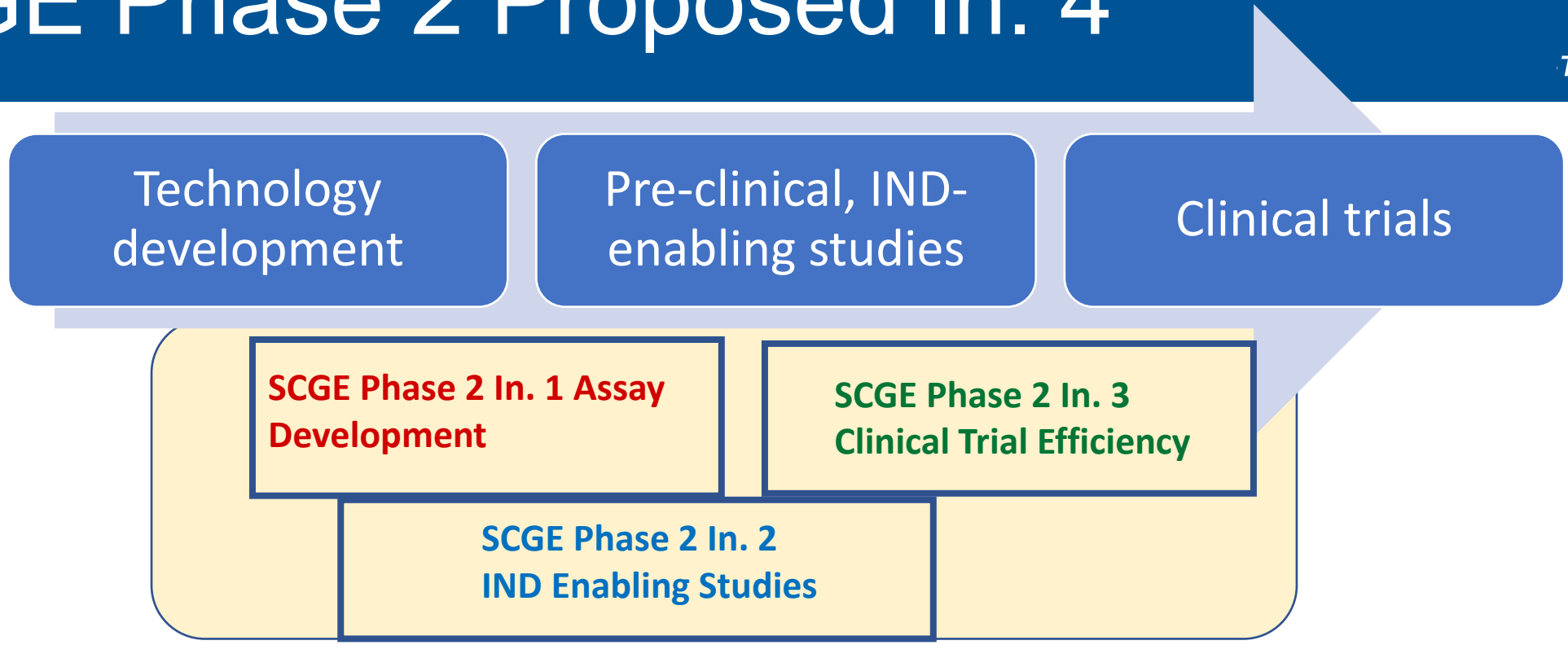
Initiative 3. (UG3/UH3) Demonstrate Efficient Clinical Trial Strategy for Platform Genome Editing Clinical Trials
Deliverable: Demonstration of streamlined regulatory pathway toward IND approval for *in vivo* genome editing trials of >1 disease at a time
Impact: Efficiencies in preclinical data generation, regulatory submissions, and clinical trial design

Will support IND-enabling studies and basket clinical trials demonstrating the platform nature of genome editing technologies

- **3-year preclinical phase (UG3) and 2-year clinical stage (UH3)**
- **Same delivery vehicle, same editor, multiple guides and diseases**
- **Required consultations with FDA thru INTERACT and pre-IND meetings**
- **Activities include pharm/tox, CMC, clinical trial planning, clinical trials**

SCGE Phase 2 Proposed In. 4

The Common Fund



Initiative 4. (U24) Dissemination and Coordinating Center
Deliverable: Broad dissemination of strategies for regulatory submissions
Impact: Accelerate and improve IND submissions for genome editing

Will support data sharing, technical, and regulatory support in therapeutic development

- **Semi-annual meetings**
- **Data and protocol sharing within the consortium and broader community**

SCGE Phase 2 supports the NIH mission and meets the CF criteria

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Transformative: Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade

SCGE Phase 2 will de-risk multiple approaches to developing *in vivo* genome editing therapeutics, and make these approaches widely and publicly available, thereby accelerating clinical trials of therapies for new disease indications.

Catalytic: Must achieve a defined set of high impact goals within a defined period of time

SCGE Phase 2 will establish Proof of Concept and support platform tools and experiences that will be broadly shared.

Synergistic: Outcomes must synergistically promote and advance individual missions of NIH ICs to benefit health

SCGE Phase 2 will synergize with and build upon ongoing studies supported by NIH, as well as industry

Cross-cutting: Program areas must cut across missions of multiple NIH ICs, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach

The deliverables from this program can be applied to a variety of genetic diseases, spanning multiple NIH ICs .

Unique: Must be something no other entity is likely or able to do

High-risk and highly impactful projects will be de-risked within the program infrastructure. SCGE Phase 2 is designed to support multidisciplinary teams, stakeholder engagement and delivery of publicly available tools.

Key Deliverables

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Facilitating Clinical Trials of Genome Editing for Multiple Diseases

In. 1: Fit for regulatory purpose assays for e.g., pharm/tox, CMC, on/off-target effects, immune response, and *in vivo* tracking of edited cells.

In. 2: Datasets to support multiple gene editing INDs targeting different diseases in different cell types

In. 3: A template for obtaining an IND and running a clinical genome editing trial of more than one disease at a time, which explicitly leverages the inherent platform capacity of genome editors

In. 4: Identification and dissemination of best practices and the most successful approaches from the projects supported by SCGE Phase 2.

SCGE Phase 2 Proposed Budget

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Initiative	Title	# Awards	FY23	FY24	FY25	FY26	FY27	
1	Assay Dev	4 x 2	$2.0M	$2.0M	$4.1M	$2.0M	$2.0M	
2	Research Programs	5	$25.0M	$25.0M	$25.0M	$25.0M	$25.0M	
3	Clinical Trial Efficiencies	2	$10.0M	$20.0M	$20.0M	$12.0M	$12.0M	
4	Coordination	1	$2.0M	$2.0M	$2.0M	$2.0M	$2.0M	
RMS		0	0	$0.25M	$0.25M	$0.25M	$0.25M	
Total			$39.0M	$49.3M	$51.4M	$41.3M	$41.3M	**$222M**

SCGE Phase 2 Planning Committee

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Program Chair: Joni Rutter, PhD, Acting Director, NCATS

Common Fund Program Leader: Mary Ellen Perry, PhD, OSC/DPCPSI/OD

Working Group Coordinator: PJ Brooks, PhD, NCATS

Working Group Program Analyst: Deanna Portero, NCATS

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