Concept Clearance on Testing Centers for Development of Somatic Cell Genome Editing in Model Organisms

The ORIP Strategic Plan 2021-2025 emphasizes development and enhancement of research-related center and resource programs to promote accessibility to animal models and biological materials and exploration of ways to improve the reproducibility of research using disease models. ORIP supports many Center and Resource Programs that serve multiple purposes for the biomedical research community, including the creation, collection, characterization, preservation, distribution, and enhancement of animal models. In addition, ORIP supports collaborative research that links current personalized medicine efforts in human subjects with advances in animal genomics and genetic manipulation technologies.

The broad applicability of targeted and programmable genome editing approaches including, but not limited to, those based on CRISPR-Cas9 raise the possibility of a fundamentally new way to treat a variety of rare genetic diseases as well as numerous therapeutic strategies for common diseases. However, many challenges need to be overcome before such techniques could be widely used for human patients, such as editing efficiency, relative difficulty in delivery, off-target effects, immunogenicity, efficacy, etc. Workshops held by NIH[1,2] and by other organizations[3,4] between 2017 and 2022 identified several research areas in need of investment, including optimized genome editors, specifically targeted delivery systems, and more predictive animal models and studies. A recent NIH Common Fund program, the Somatic Cell Genome Editing (SCGE) Program, supports cross-cutting initiatives to maximize the potential of genome editing technology. Participating in the Common Fund supported SCGE Program, ORIP currently is administrating seven cooperative agreement projects supporting creation of animal models through Small and Large Animal Testing Centers and Large Animal Reporter Systems Projects to assess genome editing for *in vivo* studies. Ongoing efforts are expected to produce reporter rodents, pigs, and non-human primates (NHPs) and to conduct validation studies for investigators currently funded under the SCGE Program's New Delivery Systems Initiative in healthy animals, not for disease conditions.

Preclinical animal studies and their translation to human therapies are usually large, expensive, and multidisciplinary projects, requiring extensive use, storage, and interpretation of animal model phenotypes. These studies also involve expert knowledge to choose the best model system for a particular application and interpretation of research results involving a variety of treatment modalities in animals and humans. New advances in animal genome modification technologies are helping investigators to create cost-effective animal resources with phenotypes more closely analogous to those of human patients with specific diseases in a relatively short period of time. Building animal model resources and services to assist studies and unbiased preclinical evaluation of future genome editing therapeutics in animal models of diseases will serve the broader research community interested in translating genome editing in animal models to the clinic.

Based on the recommendations from these previous workshops and ORIP's oversight of animal testing centers and reporter systems projects for the SCGE Program, ORIP proposes to initiate a new program on "Testing Centers for Development of Somatic Cell Genome Editing in Model Organisms." To align with ORIP's NIH-wide mission, proposed projects will: 1) cover a wide variety of disease conditions relevant to the interests of multiple NIH Institutes and Centers; 2) develop resources and testing services in animal models for the growing community developing SCGE therapeutics; 3) conduct testing in reporter animals and animal disease models; and 4) assist in development of new technologies and preclinical testing to generate high quality reproducible information required for clinical studies. Proof-of-concept studies using prenatal gene editing in large animal species (swine, NHPs) for the treatment of inherited genetic diseases will be a high priority.

Based on the success of the SCGE program and ORIP's active participation in management of the SCGE Animal Reporter, Validation & Testing Projects, ORIP requests concept clearance from the Council of Councils to support the new initiative entitled, "Testing Centers for Development of Somatic Cell Genome Editing in Model Organisms".

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[1] https://commonfund.nih.gov/sites/default/files/8.14.18SCGE_CompiledWebinarSlides_FINAL508.pdf

[2] https://commonfund.nih.gov/editing/meetings

[3] https://pharm.ucsf.edu/cersi/prenatalgenetherapy

[4] https://www.fda.gov/media/156894/download