**Concept Clearance on Development of Resources and Technologies for Enhancing Rigor, Reproducibility, and Translatability of Animal Models in Biomedical Research**

Animal research plays an essential role in the discovery of basic biological mechanisms, understanding the etiology of human diseases, and the development of treatments. However, major challenges exist in preclinical animal research, including a high level of irreproducibility of preclinical studies and elevated attrition rate of drug development based on successful animal research. To improve rigor, reproducibility, and translatability of animal research, it is critical to validate animal models by determining how well animal models recapitulate human disease phenotypes, how well the mechanisms underlying the human disease phenotypes are reflected in animal models, and how similar such models are to humans in terms of response to therapies.

A major theme of the ORIP Strategic Plan 2021-2025 is to facilitate the development and ensure the availability of the highest quality and most useful animal models and related resources for the advancement of research on human disease. To gauge the status and gaps in rigor, reproducibility, and translatability of animal research, ORIP organized in 2020 and 2021 a series of 10 virtual sessions as a workshop on "Validation of Animal Models in Biomedical Research" in collaboration with NHLBI, NIA, NIDDK, NIGMS, and NINDS. Each session had 5-7 expert presentations followed by group discussion with 200-500 researchers and NIH program officials. The topics included validation of animal models ranging from invertebrates to nonhuman primates; tools and resources needed for improving animal research; strategies for predicting unknown aspects of disease and therapeutic outcomes; and integration of various types of data for improving animal research.

Workshop participants recognized the strengths and limitations of various animal models and the need for development of tools and resources in a wide variety of animal models for improving research. The participants suggested the following gaps and opportunities for ORIP and the NIH to consider: 1) Improving genetic technologies for mutating and tagging genes, developing humanized animal models and nanoantibodies, and detecting interacting proteins in cells; 2) Systematically phenotyping animal models at multiple levels (e.g., single-cell transcriptomics, proteomics, tissue, organ, cell morphology, metabolomics, behaviors); 3) Screening technologies for facilitating high-throughput genetic and chemical screens; 4) Artificial strategies that allow integrative mining of data in various databases (e.g., model organism databases, phenotype databases); 5) Standardization and reporting of genetic background of strains, housing condition, and environmental conditions (i.e., to promote reproducibility); 6) Sophisticated imaging facilities; and 7) Enhancing stock centers to ensure the accessibility of high-quality animal models.

Based on the recommendations from the ORIP-organized workshop, ORIP proposes to initiate a program on "Development of Resources and Technologies for Enhancing Rigor, Reproducibility, and Translatability of Animal Models in Biomedical Research". To align with ORIP's NIH-wide mission, proposed projects should have broad application to multiple NIH Institutes and Centers, develop resources and technologies with significant impact across a broad range of research areas using animal models, and demonstrate how proposed resources and technologies impact rigor and reproducibility of animal studies.

Examples of suitable projects for the proposed initiative could include resources or technologies to facilitate phenotyping at multiple scales; technologies, including artificial intelligence tools, for integrating multi-omics, biochemical, physiological, morphological, and behavioral data; strategies that allow user-friendly informatic searches and integrative mining of data for comparative human-animal biology; high-throughput imaging technologies for integrative analysis of cells and cellular networks across animal species; and resources that facilitate collaborations between basic science and clinical researchers in the use of multiple animal models for studying human diseases (vertical integration). Examples of grant mechanisms to support this initiative could be, but are not limited to, R21 for 2-year exploratory/developmental research projects, R01 for 5-year research projects, R24 for 4-year resource-related research projects, U24 for 4-year resource-related research projects under cooperative agreements, and small business grant mechanisms.

Based on the urgent need to improve preclinical research using animal models, ORIP requests concept clearance from the Council of Councils to support the new initiative "Development of Resources and Technologies for Enhancing Rigor, Reproducibility, and Translatability of Animal Models in Biomedical Research".