U.S. Department of Health and Human Services
National Institutes of Health
Division of Program Coordination, Planning, and Strategic Initiatives
Office of Research Infrastructure Programs
Division of Comparative Medicine

Validation of Animal Models and Tools for Biomedical Research
Session III. Validation of Mouse Models for Preclinical Research

Tuesday, December 1, 2020
Virtual Meeting

Workshop Report

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Executive Summary

The third of 10 sessions of the Virtual Workshop on Validation of Animal Models and Tools for Biomedical Research was held on December 1, 2020. This workshop is intended as a venue to discuss the status of and needs for the validation of animal models used in biomedical research. Session III focused on the validation of mouse models and tools for preclinical research. Dr. Cathleen Lutz, Co-Chair, encouraged the participants to evaluate current strengths and areas for improvement in mouse models, noting that the validation of mouse models will require consideration of overarching questions surrounding clinical and translational research. Mice offer numerous benefits (e.g., size, cost, genetic similarity with humans) but present significant challenges (e.g., rigor and reproducibility, modeling for complex diseases, incorporation of genetic diversity) for investigators. Topics of discussion included gut microbiota, personalized medicine, humanized mice, and drug discovery platforms. The participants suggested approaches to (1) improve reproducibility (e.g., consideration of microbiota, environmental controls, genetic interactions, and genetic diversity), (2) understand innate physiological processes (e.g., molecular factors in disease progression), and (3) enhance translatability for complex diseases (e.g., candidate gene identifications across multiple species).

Session Co-Chairs
Cathleen Lutz, Ph.D., The Jackson Laboratory
Douglas Wallace, Ph.D., Children's Hospital of Philadelphia

Presenters
Kenneth Chien, M.D., Ph.D., Karolinska Institutet, Sweden
Craig Franklin, D.V.M., Ph.D., University of Missouri
Leonard Guarente, Ph.D., Massachusetts Institute of Technology
Catherine Kaczorowski, Ph.D., The Jackson Laboratory
Leonard Shultz, Ph.D., The Jackson Laboratory

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Workshop Report

Opening Remarks
Franziska B. Grieder, D.V.M., Ph.D., Director, ORIP
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

Drs. Franziska B. Grieder, Director, ORIP, and Sige Zou, Coordinator, Program Official, ORIP, welcomed the participants and expressed appreciation to the Organizing Committee and Session Chairs for their efforts in organizing the event. They explained that the meeting is the third in a series of 10 sessions. Drs. Grieder and Zou also acknowledged the support of several National Institutes of Health (NIH) Institutes: the National Heart, Lung, and Blood Institute (NHLBI); National Institute on Aging (NIA); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institute of General Medical Sciences (NIGMS); and National Institute of Neurological Disorders and Stroke (NINDS). Dr. Grieder reminded the participants that validation of animal models and tools is a critical part of ORIP's trans-NIH efforts. She expressed appreciation for the participants' input.

Validation of Mouse Models for Preclinical Research
Cathleen Lutz, Ph.D., The Jackson Laboratory

Dr. Cathleen Lutz presented an overview of the validation of mouse models for preclinical research, encouraging the participants to evaluate current strengths and areas for improvement in the field. She stated that the validation of mouse models will require consideration of overarching questions about clinical and translational research. Dr. Lutz shared a historical overview on the origin of modern laboratory mice. In the 1890s, Abbie Lathrop, a retired schoolteacher from Granby, Massachusetts, created the colony that now is the source of many present-day laboratory mouse strains. Ms. Lathrop began providing her mice to Harvard University researchers in 1902; the researchers performed breeding schemes to maintain specific phenotypes through generations of mating. Mice offer many benefits for research, including (1) similarity to the biology and genetics of humans; (2) small size, low cost, and convenient housing and maintenance; (3) a genome that is easy to manipulate; (4) resources and reagents available to ensure reproducibility in laboratories around the world; and (5) a strong track record of models for face, construct, and predictive validity for many monogenic diseases. Challenges in model validation include ensuring rigor and reproducibility, preserving physiology, modeling for complex diseases, considering environment, allowing appropriate time and funding for all studies (i.e., for studies of diseases of aging), and incorporating genetic diversity. Dr. Lutz also noted that studies of host genetics in mice might hold crucial clues in understanding the basis of COVID-19 immune responses. Last, she encouraged the participants to consider that mouse models are as complex as human patients and are affected by such factors as viruses, the microbiome, age, and the environment.

Gut Microbiota: Variability and Translatability in Rodent Models
Craig Franklin, D.V.M., Ph.D., University of Missouri

Dr. Craig Franklin spoke on the connection between gut microbiota and validation of rodent models. Reproducibility poses a major challenge for researchers. He explained that microbiota—the ecological community of commensal, symbiotic, and pathogenic microorganisms—likely play a role in the causes of many reproducibility challenges. Most microbiota reside in the gut and can outnumber host cells by a factor of 10. Dr. Franklin's group is assessing the underlying causes of gut microbiota variation and effects on model phenotypes. His group determined that variation exists between mice from different production sources. Additionally, the institutional environment appears to play a role in variation. This variation significantly alters mouse phenotypes and thus represents a possible factor in reproducibility. These effects differ among mouse models. Dr. Franklin presented a flowchart to model the influence of

gut microbiota on model phenotype; outcomes of the chart include reconstitution with target gut microbiota, reconstitution with multiple gut microbiota, and supplementation of phenotype with target species. He noted that feces banking will be crucial in understanding issues in gut microbiota. Translatable approaches include germ-free environments, mono-colonized mice, defined flora, humanized gut microbiota, and complex microbiota (e.g., barrier/specific pathogen–free, conventional, wild or pet store). Research in this area suggests that the gut microbiota of mice can be translated to mimic human immune traits. Pet store and wild mice hold promise for translation. This information can be applied for the improvement of mouse models. Options for optimization include (1) maintenance of pets or wild mice in containment facilities, (2) use of wild mouse microbiota, (3) controlled exposure to targeted pathogens, and (4) combination with humanized gut microbiota. Dr. Franklin also noted that a better understanding of gut microbiota can provide insights relevant to precision medicine. He urged researchers to (1) assess gut microbiota as a factor in their studies, (2) monitor colony gut microbiota over time, and (3) consider antigen-experienced models.

Reproducible Animal Models for Complex Human Disease: Implications for Personalized Medicine
Catherine Kaczorowski, Ph.D., The Jackson Laboratory

Dr. Catherine Kaczorowski discussed the application of animal models in personalized medicine. Her former graduate student, Dr. Sarah Neuner, created a model for late-onset Alzheimer's disease in mice because traditional models are not well validated for human disease. Goals for the project included (1) initial characterization of cognitive and pathological variation and (2) validation of the resource as a model for the disease. She explained that neurodegenerative disease models have become less robust over time; the reasons for this are poorly understood. Aging is a leading risk factor that contributes to many diseases, and genetic makeup plays an important role in determining susceptibility to dementia. Identification of specific genes will be critical for understanding and developing treatments for the disease. Age at onset varies broadly and likely reflects genetic protective and risk factors. Dr. Neuner developed a preclinical model with autosomal dominant mutations to better reflect the diversity of human patients. She combined two well-established resources—transgenic mice and a genetic reference panel with a recombinant inbred strain—to detect genetic regulatory pathways involved in the complex variation observed. Dr. Neuner then developed a panel of "high-risk" carriers and non-transgenic age-matched littermates. Detailed phenotyping assessments were performed at 6 and 14 months of age. The mice next were assessed for working memory performance every 2 months. Different strains show variability in age at onset of working memory deficits, capturing the individual variation among humans. Short- and long-term memory also were assessed during this time period. Some strains are more susceptible than others to the mutation of interest. Additionally, a wide range of amyloid levels in the brain were observed. Dr. Kaczorowski explained that these innate processes should be considered for model validation. Dr. Neuner also assessed the validity of experimental cognition tests, demonstrating the effect of the *APOE* gene on cognitive outcomes. She developed a polygenetic genetic risk score to assess sensitivity to variation in risk loci; risk and protective factors were associated with cognitive traits. Dr. Kaczorowski's group also has demonstrated the complex effects of diet and genetic interactions. She concluded by emphasizing the importance of naturally occurring mouse genetic variability and relevant environmental exposures to enhance translational relevance of preclinical findings. The reproducible nature of the model can facilitate future studies regarding specific gene candidates.

Next-Generation Humanized Mice in Biomedical Research
Leonard Shultz, Ph.D., The Jackson Laboratory

Dr. Leonard Shultz spoke on findings in humanized mice models for diseases. He explained that humanized mice are immunodeficient animals engrafted with human immune cells or tissues and can support clinically relevant *in vivo* studies of human hematopoietic and immune systems without putting patients at risk. The need for humanized mice initially was driven by HIV research. These models now

are used across numerous research areas (e.g., hematology, immunology, cancer, regenerative medicine, diabetes). Dr. Shultz presented a list of major humanized mouse strain platforms. Engraftment can be performed via injection in adult or newborn mice; specific techniques are dependent on the question of interest. Limitations of humanized mouse models include the challenges of engraftment with different cell populations, complications of remaining innate immunity, and suboptimal lymphoid architecture and immune function. Dr. Shultz's group is developing emerging models using genomic editing to address these limitations. The models are validated for germline transmission and can be used to target genes. Engraftment can be performed to model a severe cytokine storm in response to immunotherapeutics. Injection of human peripheral blood mononuclear cells can be performed in NSG-MHC Class I/II knockout mice for increased survival. Engraftment of NSG mice with human hematopoietic stem cells can be used to develop all hematopoietic stem cell lineages; limitations in certain lineages can be addressed with transgenic expression of human leukocyte antigen molecules and human hematopoietic growth factors. Many human infectious agents, including SARS-CoV-2, can be studied in humanized mice. Additionally, humanized mouse models can be used for regenerative medicine studies for such diseases as diabetes, muscular dystrophy, amyotrophic lateral sclerosis and Alzheimer's disease. Many different types of human cancers engraft in humanized mice, supporting studies of tumor immunotherapy.

Humanized Mouse Models for Cardiovascular Regenerative Therapeutics
Kenneth Chien, M.D., Ph.D., Karolinska Institutet, Sweden

Dr. Kenneth Chien discussed the use of humanized mouse models for next-generation cardiovascular regenerative therapeutics. His group created a genetically modified vascular endothelial growth factor (VEGF) pathway that can escape innate immunity *in vivo* and *in vitro*, inducing a regenerative response. The RNA can be used across species, creating new capabilities for validation. Dr. Chien predicted that mouse models will play a major role in RNA-based therapies in the future. The model has been extended to larger animals (e.g., pigs). Solid validation data are needed for the application of models across species. Dr. Chien's group reported that intradermal administration of VEGF-A modified RNA gives rise to dose-dependent VEGF-A protein production. The injection acutely restored baseline skin blood flow in patients with type 2 diabetes. An ongoing Phase 2 study is being pursued to apply this approach to coronary artery bypass graft tissues. Dr. Chien's group now is applying this approach to enrich human ventricular progenitor (HVP) cells. HVP cells are critical to this research because they are lost in heart failure. The group reported self-assembly of HVP cells into a functional epicardial muscle patch. The cells can be purified, stored, and used as needed. In larger animals, however, the engraftment leads to increased wall thickening and ejection fraction. Next steps for translation to humans include (1) immunosuppressive regimes established in minipigs (e.g., tolerization to product using mRNA), (2) HVP cells injected in heart post-myocardiac infraction in immunocompromised minipigs and rodents, (3) interactions with health authorities, and (4) options for cell manufacturing.

Development of a Drug Discovery Platform for Dysferlinopathy-based Muscular Dystrophies
Leonard Guarente, Ph.D., Massachusetts Institute of Technology

Dr. Leonard Guarente discussed dysferlinopathy—*DYSF*-based muscular dystrophies—in the context of drug discovery. Mutations in the *DYSF* gene lead to recessive muscular dystrophies characterized by weakness and atrophy of pelvic and shoulder girdle muscles. Symptoms appear in adulthood, and progression is age-dependent. Currently, no treatment is available. DYSF plays a role in calcium-mediated repair of damaged skeletal muscle fibers, promoting membrane fusion at damaged sites. Many patients with the disease produce an unstable version of DYSF that degrades or aggregates and thus fails to localize to the plasma membrane. Dr. Guarente's goals are to develop (1) an assay to identify patient missense *DYSF* mutants that demonstrate protein stability or mislocalization and (2) a screening platform to identify compounds that can restore DYSF function. They used a cell-based assay to determine expression localization of patient DYSF protein variants. His group has screened 115

missense mutants; about 50 percent showed no localization—results that were confirmed by immunostaining. They also found that about 50 percent of the mutations were rescued by a chemical chaperone. They applied the system to a mouse model—performing a chaperone treatment, as well as a histological analysis in skeletal muscle tissue—to determine the efficacy of the treatment to prevent the onset of muscular dystrophy. Results show that DYSF is expressed following treatment. Next, they performed a wound-healing assay in isolated muscle fibers to demonstrate DYSF function. Dr. Guarente noted that the treatment also might be applied to repair muscle damage associated with normal aging.

Group Discussion
Cathleen Lutz, Ph.D., The Jackson Laboratory
Douglas Wallace, Ph.D., Children's Hospital of Philadelphia

Drs. Lutz and Douglas Wallace, Co-Chairs, reviewed comments submitted through the Zoom chat and encouraged participants to contribute additional comments for discussion. Dr. Lutz asked the participants to consider novel technologies that can bring the findings from mouse models into clinical and translational settings. She noted that important topics for further discussion include humanized mice, the microbiome, and physiological factors. Dr. Wallace emphasized the importance of model validation for reproducibility across experiments and laboratories.

Dr. Larry Carbone asked Dr. Franklin whether researchers should report gut microbiota data for studies not related directly to the microbiome. Dr. Franklin voiced his support for the practice but stated that technology for standardization requires further development. Many methodologies are used for metagenomic analyses. Dr. Franklin added that databases for metagenomic data might help provide initial support for this effort. In response to a follow-up question from Dr. Lutz, Dr. Franklin stated that rodent diets are controlled in experiments. He also noted that dietary effects of rat chow on microbiota are minimal.

In response to a question from Dr. Keith Cheng about cognitive neurological phenotypes, Dr. Kaczorowski explained that her group characterized hyperphosphorylated tau protein, which is indicative of early-stage neurofibrillary tangle development. They also developed brain-wide maps of cellular load, which is correlated with cognitive outcomes in later stages. In response to a follow-up question from Dr. Lutz, Dr. Kaczorowski said she is working to identify early-driver genes. Additionally, networks related to cognitive decline contain robust signatures early in progression. Further studies of potential gene variants across both mice and humans must be explored.

Dr. Wallace asked whether a nicotinamide nucleotide transhydrogenase mutation of mice strains might affect the phenotype expression. Dr. Grant MacGregor agreed that the mutation might be a factor; a screening panel would help resolve this question. He suggested using diversity-outbred models. Dr. Kaczorowski added that titration of genetic complexity is crucial.

Dr. Lutz stated that many methods for controlling genetic diversity can be explored. Dr. Cory Brayton noted that many mouse strains are not as genetically "clean" as was previously thought and arise from different backgrounds. Additionally, Dr. David Beier expressed concern that knowledge related to the genetic properties of models is not widely accessible within the research community; he suggested facilitating communication among investigators.

Dr. Lutz noted that many environmental factors (e.g., activity, enrichment) are likely to affect the validation of mouse models. She asked the participants to comment on the future of mouse research. Dr. Franklin commented that microbiota manipulation would provide new data but might create biosecurity concerns. Other procedures (e.g., vaccination) also might address issues of reproducibility.

In response to a question from Dr. Lutz about divergence of the immune system in laboratory mice, Dr. Shultz commented that some investigators employ antibiotic therapies to minimize their immune response. He suggested a standard approach with an antibiotic cocktail to create common microflora across laboratories. A participant noted that variation in laboratory environments also can play a role in the immunological maturity of laboratory mice.

Dr. Shultz also commented that many researchers are working to understand the variability between cytokine storms. Dr. Lutz asked whether the responses could be predictive. Dr. Shultz stated that experiments in this area are ongoing; access to hematopoietic progenitor cells would be ideal. Further technological development, however, is needed in this area.

Dr. Wallace noted that many investigators are interested in the connection between the microbiome and longevity. Dr. Franklin stated that fecal transplants would be helpful in providing insight on this topic. Dr. Wallace noted that the microbiome often readjusts to the host genotype after fecal transplantation. Dr. Franklin agreed and noted that the early periods of development are critical for microbiota properties; genetic influences also are important.

Dr. Cheng asked about the histological characteristics of the *DYSF* dystrophy and rescued animals. He stated that a coordinated system is necessary to compare histological data among models.

Additional Comments

In the Zoom chat, Dr. Cheng asked Dr. Franklin whether diet (1) was controlled in experimental conditions and (2) could influence the animals' microbiota. Dr. Jessica Bolker wondered whether microbiota stability is related to consistency in diet throughout the life cycle. Dr. Marco Brotto wondered whether the effect of regular exercise should be explored in mouse studies.

Dr. Cheng also noted that papillomavirus is modeled in mouse. Dr. Brayton stated that conditional mutants also include transgenic backgrounds, and mice in many programs might not be as immunologically or microbially stable as those from reputable vendors. Dr. MacGregor stated that the issue of reproducibility represents an area for continuing conversation.

Summary and Suggestions

Mouse models offer numerous benefits for biomedical research but present significant challenges for investigators. The participants discussed and provided the following areas that require new or continued support from ORIP and the NIH:

- Consistency in sourcing and reporting of inbred mouse strains
- Monitoring of genetic drift in inbred strains via nuclear and mitochondrial genomic sequencing
- Confirmation that the mouse genetic and metabolic systems for a trait of interest are shared between mice and humans
- Consideration of whether the experimental environment approximates that of the human trait of interest (e.g., maturity of the immune system)
- Use of humanized mice in areas where the laboratory mouse is divergent from the human condition (e.g., the immune system, amyloid beta precursor protein sequence, viral infection) to better approximate the human condition

- Storage of mouse fecal pellets for gut microbiome analysis to assess the influence of the gut microbiome on experimental differences
- Confirmation that models for diseases of aging are relevant to the human condition

Appendix A: Meeting Agenda

Session III. Validation of Mouse Models for Preclinical Research
2:00–4:00 p.m. EST
December 1, 2020

Chairs
Cathleen Lutz, Ph.D., The Jackson Laboratory
Douglas Wallace, Ph.D., Children's Hospital of Philadelphia

2:00–2:05 p.m. **Opening Remarks**

Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP)
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

2:05–3:30 p.m. **Presentations**

Cathleen Lutz, Ph.D., The Jackson Laboratory
Validation of Mouse Models for Preclinical Research

Craig Franklin, D.V.M., Ph.D., University of Missouri
Gut Microbiota: Variability and Translatability in Rodent Models

Catherine Kaczorowski, Ph.D., The Jackson Laboratory
Reproducible Animal Models for Complex Human Disease: Implications for Personalized Medicine

Leonard Shultz, Ph.D., The Jackson Laboratory
Next-Generation Humanized Mice in Biomedical Research

Kenneth Chien, M.D., Ph.D., Karolinska Institutet, Sweden
Humanized Mouse Models for Cardiovascular Regenerative Therapeutics

Leonard Guarente, Ph.D., Massachusetts Institute of Technology
Development of a Drug Discovery Platform for Dysferlinopathy-based Muscular Dystrophies

3:30–4:00 p.m. **Group Discussion**

Appendix B: Discussants List

Session III. Validation of Mouse Models for Preclinical Research
2:00–4:00 p.m. EST
December 1, 2020

Kristine Abraham, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases
Lola Ajayi, Office of Research Infrastructure Programs (ORIP)
Douglas Albrecht, Ph.D., Jain Foundation
Alan Attie, Ph.D., University of California, San Diego
David Beier, M.D., Ph.D., Seattle Children's Hospital
Hugo Bellen, Ph.D., Baylor College of Medicine
Sonja Best, Ph.D., National Institute of Allergy and Infectious Diseases
Jessica Bolker, Ph.D., University of New Hampshire
Thea Brabb, D.V.M., Ph.D., University of Washington
Cory Brayton, D.V.M., Johns Hopkins University
Michael Brehm, Ph.D., University of Massachusetts Medical School
Marco Brotto, Ph.D., The University of Texas at Arlington
Elizabeth Bryda, Ph.D., University of Missouri
Rebecca Burdine, Ph.D., Princeton University
Robert Burgess, Ph.D., The Jackson Laboratory
Larry Carbone, D.V.M., Ph.D., University of California, San Francisco
Michael Chang, Ph.D., ORIP
Marc Charette, Ph.D., National Heart, Lung, and Blood Institute (NHLBI)
Keith Cheng, M.D., Ph.D., Pennsylvania State University
Kenneth Chien, M.D., Ph.D., Karolinska Institutet
Miguel Contreras, Ph.D., ORIP
Mary Dickinson, Ph.D., Baylor College of Medicine
Stefania Forner, Ph.D., University of California, Irvine
Craig Franklin, D.V.M., University of Missouri
Franziska B. Grieder, D.V.M., Ph.D., ORIP
Amelie Gubitz, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)
Joseph Hacia, Ph.D., University of Southern California
Catherine Kaczorowski, Ph.D., The Jackson Laboratory
Shimako Kawauchi, Ph.D., University of California, Irvine
Michael Koob, Ph.D., University of Minnesota
Neil Lipman, V.M.D., Memorial Sloan Kettering Cancer Center
Lisa Schwartz Longacre, Ph.D., NHLBI
Cathleen Lutz, Ph.D., The Jackson Laboratory
Grant MacGregor, Ph.D., University of California, Irvine
Stephanie Murphy, V.M.D., Ph.D., ORIP
Kelly Pate, D.V.M., Ph.D., Johns Hopkins Medicine
John Postlethwait, Ph.D., University of Oregon
Rebecca Roof, Ph.D., NINDS
Susan Sanchez, Ph.D., The University of Georgia
Leonard Shultz, Ph.D., The Jackson Laboratory
Mark Suckow, D.V.M., University of Kentucky
Alton Swennes, D.V.M., Baylor College of Medicine
Betty Theriault, D.V.M., The University of Chicago
Christopher Tuggle, Ph.D., Iowa State University

Douglas Wallace, Ph.D., Children's Hospital of Philadelphia
Jill Weimer, Ph.D., Sanford Research
Michael Yeager, Ph.D., University of Colorado Denver
Xiaoli Zhao, Ph.D., National Institute of General Medical Sciences
Sige Zou, Ph.D., ORIP