Concept Clearance – Reissue of Development of Models, New Approach Methodologies, and Biological Materials for Studying Human Health and Diseases (R21)

ORIP advances the NIH mission by supporting research resources and infrastructure. Through continued engagement with NIH Institutes, Centers, and Offices (ICOs) and the biomedical research community, ORIP empowers and expands existing programs and develops new initiatives to support NIH at the forefront of scientific progress. The ORIP Strategic Plan 2026-2030 centers on *"Infrastructure for Innovation,"* with Priority 1 focused on *Model Resources to Advance the Study of Human Diseases* as a core priority. This R21 Program directly implements this priority by supporting innovative exploratory or developmental projects to develop, characterize, improve, or preserve research models, new approach methodologies (NAMs), and related biological materials for research relevant to human health and diseases.

ORIP has issued a series of Notices of Funding Opportunity (NOFOs) for this program, including PA-16-141 (2016-2019), PAR-19-369 (2019-2021), and PAR-21-167 (2021-2024). Since 2016, ORIP has funded 102 two-year projects from over 450 submissions under the auspice of these three NOFOs; 35 projects under PA-16-141, 19 under PAR-19-369, and 48 under PAR-21-167. These projects support a broad range of research models, including worms, flies, fish, frogs, mice, and rats, with approximately 50% of projects supporting or engaging rodents followed by approximately 8% involving flies and 8% involving zebrafish. The projects are for a broad range of resource initiatives, including disease models, novel technologies, gene editing, synthetic biology, phenotyping, informatics, microbiome, cryopreservation, and tissue-on-a-chip.

Genome engineering for model development is the largest cross-cutting theme for these projects, followed by disease modeling (i.e., mitochondrial diseases, diabetes, and neurological diseases), imaging tools and technologies, and regeneration. These resources make *in vivo* studies more precise, rigorous, reproducible, scalable, and accessible. Substantial scientific output has been reported. From 2017 to 2026, the majority of projects (about 75%) resulted in one or more publications, reaching approximately 290 publications. These publications have been widely cited around 5,725 times in total. Nine granted US patents cited three of these publications. The R21 projects broadly disseminate models and technologies for many biomedical research areas.

The R21 projects have not only addressed major gaps in particular research areas, but also produced broadly useful research resources, genome editing tools, genetic lines, reporters, imaging systems, atlases, and high-throughput methods that laid the foundation for development and preservation of large-scale resources. For example, ORIP supported the development of transgenic methods for stable genetic modification of sea urchin embryos; resources for illuminating apical extracellular matrix structure and biogenesis in worms; tools and resources for making genetic modifications and marking clones on the fly 4th chromosome at single cell levels; cryopreservation of fly strains; high-throughput microinjection for fly embryos; low temperature adapted CRISPR-Cas gene editing tools for disease modeling in *Xenopus*; tools to generate models of mitochondrial diseases in zebrafish and mouse; humanized mouse models to study CAR-T therapy; and organoids for studying T cell development and HIV/SIV infection.

The developments supported by the R21 program improved rigor and reproducibility of research models for a broad range of biomedical research, including research on infectious diseases, immune disorders, cancer, cardiovascular diseases, and neurological syndromes. These projects have addressed long-standing technical barriers such as transgenesis in sea urchins and cryopreservation of fly strains. They also led to investigators securing funding for R01 research projects and for generating large-scale resources for transgenic sea urchins, zebrafish models of mitochondrial diseases, and the *Drosophila* 4th chromosome. Some even led to the founding of small businesses, such as Objective Biotechnology, Inc. which is focused on automated microinjection systems based on their R21 research on high-throughput injection for fly embryos.

The purpose of the current R21 NOFO, PAR-25-273, which expires in 2028, is to support developing, improving, characterizing, or preserving models and related biological materials and technologies as well as expand support of NAMs, a current NIH research priority, for studies relevant to human health and disease. To maintain ORIP's NIH-wide role, proposed R21 projects must have broad applicability to multiple NIH ICs and explore multiple body systems or multiple categories of diseases affecting multiple body systems.

Based on continued demand for predictive, accessible, and reproducible models and NAMs; documented productivity; and strong alignment with the ORIP Strategic Plan 2026-2030, ORIP seeks approval from the Council of Councils to reissue PAR-25-273 in FY2028 and continue support for the *"Development of Models, New Approach Methodologies, and Biological Materials for Studying Human Health and Diseases (Clinical Trial Not Allowed)"* R21 program.