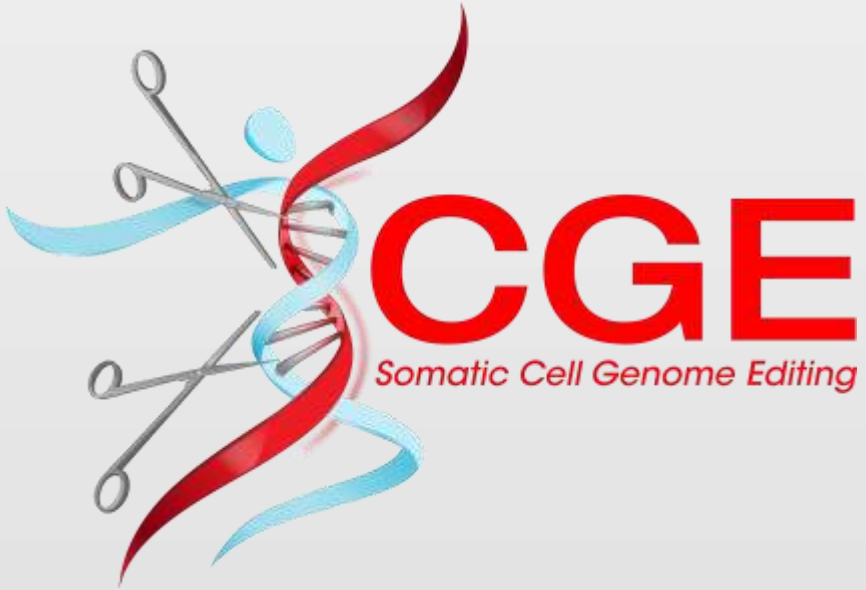
NIH Somatic Cell Genome Editing Consortium (SCGE)



Betty Poon, PhD
National Institute of Allergy and Infectious Diseases (NIAID)
On behalf of the NIH SCGE Consortium

https://youtu.be/27o3s3TktHI

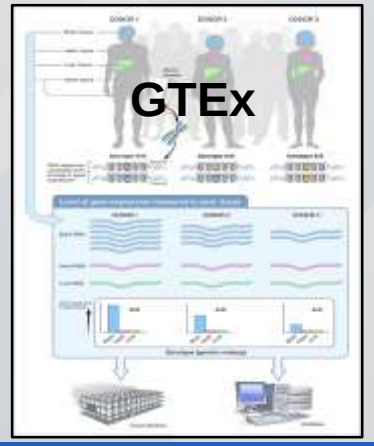
The NIH Common Fund
~$600M FY2019

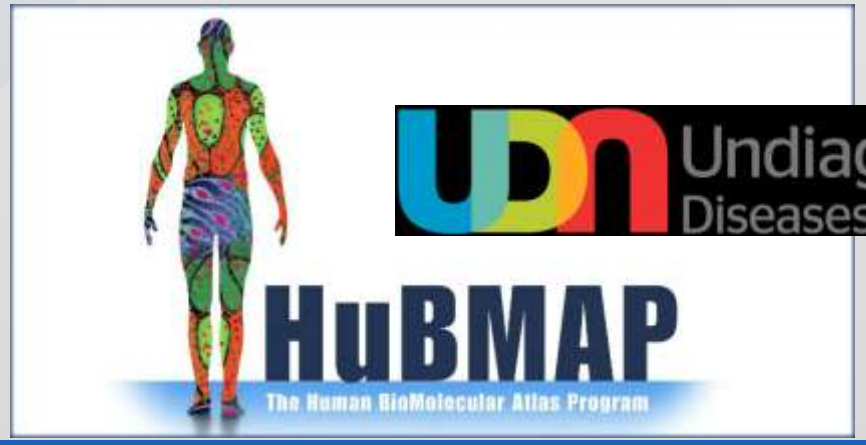
- Is managed by the Office of Strategic Coordination within the Office of the NIH Director, in partnership with the NIH Institutes and Centers.
- Is a “venture capital” space for high-risk, innovative programs with potential for extraordinary impact
- Funds short-term (5-10 year), goal-driven projects focused on developing specific deliverables (data, tools, technologies, etc.) to catalyze research

https://commonfund.nih.gov/

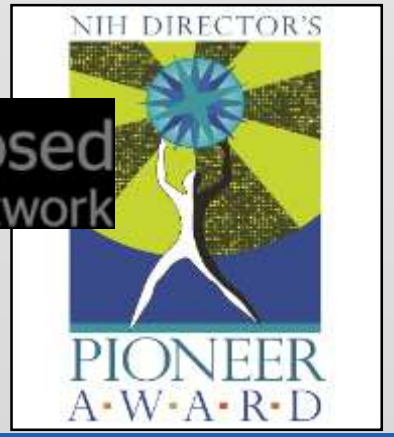
Criteria for Common Fund Programs

- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic**: Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health
- **Cross-cutting:** Program areas must cut across missions of multiple NIH Institutes and Centers, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach
- **Unique:** Must be something no other entity is likely or able to do

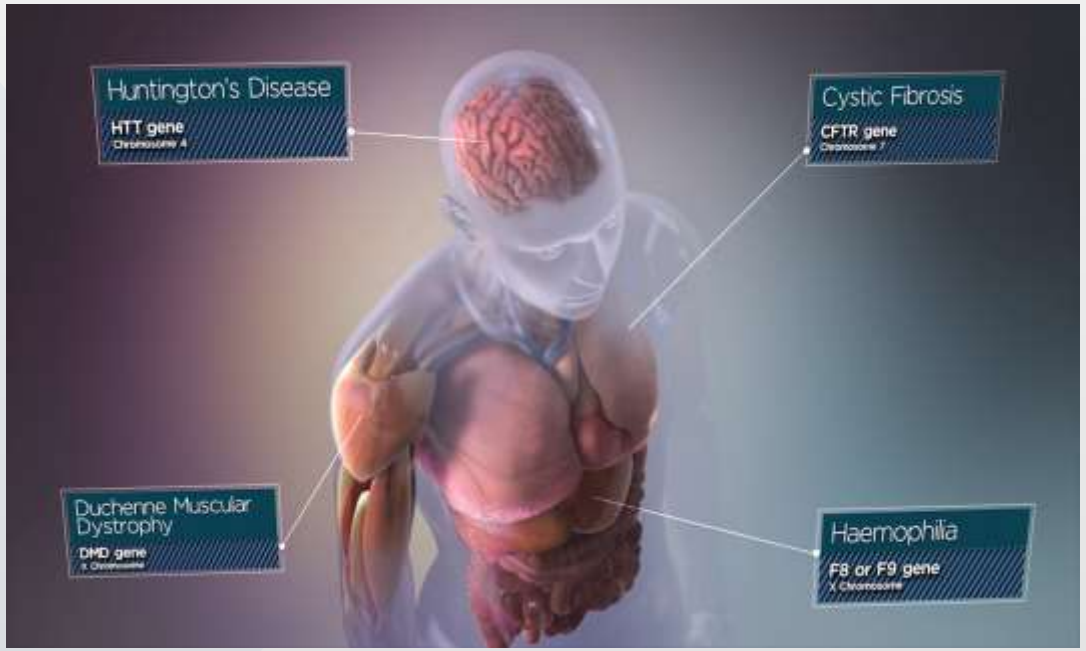




Undiagnosed Diseases Network

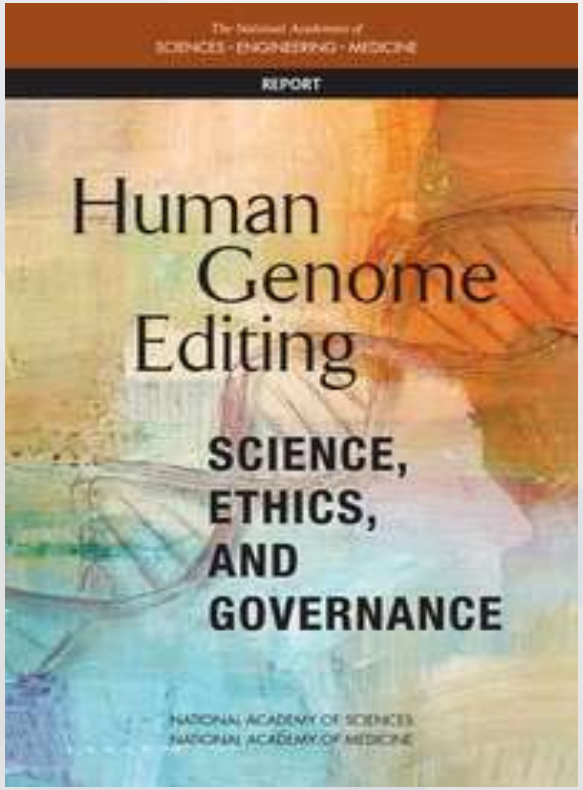


Opportunity for Common Fund Investment?



- Thousands of incurable genetic diseases are now theoretically treatable by gene editing approaches.
- Simple and versatile genome editing methods are democratizing therapeutic development.
- For some indications, a single treatment could be a cure.
- Therapeutic development is still inefficient.
- Development costs for ultra-rare diseases are prohibitive for industry.

National Academies Human Genome Editing Consensus Study:



Major Recommendations (February 2017):

Somatic Genome Editing

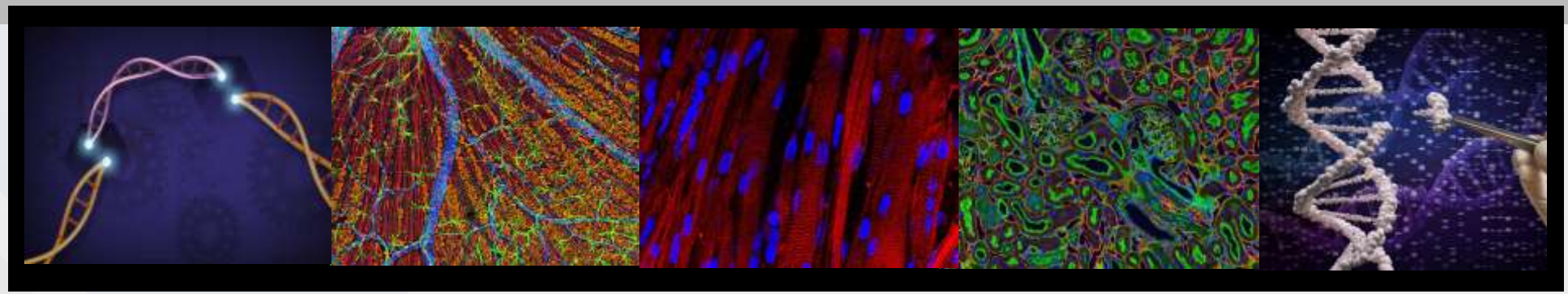
- Limit clinical trials or therapies to treatment and prevention of disease or disability
- Encourage public discussion and policy debate with respect to somatic human genome editing for uses other than treatment or prevention of disease and disability

Germline (Heritable) Genome Editing

- Permit clinical research trials only for compelling purposes of treating or preventing serious disease or disabilities, and only if there is a stringent oversight system able to limit uses to specified criteria
- Ongoing reassessment and public participation should precede any heritable germline editing

The NIH does not support the use of gene-editing technologies in human embryos. Furthermore, the NIH Guidelines state that the Recombinant DNA Advisory Committee, "…will not at present entertain proposals for germ line alteration".

https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-claim-first-gene-edited-babies-chinese-researcher



The NIH Common Fund Workshop:

Making *Somatic* Cell Genome Editing Therapies a Reality

July 24, 2017

Major Gaps Identified:

- Relevant human and animal models systems for pre-clinical testing
- Cell- and tissue-specific delivery systems
- Error-free editing machinery (nuclease alternatives)
- Standardized assays for measuring genetic off-target effects
- Long-term cell tracking assays

NIH National Institutes of Health
Office of Strategic Coordination - The Common Fund

Somatic Cell Genome Editing Working Group

Program Chair: Chris Austin, MD, Director, NCATS

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

Working Group Coordinator: PJ Brooks, PhD, NCATS

Project Team Leads: PJ Brooks, PhD, NCATS
Tom Cheever, PhD, NIAMS
Colin Fletcher, PhD, NHGRI
Oleg Mirochnitchenko, PhD, ORIP/OD
Betty Poon, PhD, NIAID

Working Group Members:

Tatjana Atanasijevic, PhD, NIBIB
Olivier Blondel, PhD, NIDDK
Bonnie Burgess-Beusse, PhD, NIDDK
Linda Griffith, MD, PhD, NIAID
Min He, PhD, NCI
Keith Hoots, MD, NHLBI
Chamelli Jhappan, PhD, NCI
Danuta Krotoski, PhD, NICHD
Tim LaVaute, PhD, NINDS
Jerry Li, MD, PhD, NCI
James Luo, PhD, NHLBI
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Aron Marquitz, PhD, OSC/OD
Stephanie Morris, PhD, OSC/OD
Nasrin Nabavi, PhD, NIAID
Lisa Neuhold, PhD, NEI
Margaret Ochocinska, PhD, NHLBI
David Panchision, PhD, NIMH
Lisa Postow, PhD, NHLBI
David Rampulla, PhD, NIBIB
John Satterlee, PhD, NIDA
Seila Selimovic, PhD, NIBIB
Wendy Wang, PhD, NCI

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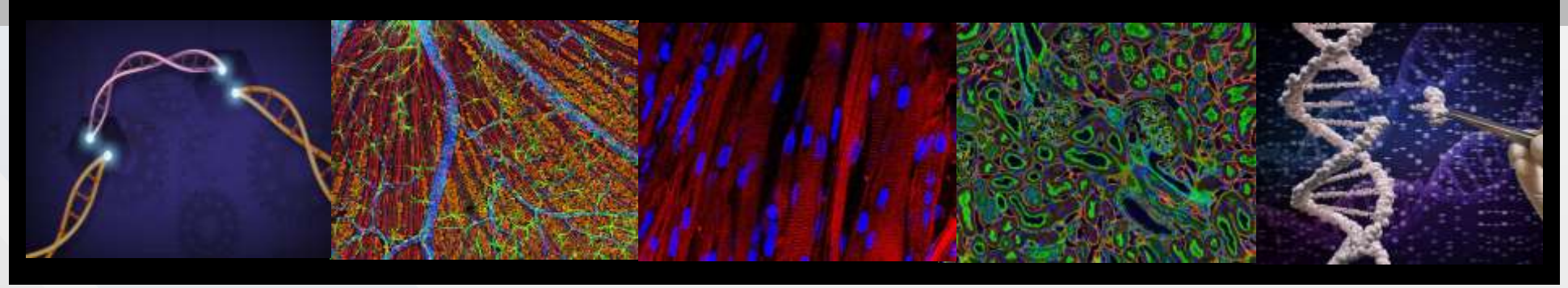
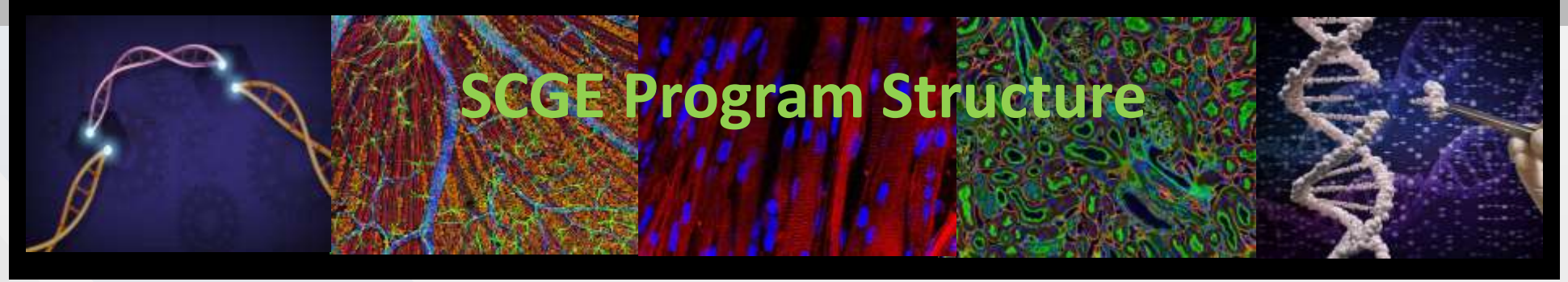


SCGE Program Goals

Lower the Barriers for New Genome Editing Therapies by:

- Testing Genome Editing Reagents and Delivery Systems in Better Animal Models
- Assessing Unintended Biological Effects
- Improving *In Vivo* Delivery of Genome Editing Machinery
- Expanding the Human Genome Engineering Toolkit
- Coordinating Partnerships and Disseminating Information



SCGE Program Structure

SCGE Dissemination & Coordinating Center

Facilitate interactions and communication between consortium components

Disseminate a SCGE Toolkit to the research community

large and small animal testing systems

cell and tissue platforms to detect adverse biological consequences

new delivery systems

expanding the repertoire of genome editors

Initiative 1: Small & Large Animal Reporters & Testing Centers

Project Team Leader: Oleg Mirochnitchenko (ORIP/OD)

Goals:

- Develop small (mice) and large (pigs and NHP) reporter animals to detect on-target and off-target genome editing
- Distribute new strains to national repositories
- Validate delivery systems developed under Delivery initiative
- Collaborate to test new editors developed under Genome Editor initiative

Scope:

- Enable quantitative evaluation of targeted genome editing, as well as off-target events, in all individual cells types (including germ cells)

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Goals:

- Develop small (mice) and large (pigs and NHP) reporter animals to detect on-target and off-target genome editing
- Distribute new strains to national repositories
- Validate delivery systems developed under Delivery initiative

Awardees, Small Animal Reporters and Testing Centers

- Jason Heaney; Baylor College of Medicine: Murine reporters and testing
- Stephen Murray; Jackson Labs: Murine reporters and testing

Awardees, Large Animal Reporters:

- Daniel Carlson; Recombinetics, Inc.: Pig reporters
- Guoping Feng; Massachusetts Institute of Technology: Marmoset reporters
- Jon Hennebold; Oregon Health & Science University: Rhesus reporters

Awardees, Large Animal Testing Centers:

- Alice Tarantal; University of California-Davis: Non human primates
- TBA (2019)

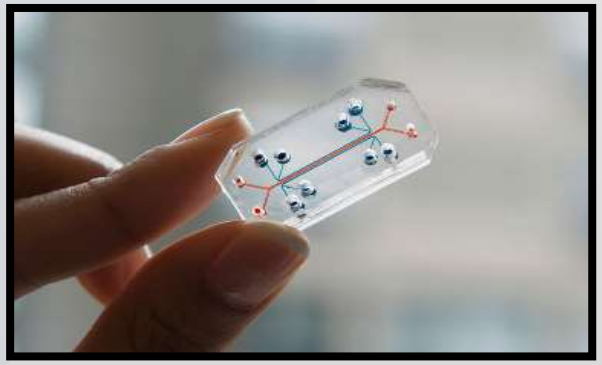
Initiative 2: Assessing Unintended Biological Effects

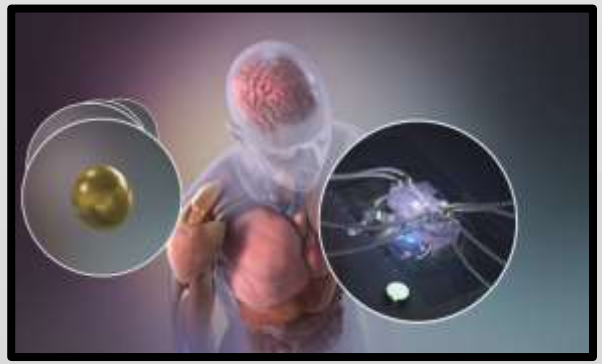
Project Team Leader: Tom Cheever (NIAMS)

Goals:
Develop and test new and existing human cell- and tissue-based platforms that can provide information on the safety of genome editing technologies and delivery systems.

Scope:

- Replicate normal human biology
- Enable sequencing-based approaches to monitor off-target editing
- Monitor unintended biological effects (i.e. genotoxicity, immunogenicity, neurotoxicity, etc.)





Initiative 2: Assessing Unintended Biological Effects

Project Team Leader: Tom Cheever (NIAMS)

Goals:
Develop and test new and existing human cell- and tissue-based platforms that can provide information on the safety of genome editing technologies and delivery systems.

Awardees:

- Todd McDevitt; UCSF: Cardiac, neural, & liver microtissue platforms
- Samira Kiani; Arizona State University: Liver-on-a-chip platform
- Krishanu Saha; University of Wisconsin-Madison: Retinal organoid platform
- **Shengdar Tsai;** St. Jude Research Hospital: T-cell platform

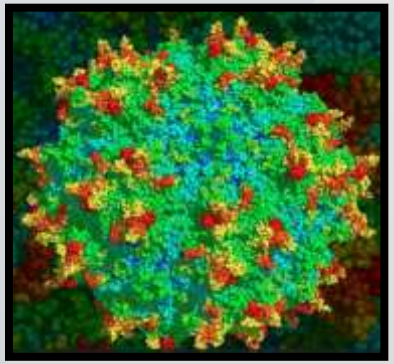
Initiative 3: New Delivery Systems

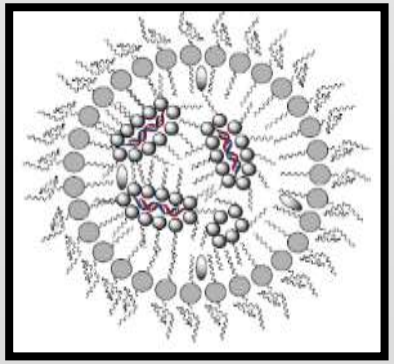
Project Team Leader: PJ Brooks (NCATS)

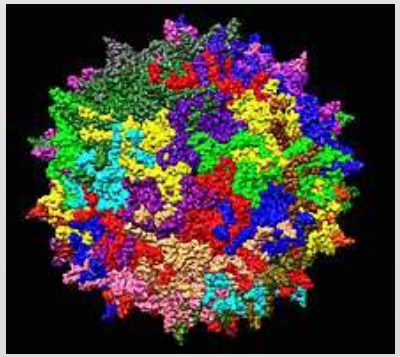
Goal:
Develop and evaluate innovative approaches to deliver genome editing machinery into somatic cells in vivo

Scope:

- Focus on a single cell type or multiple cell types
- Produce substantial qualitative improvements in clinical application
- Validate at the small animal testing centers = required to receive funds after three years







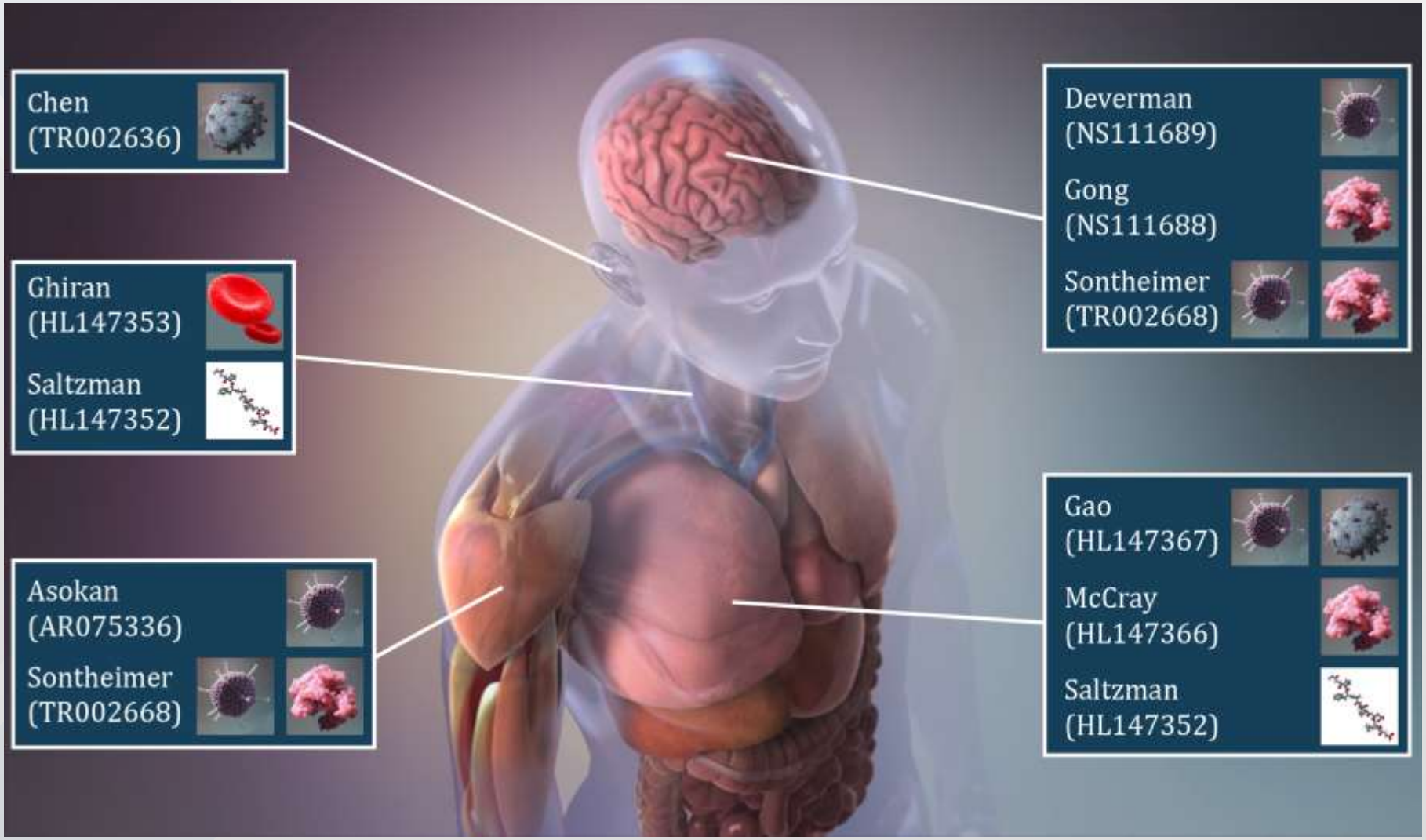
Initiative 3: New Delivery Systems

Project Team Leader: PJ Brooks (NCATS)

Goal:
Develop and evaluate innovative approaches to deliver genome editing machinery into somatic cells in vivo

Awardees:
Aravind Asokan; Duke University: Adeno-associated viruses (AAVs)
Zheng-Yi Chen; Massachusetts Eye & Ear Infirmary: Lipid nanoparticles
Benjamin Deverman; Broad Institute: AAVs
Guangping Gao; University of Massachusetts-Worcester: AAVs & nanoparticles
Ionita Ghiran; Beth Israel: Red blood cell-derived extracellular vesicles
Shaoqin Gong; University of Wisconsin-Madison: Nanocapsules
Paul McCray; University of Iowa: Amphiphilic peptides
Mark Saltzman; Yale University: Peptide nucleic acids
Erik Sontheimer; University of Massachusetts-Worcester: Chemically-modified nucleic acids

Delivery Awardees



Initiative 4: Expanding the Repertoire of Genome Editors

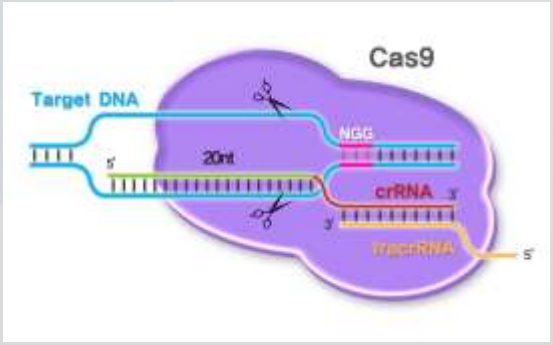
Project Team Leader: Betty Poon (NIAID)

Goal:

Develop innovative genome editing systems with improved specificity, efficiency, or functionality over currently available systems.

Scope:

- Develop nuclease-dependent or nuclease-independent targeted editing, epigenetic modifiers, transcriptional repression and activation approaches, and RNA editors
- Identify novel enzymatic activities and substrate specificities or significantly enhance existing nucleases
- Manipulate inaccessible genomes or genomic regions and reduce non-specific events



Initiative 4: Expanding the Repertoire of Genome Editors

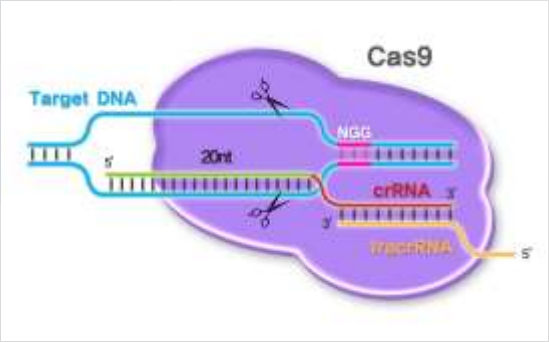
Project Team Leader: Betty Poon (NIAID)

Goal:

Develop innovative genome editing systems with improved specificity, efficiency, or functionality over currently available systems.

Awardees:

- Jennifer Doudna; University of California-Berkeley: Novel Cas proteins and DNA repair systems
- Stephen Ekker; Mayo Clinic: Mitochondrial genome editors
- David Liu; Broad Institute: Improved base editors



Initiative 5: Dissemination and Coordinating Center

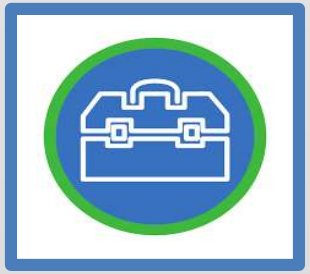
Project Team Leader: Colin Fletcher (NHGRI)

Goal:

Coordinate consortium activities and assemble the SCGE Toolkit

Scope:

- Consortium Coordination Activities: Provide logistical and administrative assistance, facilitate information exchange and discussion
- SCGE Toolkit: Present resources generated from the Consortium in an intuitive and readily accessible online interface
- Collaboration Support: Promote the exchange, cross-testing and evaluation of the improved technologies within the Consortium



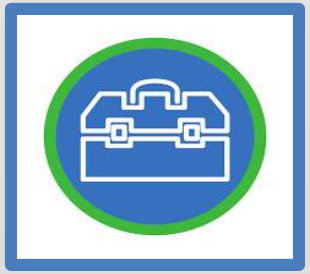
Initiative 5: Dissemination and Coordinating Center

Project Team Leader: Colin Fletcher (NHGRI)

Goal:

Coordinate consortium activities and assemble the SCGE Toolkit

Awardees:
Melinda Dwinell and Mary Shimoyama; Medical College of Wisconsin:
Dissemination and Coordinating Center for the SCGE Consortium

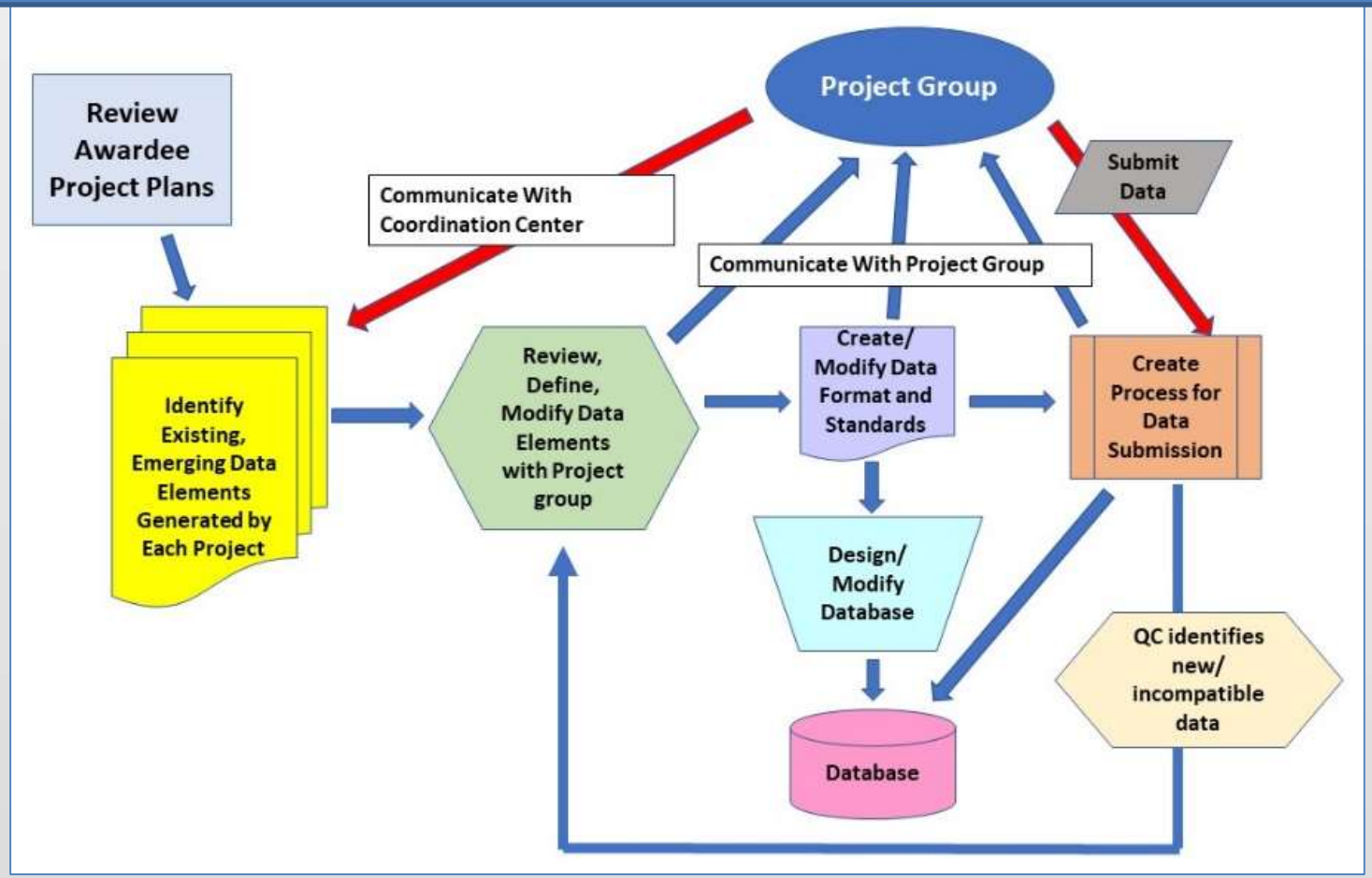


SCGE Program Structure

- The SCGE program will utilize milestone-driven cooperative agreements
- Awardees will be required to collaborate and share data, resources and information with other consortium members and the Dissemination and Coordinating Center (DCC)
- Resources and information generated by the SCGE will be disseminated by the DCC to the broader research community through the SCGE Toolkit for Therapeutic Genome Editing (“SCGE Toolkit”)
- The SCGE Toolkit is envisioned as a Community Resource to enable future preclinical studies of genome editing therapies
- The SCGE toolkit may include the characteristics and associated validation data about the various animal models, delivery systems, editors, and biological platforms developed by the Consortium, along with methods and best practice protocols

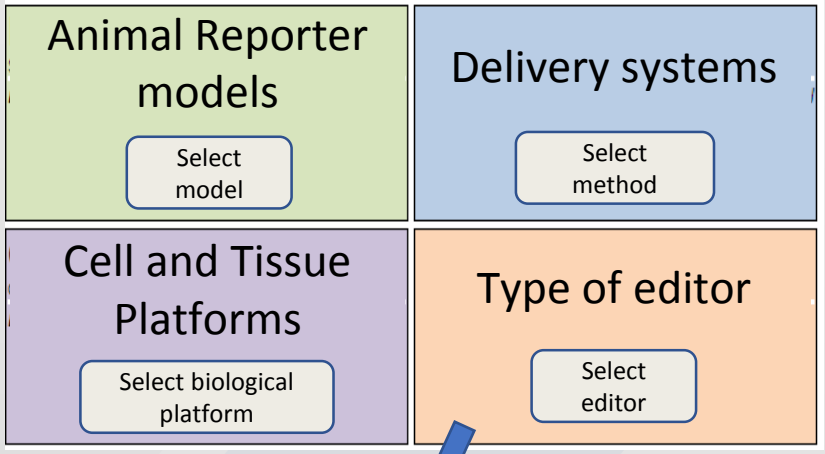
The SCGE Toolkit

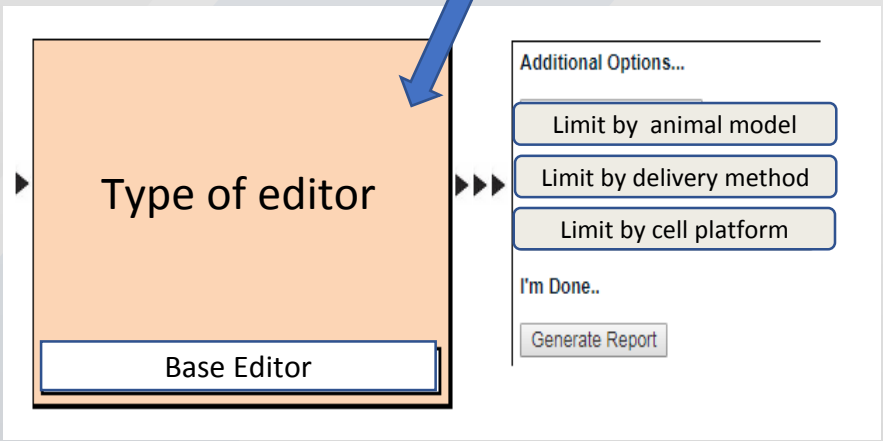
Iterative process for identifying, standardizing data, and database structures



SCGE Toolkit: Prototype

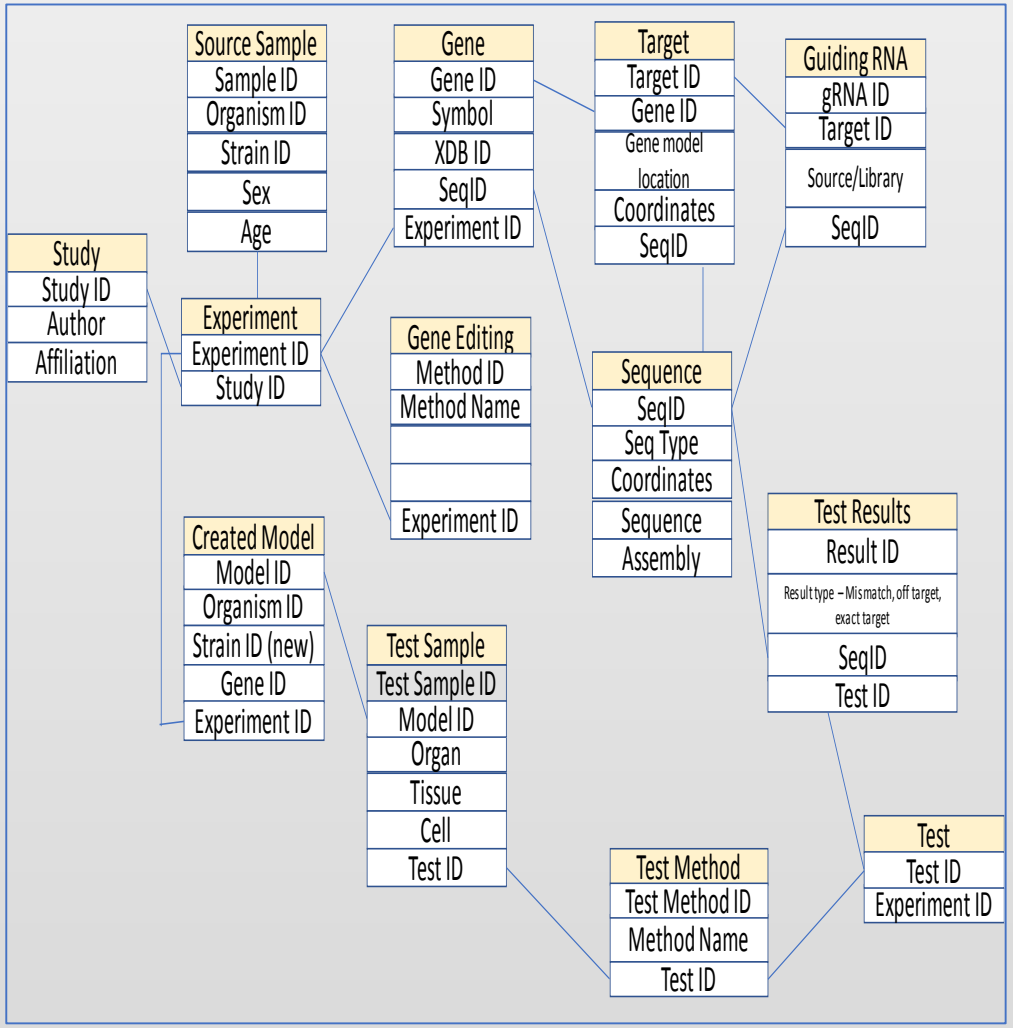
Common data elements will be used to facilitate integration & search by reporter models, delivery systems, cell and tissue platforms, & editing





Data characteristics and testing

Sample table structure for data related to animal reporter models

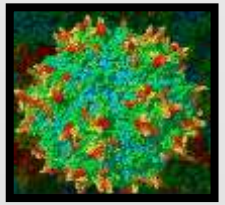
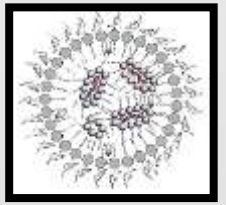
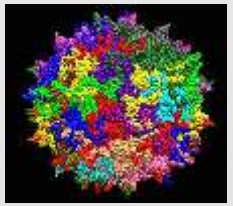


Program Timeline


<u>Proof of Concept</u>
- Technology development
- Editing demonstration
- Policy establishment

<u>Collaboration</u>
- Validation
- Optimization
- Data deposition

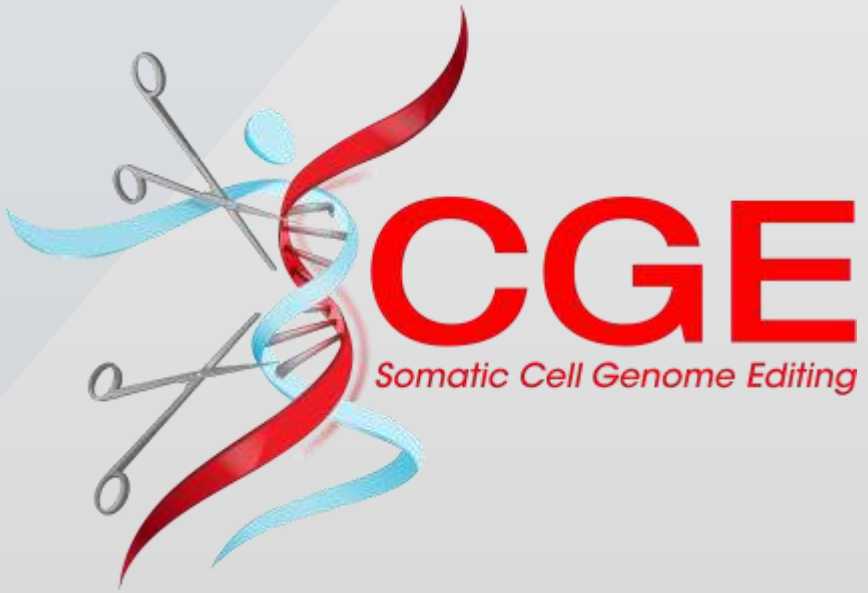
Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6

- September 2018 – Awards made (first round)
- December 2018 – Kick-off meeting
- April 2019 – Large Animal Testing Centers Awards made
- July 2019 – New awards made for Delivery, Editors, Biology
- August 2020 – Delivery vehicles to Testing Centers
- April 2021 – Delivery vehicles validated
- December 2021 – Toolkit launched

Potential Impact of SCGE Consortium

- Increased access to IND-enabling technologies
- Accelerated filings of new INDs for gene editing therapies
- Faster approval of gene editing therapies
- New therapeutic approaches for both rare and common diseases
- Cures for monogenic diseases



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Questions?