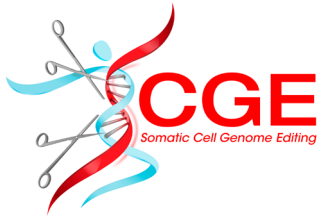
Introduction to the NIH Common Fund Somatic Cell Genome Editing (SCGE) Program



PJ Brooks, PhD

NIH SCGE Program Coordinator

National Center for Advancing Translational Sciences (NCATS)

https://commonfund.nih.gov/editing

National Institutes of Health

Office of Strategic Coordination - The Common Fund

The Common Fund Moves the NIH Mission Forward Faster

CGE Somatic Cell Genome Editing

NIH The Common Fund

- Supports **bold, five-year, goal-driven** scientific programs that **catalyze** biomedical research
- **Complements the missions** of the NIH Institutes and Centers
- Addresses **emerging opportunities and challenges** that **no single IC** can address on its own
- Is supported by the Office of the NIH Director and managed in **partnership with the Institutes and Centers**

SCGE Phase I (2018-2023) was Designed to Fill Gaps Identified by Experts at 2017 NIH Workshop

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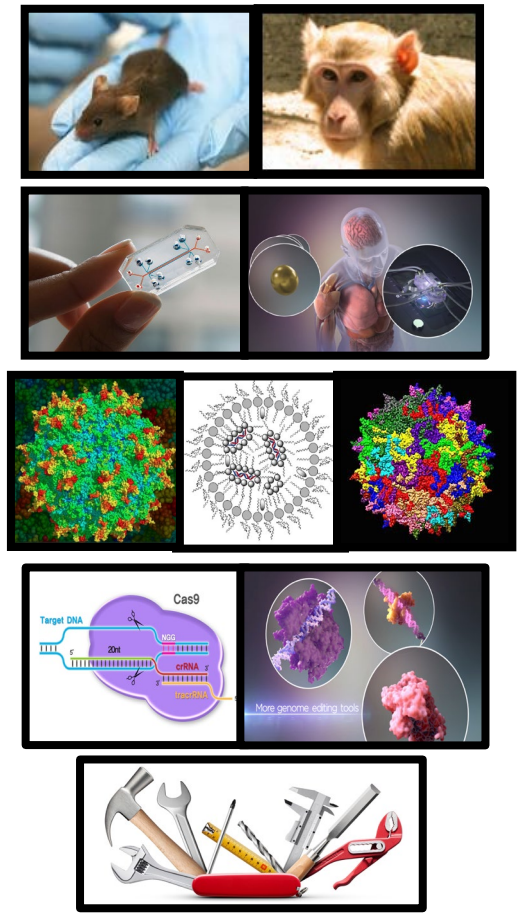
- Needs Identified in 2017 Phase I Planning Workshop:
  - More informative, predictive animal models
  - Assays and technologies to detect unintended consequences of genome editing
  - More effective delivery vehicles for clinically relevant cells and tissues
  - Safer, more specific editors
  - Access to advanced technologies



Initiative 1:
Animal Reporter & Testing Centers

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Goals:

- Develop and validate reporter animals to allow quantitative evaluation of targeted genome editing in all cells and tissues, including germ cells.
- Establish assays and standard operating procedures (SOPs) to detect genome editing in cells of the wild type animals.
- Evaluate the ability of delivery technologies developed by SCGE Delivery Technologies investigators to deliver genome editing tools to target cells and tissues

Progress to Date:

- Generated multiple lines of fluorescent reporter mice
- Designed reporter pigs and NHPs
- Validated several new delivery methods
- Collaborating to map tropism of popular AAV serotypes

Organism	Editing events detected	Primary readout	Secondary readout	Editors	PIs[a]
Mouse	NHEJ, HDR, off-target cutting	Fluorescent signal in situ	Luciferase	SpyCas9, SauCas9, Cas12a	J. D. Heaney, M. E. Dickinson, W. R. Lagor
Mouse	NHEJ, HDR, base editing, PNA	Fluorescent signal in situ	Luciferase, NaI symporter	SpyCas9, SauCas9, Cas12a, Nme2Cas9, CjeCas9, ABE, CBE, PNA	S. A. Murray, C. M. Lutz
Pig	NHEJ, HDR	Fluorescent signal	NaI symporter	SpyCas9, SauCas9, Cas12a, ABE	D. F. Carlson; K. D. Wells, R.S. Prather
Macaque	NHEJ, HDR, C base editing	Fluorescent signal	Luciferase	SpyCas9, SauCas9, Cas12a, CBE	J. D. Hennebold; A. F. Tarantal, D. J. Segal
Marmoset	NHEJ	Akaluciferase	Fluorescence	SpyCas9, SauCas9, Nme2Cas9, Cas12a, ABE	G. Feng; A. F. Tarantal, D. J. Segal

Initiative 2: Biological Effects and In Vivo Monitoring

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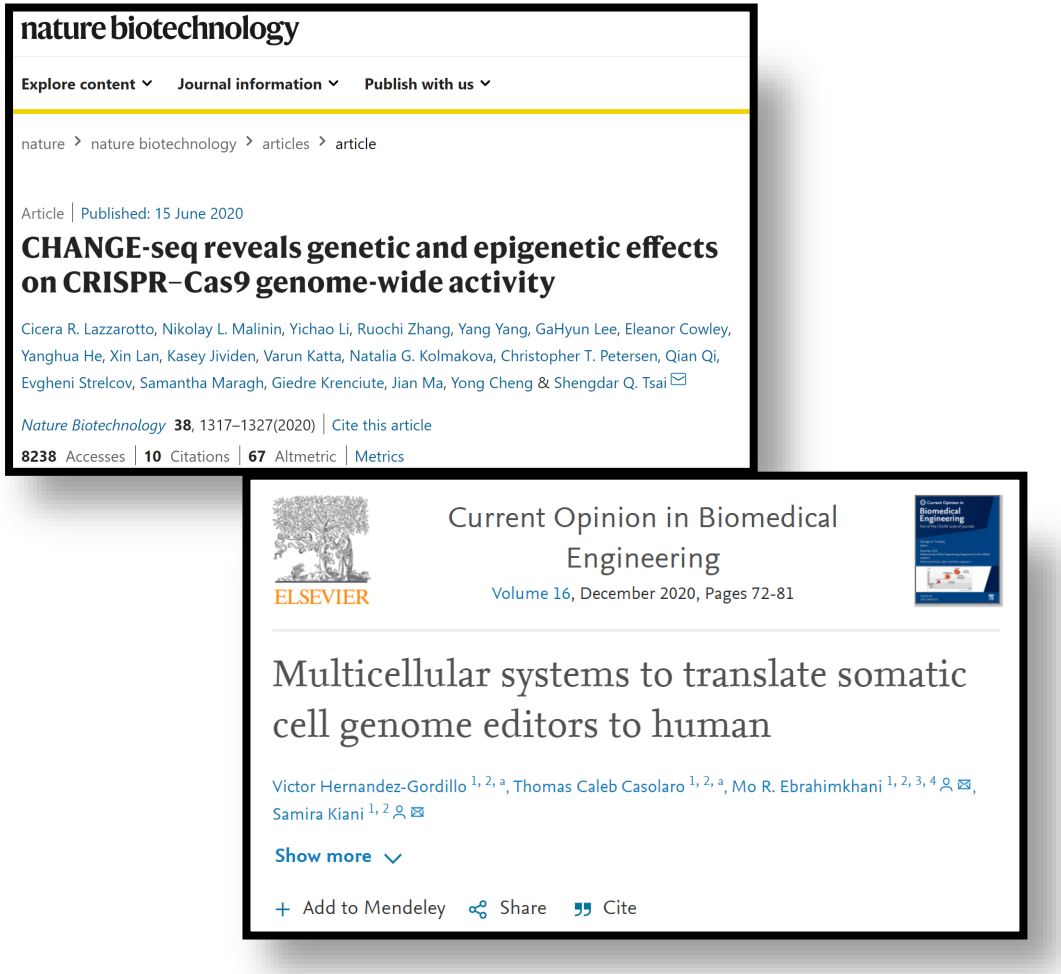
Goals:

- Develop and validate of human tissue- and cell-based platforms for predicting adverse consequences of genome editing
- Support the development of tools and technologies that will enable longitudinal monitoring and tracking of genome edited cells in humans to better assess the safety and efficacy of genome editing therapies

Progress to Date:

- Demonstrated unintended consequences in multiple human cell systems
- Improved off-target assays
- Designed assays for long-term tracking



Initiative 3:
New and Improved Delivery Systems

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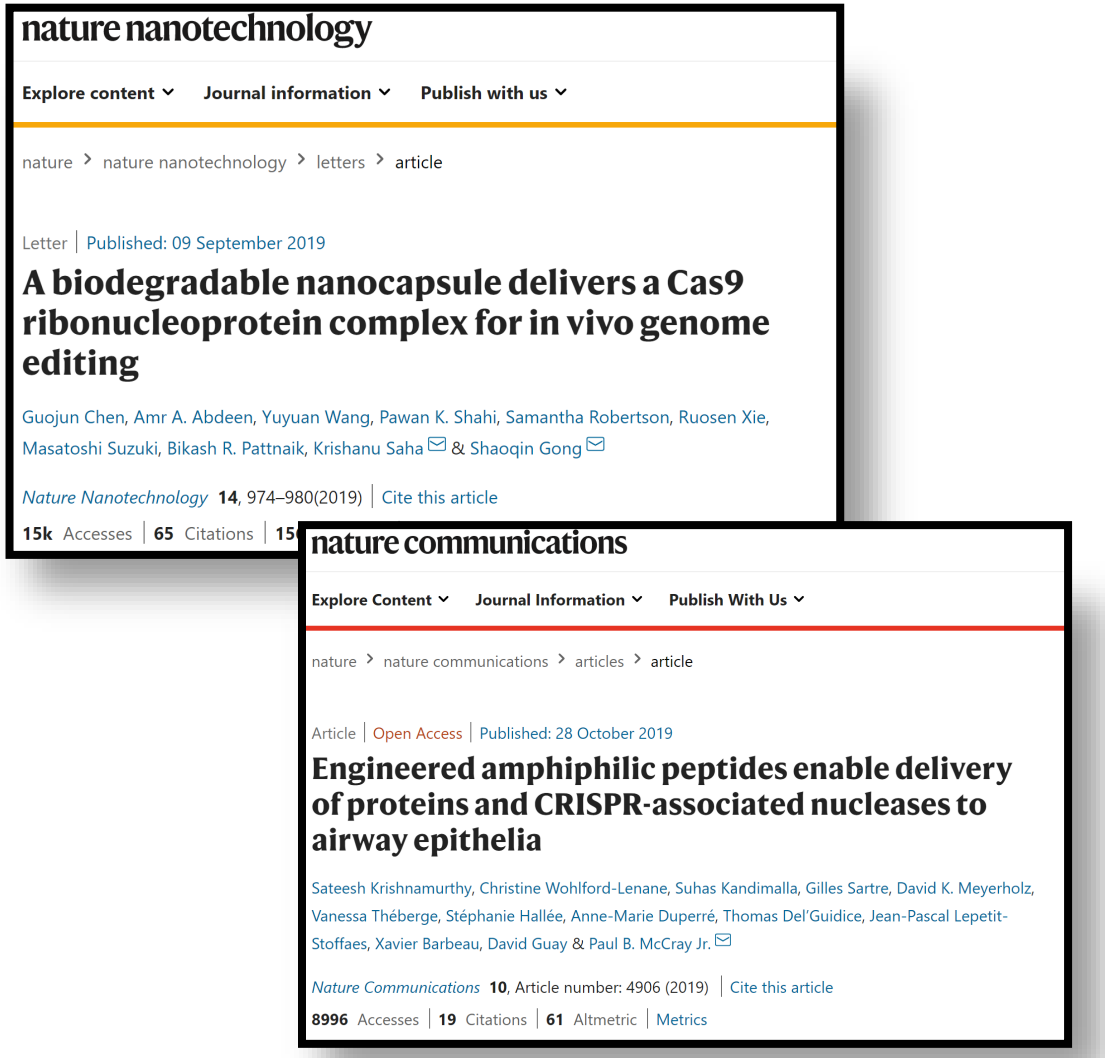
Goals:

- Development of safe and effective technologies to deliver genome editing machinery into a diverse set of disease-relevant somatic cells and tissues

Progress to Date:

- Generated several new delivery methods including improved AAVs and NPs
- Upon achievement of in-house, *in vivo* proof of concept, the delivery systems are independently validated by SCGE-funded animal testing centers.



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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

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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

Initiative 4: Expanding the Human Genome Engineering Repertoire

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Goals:

- Develop novel and optimized alternative genome editing platforms

Progress to Date:

- Improved base editors
- Discovered mitochondrial DNA, PRIME and casΦ editors

Initiative 5: Dissemination and Coordination

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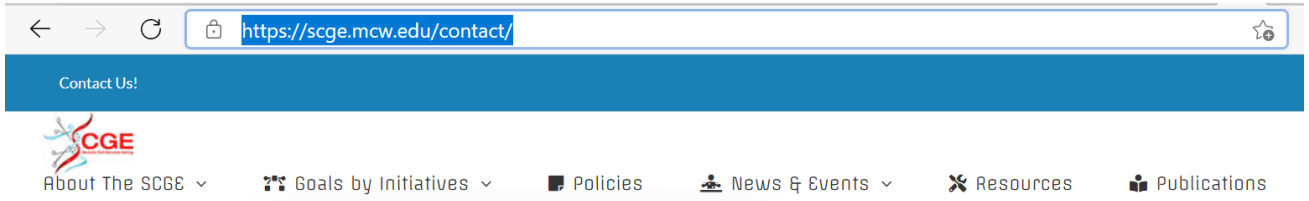
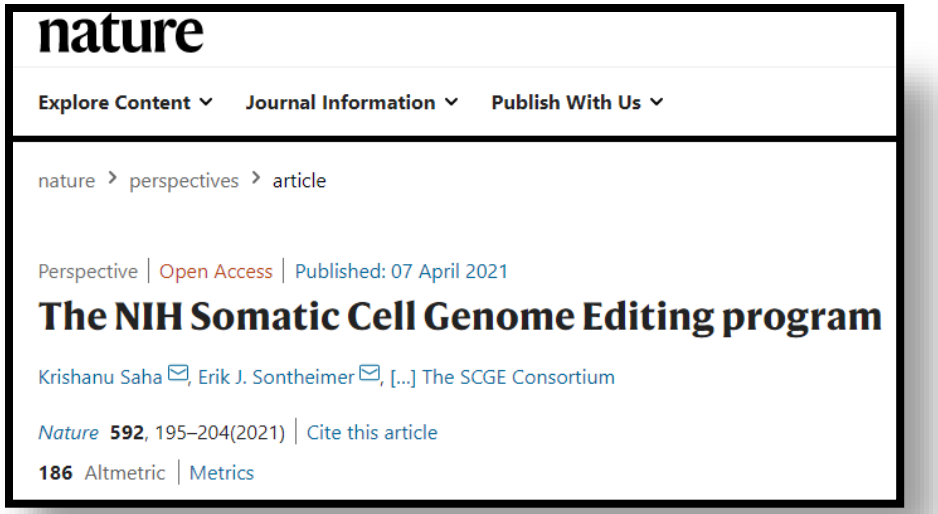
Goals:

- Enable close interactions and efficient lines of communication between the SCGE Phase I Awardees
- Develop and disseminate a SCGE Toolkit for Therapeutic Genome Editing present resources generated from the Consortium in an intuitive and readily accessible online interface.

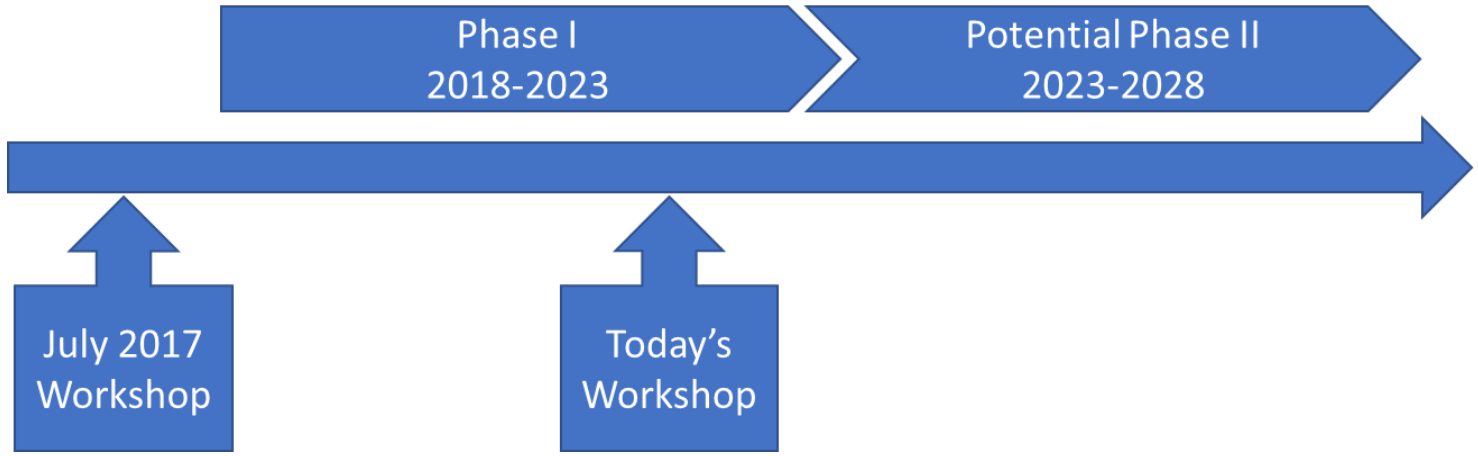
Progress to Date:

- Coordinated Marker Paper
- Internally beta-testing the SCGE Toolkit
- Awarded 15 collaborative projects among SCGE Phase I Awardees to exchange, cross-test and evaluate SCGE-funded technologies





SCGE Program Timeline



Phase II can **continue to address the needs, gaps and opportunities** identified in Phase I

and / or

Phase II can **address new needs, gaps and opportunities** based external and internal input.

Today's Agenda

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Session 1: Clinical Trial and Regulatory Innovation

BREAK

Session 2: Prospects for Advancing *In Utero* SCGE

LUNCH

Session 3: Gaps and Opportunities in Basic Development and Discovery

BREAK

Session 4: IND-Enabling Preclinical Tools

BREAK

Session 5: Issues in Immunogenicity

- **These are not "the new five initiatives."** The structure and priorities of Phase II have not been determined.
- These topics and the underlying discussion questions were identified from **internal and external input** (including input from many of you).

Before we move on to introductions…

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Are there any questions about

- **The NIH Common Fund,**
- **Phase I of the SCGE Program, or**
- **What we hope to achieve in today's workshop?**