

Diversity Outbred Pilot Grant Program – Understanding the Impacts of Genetic Diversity on Experimental Outcomes

Purpose: The purpose of the Diversity Outbred Pilot Grant Program is to explore new uses for genetic diversity in biomedical research. This program aims to enable a greater understanding of the impact of genetic diversity on experimental outcomes and to assess its contribution to phenotypic variability across a range of research areas.

Background: Research studies are typically designed with the intention of reducing the number of experimental variables to better understand specific biological processes. While this can be helpful in early-stage research, reducing variability at later stages may negatively impact translatability. This is particularly relevant to mouse biomedical research as inbred mice are genetically homogeneous populations. Although inbred mice can enable researchers to isolate and interrogate defined experimental variables, they are unable to recapitulate the genetic diversity observed across human populations. Testing in a single inbred mouse strain is thus genetically akin to testing in a single person, and this can lead to numerous challenges when attempting to translate experimental findings to humans.

In the past, it has been challenging to address the impact of genetic diversity on experimental outcomes due to difficulties recapitulating the breadth of human genetic variation. However, recently developed resources such as the Diversity Outbred (DO) mouse stock have improved upon these models and increased the accessibility of genetically diverse platforms. DO mice are a highly diverse population derived from the intercrossing of 8 inbred founder strains with distinct characteristics (5 common laboratory strains and 3 wild-derived strains). These founders represent ~90% of the genetic diversity observed in the *Mus musculus* species, resulting in an estimated >50 million genetic variants across the DO population. This level of genetic diversity is well above that of traditional models, and enables researchers to assess whether findings observed in early-stage studies can be reproduced in more diverse genetic backgrounds.

To better understand genetic diversity and its role in translatability, The Jackson Laboratory is launching the Diversity Outbred Pilot Grant Program. The Jackson Laboratory's mission is to discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health. Through the Pilot Grant Program, we aim to identify novel solutions to more accurately model human biology in experimental systems.

Program Goal: The goal of the Diversity Outbred Pilot Grant Program is to support projects that leverage genetic diversity to improve the translational impact of mouse studies in biomedical research. Genetically diverse mice have been used for a wide range of applications in oncology, immunology, neurobiology, infectious disease, and others. With the Pilot Grant Program, our intention is to expand upon this work, and provide a basis for further research into the dynamics of genetic diversity and phenotypic variability.

Areas of Research Interest: The Diversity Outbred Pilot Grant Program is open to investigators across all biomedical research areas including, but not limited to: oncology, immunology, neurobiology, infectious disease, metabolism, cardiology, pulmonology, gastroenterology, and hematology.

Funding is intended to support research that incorporates DO mice into standard experimental workflows, such as including DO mice in an existing study as a discrete study arm. See "Experimental

Guidance” for details. The Pilot Grant Program is not meant for quantitative trait loci (QTL) mapping studies, but may be used to generate preliminary data for future work in this area.

Award Information: The Diversity Outbred Pilot Grant Program will provide awards in one of two forms:

- JDO1: The Jackson Laboratory will provide up to \$10,000 USD in direct research funds and up to 50 DO mice
- JDO2: The Jackson Laboratory will provide up to 50 DO mice

Applicants are requested to submit a single proposal, and applications will be evaluated and tiered based on the criteria outlined in the Review Criteria section.

For proposals requesting >50 mice, a supplement is requested to justify the need for this number of mice.

The Pilot Grant Program is not intended to support indirect costs such as overhead, salaries, major equipment, travel, or publication submission fees.

Eligibility: Applicants must be affiliated with an academic, government, or other nonprofit institution in North America to be eligible for award.

Application Components: Applicants must submit the following separate components compiled into a single PDF in the indicated order:

- **Project Title (200 characters maximum including spaces)**
- **Project Summary (750 word maximum)** – including specific study goals / objectives, project background and significance, existing knowledge in the field, rationale for the use of genetically diverse mice, and relevance of project to human health
- **Research Plan (1,000 words maximum; if figures or tables are added, the total may not exceed 2 pages)** – including experimental design, project timeline, description of methods, expected outcomes, potential difficulties / limitations, preliminary data (as applicable)
- **References (2 page maximum)** – no specific citation format required
- **Budget and Justification (1 page maximum)** – including project budget and justification for the requested funds in US dollars
- **Biosketch (5 page maximum)** – NIH-style Biosketch including position / title, education and training, personal statement, scientific appointments and honors, publications relevant to the project
- **Supplement (1 page maximum)** – justification for requesting more than 50 mice

Application formatting:

- Use 11-pt Arial font for the main text of each component (Use no less than 9-pt Arial font for text in figure legends or tables)
- Use 0.5-inch margins on all sides on standard US letter-sized pages (8.5 X 11 inches)
- Include a heading for each component (e.g., "Project Summary")
- Figure panels should be reasonably sized, and not exceed page maximums
- Figure and legend text will not be counted as part of word maximums, but applicants are encouraged to be concise
- Page numbers are not necessary but are allowed
- Final document must be submitted as a PDF

Key Dates:

- Applications Open – 10/03/2022
- Application Due Date – 12/02/2022, 11:59 PM ET
- Award Announcements – 01/20/2023

Terms and Conditions: All recipients will be required to publish a research product of their project results within 18 months of award receipt. Acceptable research products include:

- Publication in a preprint or peer-reviewed scientific journal
- Presentation of data at a public conference in poster or talk format

Awardees will also be required to submit a brief project summary to The Jackson Laboratory upon project completion that includes a concise overview of project outcomes.

Applicants who are offered an award will be provided a Research Grant Agreement. The current Agreement can be found at <https://www.jax.org/-/media/jaxweb/files/jax-mice-and-services/grant-agreement-terms.pdf>.

Awards will be issued to an Applicant's Institution provided all contingencies are met. The Institution's financial officer and external grants management representatives will be responsible for receiving and disbursing research funds under the terms of the approved award.

Review Criteria: All proposals will be evaluated in three key areas:

- **Significance** – What is the anticipated impact of the proposed project on human health and disease? Does the study meaningfully build on existing knowledge in the field? Does the project adequately address needs related to genetic diversity in a given research area? How will the use of Diversity Outbred mice effect future research in this area?
- **Approach** – Is the use of Diversity Outbred mice appropriate for answering the proposed research question? Are the hypotheses and study aim(s) well-defined with appropriate experimental groups and controls? Will the methods allow for an adequate interpretation of results? How does the proposed study align with an investigator's broader research project?
- **Feasibility** – Is the experimental design suitable to accomplish the specified goals / objectives of the project? Does the investigator possess the necessary expertise and equipment required to execute the proposed experiments? Does the investigator have sufficient capabilities to house and perform experiments with Diversity Outbred mice? Can the results be reasonably published as part of a larger project within the 18 month time frame? Is the budget appropriate for the proposed experiments?

Experimental Guidance: The intent of the Diversity Outbred Pilot Grant Program is to fund projects that explore new uses for genetically diverse mice as a means to better understand the impact of genetic diversity on experimental outcomes. The ideal project will investigate the results of DO mice in comparison to standard inbred lab strains, primary human cells / tissues, human cell lines, or other common biomedical research models. As DO mice exhibit increased phenotypic diversity compared to standard inbred strains, The Jackson Laboratory recommends that experiments include separate control and experimental arms (or baseline and post-treatment groups), and sample sizes of at least two times

the number of mice that would be planned for inbred mice. For example, if an experiment using C57BL/6J mice would typically include n=10 control mice and n=10 experimental mice, it is recommended that an experiment using DO mice include n≥20 control mice and n≥20 experimental mice. Sample sizes may also be informed by the baseline variability of outcomes observed in inbred mice. Two example studies are provided below:

Pal A, Al-Shaer AE, Guesdon W, et al. Resolvin E1 derived from eicosapentaenoic acid prevents hyperinsulinemia and hyperglycemia in a host genetic manner. *FASEB J.* 2020;34(8).

- **Overview:** Researchers assessed the impact of the RvE1 metabolite of Eicosapentaenoic acid (EPA) on hyperinsulinemia and hyperglycemia. RvE1 consistently reversed hyperinsulinemia and hyperglycemia in C57BL/6J, but resulted in a range of responses in DO mice.
- **Impact:** This study used a DO study arm to show that genetic diversity may impact physiological responses to EPA metabolites, and that work in standard inbred mice may obscure the spectrum of responses to RvE1 seen in human populations.

Moshkani S, Chiale C, Lang SM, Rose JK, Robek MD. A Highly Attenuated Vesicular Stomatitis Virus-Based Vaccine Platform Controls Hepatitis B Virus Replication in Mouse Models of Hepatitis B. *J Virol.* 2018;93(5).

- **Overview:** The immunogenicity of an experimental HBV vaccine was evaluated in multiple mouse models. The successful elicitation of immune responses by the HBV construct was reproducible in DO mice.
- **Impact:** This study used a DO study arm to demonstrate the translatability of immune responses to their experimental vaccine across a genetically diverse population.

Questions about the Diversity Outbred Pilot Grant Program? If you have questions or need assistance, please contact us via email at micetech@jax.org or by phone at 1.800.422.6423 (US).