Proposal to Launch a Second Phase of the Somatic Cell Genome Editing (SCGE) Program

Background: The SCGE program was developed in 2017 in response to an NIH workshop identifying several barriers to the discovery and translation of new genome editing technologies towards clinical applications, including safer and more effective editors and delivery methods for *in vivo* therapeutic approaches. This proposal for a second phase of SCGE relies on progress within the program and developments across the broader genome editing field. An environmental scan, workshops, and consultations with fellow federal agencies indicated that, while *in vivo* somatic cell genome editing therapeutics have entered the clinic targeting the liver and eye, regulatory guidance and financial support is needed to de-risk development, especially for other tissues.

SCGE Phase 1 Progress: Significant progress is exemplified by the discovery of prime editing by David Liu whereby a catalytically impaired Cas9 editor fused to reverse transcriptase targets insertions, deletions, and all possible base-to-base conversions in human cells. Liu's lab also developed more efficient and precise base editors with 10–100-fold lower off-target DNA editing. Jennifer Doudna and Jill Banfield identified a hypercompact genome editor, CRISPR-CasΦ, that may overcome the packaging size limitations of AAV delivery vectors. Impressive progress with both viral and non-viral delivery has been made by both Guangping Gao (AAV) and Paul McCray's (RNPs) projects, both of which surpassed published editing levels in murine lung epithelial cells. In addition, improved delivery vehicles have been identified for brain neuronal and glial cells and multiple cells of the inner ear. As required by the program, *in vivo* editing with these improved delivery methods was validated by a third party (Jason Heaney's SCGE Small Animal Testing Center). As a result, SCGE delivery vehicles are now being tested in large animals, anticipating the integration of these and other SCGE technologies into experimental genome editing therapeutic approaches for a broader range of clinically relevant target tissues.

SCGE Phase 2 Program Goal: Accelerate the clinical development of genome editing

Initiative 1. *Technology Development for in vivo Genome Editing Clinical Trials (U01)* - Develop and validate improved assays that can enable IND submissions.
Initiative 2. *Optimization of Genome Editing Therapeutic Candidates toward IND Submissions (U19)* - Stimulate the optimization and application of novel, safe and effective genome editing therapeutic candidates.
Initiative 3*. Basket Clinical Trials of Genome Editors in Multiple Diseases (UG3/UH3)* - Demonstrate the regulatory efficiency of exploiting the platform nature of genome editing technologies by supporting basket clinical trials utilizing the same editor and the same delivery vehicle for multiple diseases.
Initiative 4. *Dissemination and Coordinating Center (U24)* - Support the development of genome editing therapeutics and coordinate the exchange of knowledge across the program and broader community.

Proposed Budget:

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	$25M	$25M	$25M	$25M	$25M
3	Clinical Trial Efficiencies	2	$10M	$20M	$20M	$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		16	$39.0M	$49.3M	$51.4M	$41.3M	$41.3M