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 VIII. Technologies, Phenotyping, and Data Science for Animal Models

Tuesday, January 5, 2021
Virtual Meeting

Workshop Report

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Executive Summary

The eighth of 10 sessions of the Virtual Workshop on Validation of Animal Models and Tools for Biomedical Research was held on January 5, 2021. This workshop is intended as a venue to discuss the status and needs regarding the validation of animal models and tools used in biomedical research. Session VIII focused on technologies, phenotyping, and data science for animal models. Topics of discussion included cellular and tissue phenomics as a framework for unifying -omics at multiple length scales, multiplex and intravital imaging, real-time genotyping and phenotyping in live embryos, clinician and patient roles in validation, machine learning (ML) for data integration, and genome illumination using protein trap mutagenesis. Dr. Keith Cheng, Co-Chair, noted that the history of scientific research has demonstrated repeatedly that advances in science result from new technologies and new ways of thinking applied to old problems. He also noted a recurring validation theme across sessions: the critical role of comparisons and integrations between different data types. Advances in technology have made researchers ask how they can make massive, complex, and multiscale imaging and -omics data more usable for researchers in a way that facilitates cross-referencing and interdisciplinary collaboration. Biology and medicine, including diagnostic sciences, focus largely on phenotype. Dr. Cheng suggested a cell- and tissue-centric "Geometry of Life" approach that mathematically and statistically represents all cell types, cellular arrangements, and phenotypic diversity. Histological studies of zebrafish mutants have demonstrated that pleiotropy frequently is associated with single-gene mutations. Clinical data demonstrate that phenotypes vary with different mutations in the same gene, while the study of cancer and Mendelian diseases has shown that mutations in multiple genes can lead to the same phenotype. Sets of phenotypes are associated with specific molecular pathways, whose patterns will differ among organisms, genetic backgrounds, and environmental factors. Thus, gene-oriented analysis alone is insufficient for integration and cross-validation. As big data within biology has grown exponentially in volume, velocity, and variety of data collected, a facile and predictive understanding of these complex data sets is urgently needed. In discussion, participants emphasized the need for interdisciplinary coordination and knowledge-sharing, and observers noted that the tissue pathology of models must be checked against that found in the corresponding human disease. Validation thus requires mechanisms for data archiving, associated with facile recall and comparison—a foundation for transparency and reproducibility. The participants agreed that validation and a better understanding of disease and gene function would require more comprehensive phenotypic analysis, accomplished by the use of multiple technologies in multiple organisms and across atomic to organismal length scales, including that of humans.

Session Co-Chairs
Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Stephen Ekker, Ph.D., Mayo Clinic

Presenters
Scott Fraser, Ph.D., University of Southern California
Vasant Honavar, Ph.D., The Pennsylvania State University
Lisa Schimmenti, M.D., Mayo Clinic
Bo Zhang, Ph.D., Peking University

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Workshop Report

Opening Remarks
Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine, ORIP
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

Drs. Stephanie Murphy, Director, Division of Comparative Medicine (DCM), ORIP, and Sige Zou, Coordinator, Program Official, ORIP, welcomed the participants and offered thanks to the Organizing Committee and Session Co-Chairs for their efforts in organizing the event. Dr. Murphy explained that the meeting is the eighth in a series of 10 sessions. Drs. Murphy 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. Murphy 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.

Pan-cellular, Computational, and Integrative Tissue Phenomics as a Framework for Cross-species, Multiscale Multi-omics
Keith Cheng, M.D., Ph.D., Penn State College of Medicine

Dr. Cheng began by reminding the participants that a revolution in the understanding of biology arose from light microscopy, yielding the cell theory (i.e., that all living things are made of cells [Schlieden and Schwann]), the realization that all cells come from other cells (i.e., *Omnis cellula e cellula* [Virchow]), and the understanding that all diseases can be characterized and understood from cellular changes in tissue—a foundation of modern medicine. He noted several principles that demonstrate how genes and molecules alone cannot yield a complete understanding of biology and disease: (1) sets of phenotypes that define clinical syndromes frequently are caused by single-gene deficiencies, (2) comprehensive histology-based tissue phenotyping in zebrafish has shown that single-gene deficiencies frequently cause multiple phenotypes across cell types and organ systems, (3) different mutations in single genes can cause different phenotypes, and (4) different gene deficiencies often cause the same phenotype. Genes and molecules alone, therefore, cannot provide—without cellular, tissue, and organismal context—a full understanding of biology or disease. These facts underscore the need for more fully developed phenomics. Genetic variation arguably is most relevant when it causes phenotype. Notably, clinical work is driven by phenotype. Virtually all human diseases—whether infectious, neoplastic, or degenerative—are associated with 3D micron-scale changes in cells and their arrangements in tissues. Histology, which provides tissue phenotype, serves as a relatively unbiased way to understand human disease. Histology's 2D, descriptive, and relatively subjective nature and the inability to provide volumetric tissue phenotypes, however, limit the capacity to connect tissue phenotype with genotype and molecular phenotypes. This challenge motivated an interdisciplinary team to develop X-ray histotomography—a 3D form of digital histology based on micro-computed tomography (micro-CT)—over a 20-year period. Like histology, all cell types can be studied without bias; unlike histology, however, volumetric measurements of the geometry of cells, tissues, and disease phenotypes can be derived and correlated computationally with genotype and molecular phenotype to address the issue of integration across scales and -omics.

Dr. Cheng described a "computational phenomics" based on histotomography in which cell shape, volume, texture, and relationships potentially can be measured, modeled, and used to provide spatial context for -omics data across transcripts, proteins, and metabolites. He emphasized that validation requires computational phenotyping across models, including that of humans. Automated phenotypic profiling integration across model systems—incorporating genetic, chemical, and disease phenotypes—will play a role in this effort. The first principles for tissue phenotyping will require capabilities for

cellular, whole-animal, 3D, opaque tissue, pan-cellular, and computational imaging across wide (i.e., >1 cm) fields of view at submicron voxel resolution—for example, kits for research and clinical communities to enable sample submission and cloud-based analysis and user access. With commitment, model system scientists can, within the next 5 years, create a reference atlas that is inclusive of all model systems, including humans, leading to increased understanding of disease, improved diagnostics and toxicology, and a cell-based anchor for multiscale multi-omics. Within 10 years, linkages between phenotypic signatures and molecular pathways can be made, and multiscale multi-omics can be placed in cell, tissue, and organismal contexts using big data tools and artificial intelligence (AI). Dr. Cheng summarized the key points of his presentation: (1) reference atlases are needed as digital "Rosetta Stones" for cross-referencing data across cell types in tissue and organismal contexts; (2) computational phenomics based on X-ray histotomography can be developed as a foundation for genetic, chemical, and disease phenomics of cells, tissues, and organisms; and (3) centralized, cloud-based access, high-throughput open-source data, and analytical tools must be made available through a user-friendly computational workflow system, such as Galaxy (usegalaxy.org), to enhance discovery and validation from model systems.

Multiplex and Intravital Imaging for Model Validation
Scott Fraser, Ph.D., University of Southern California

Dr. Scott Fraser discussed multiplex, multimodal, and intravital imaging for mechanistic characterization of human biology and disease. He highlighted the Bridge Institute, which was initiated to converge gaps across - the broad areas of research in tools and analyses. To illustrate a highly collaborative approach across institutions—consisting of a multidisciplinary team of biologists, chemists, engineers, physicians, computational scientists, and digital media artists—Dr. Fraser described the Pancreatic β-Cell Consortium (https://www.pbcconsortium.org), whose objective is the accelerated development of next-generation drug and cell therapies. He emphasized that treatments should be considered from all biological levels. Cells, the smallest units of life, are ideal to serve as the common ground in analyses of multiscale structure and function. X-ray tomographic images can serve as a foundation for 3D mapping of biological structures. Dr. Fraser also highlighted examples of fluorescence imaging for data visualization in organisms (e.g., tracking of endogenous metabolites by following autofluorescence over space and time). As new capabilities are developed, data integration (e.g., meta-modeling) has become increasingly crucial for a fuller understanding of biology. Data archiving—based on best practices for transparency and reproducibility (i.e., findable, accessible, interoperable, reusable)—must be emphasized to facilitate integration across the scientific community. Dr. Fraser concluded by highlighting the following needs: (1) mandated and funded imaging for validation, (2) mandated and funded meta-analyses and data storage archives, (3) requirements to link figures to full study details, (4) funding for public access to computational tools, and (5) imaging tool development.

Real-Time Genotyping and Phenotyping in Live Embryos for Disease Modeling and Validation
Bo Zhang, Ph.D., Peking University

Dr. Bo Zhang discussed real-time genotyping and phenotyping to couple disease modeling and validation in live zebrafish embryos. She explained that disease modeling requires generation and manipulation of mutant genotype, and validation requires characterization of phenotype at different levels (i.e., from molecular and cellular to organismal and morphological levels). Revealing genotype before morphologically visible phenotype is important because molecular events emerge before morphological events are detected. Dr. Zhang's group developed Bi-FoRe, a highly efficient and multipurpose knock-in strategy to enable coupling of molecular genotyping and cellular phenotyping. This approach employs CRISPR to mediate bidirectional targeted insertion of a dual-function plasmid donor, which enables the simultaneous generation and fluorescent labeling of floxed positive and negative allele pairs and further

enables reciprocal conditional manipulation of target gene function in response to Cre recombinase. Applications of the approach include (1) early molecular genotyping (i.e., *in vivo* real-time fluorescent genotyping of live embryos) to ensure genotype is revealed prior to and independent of the emergence of morphological phenotype or large-scale timely isolation of live embryos by genotype (e.g., for gene expression and regulation analysis, particularly at the single-cell level), (2) efficient genotype switch (i.e., conditional manipulation of knock-in alleles of whole embryos, or an entire tissue or organ, through the Cre/*loxP* system) to achieve conditional knockout effect from forward alleles or conditional rescue effect from reverse alleles in conjunction with switch of the corresponding fluorescent reporter, and (3) mosaic genotype switch (i.e., less efficient conditional manipulation and fluorescent switching of knock-in alleles) to generate mosaic embryos for mosaic phenotype analysis at the cellular level (e.g., for lineage tracing). Dr. Zhang further demonstrated the efficient elimination of the bacterial plasmid backbone from the donor vector by both *in vivo* and *in vitro* deletion through the phiC31 mRNA and the *attB*/*attP* system. Dr. Zhang outlined potential expansions of the Bi-FoRe strategy to other applications, such as protein tagging or fusion, knocking in other functional genes, and modeling or mimicking disease alleles. Further improvements include incorporating other functional sequences, recruiting more functional elementals, and improving the targeting capacity of target sites.

Clinician and Patient Roles in Validating Animal Models of Human Disease
Lisa Schimmenti, M.D., Mayo Clinic

Dr. Lisa Schimmenti presented her clinical perspective on patient data for validation of animal models. Her expertise includes work with Usher Syndrome Type 1, which leads to deafness, impaired vision, and vestibular dysfunction. Her group uses zebrafish as a model organism for hearing loss. She provided an overview of inner ear hair cells and ribbon synapses, a type of synapses for calcium-triggered rapid neurotransmission often associated with hearing, which differ between mutant and wild-type fish. The 3D ribbon synapse structure and the normal number of ribbons per hair cell are unknown. Dr. Schimmenti's group used a Volumescope 2 scanning electron microscope that creates single-cell, 3D renderings of nuclei and ribbon synapses. Next steps include comparison of lateral line and inner ear hair cells, comparison of ribbon synapses and cells, identification of developmental changes in synapse number and size, mitochondrial localization, and assay development. Dr. Schimmenti is interested in improving the ability of block-face imaging to create 3D models with ultrastructural resolution and integrating those findings with model system and clinical phenotypes. She concluded that validation requires the integration of insights between laboratory research and clinical practice.

The Promise and Potential of Artificial Intelligence, Machine Learning, and Data Science in Integrating Data and Models Across Modalities, Scales, and Model Systems
Vasant Honavar, Ph.D., The Pennsylvania State University

Dr. Vasant Honavar shared computational insights on the topic of data integration and model validation. The big data revolution within biology has led to exponential growth in the volume, velocity, and variety of data collected. These data sets include the genome, transcriptome, proteome, interactome, and metabolome. Dr. Honavar emphasized that a better predictive understanding of complex data sets is needed. Hypothesis generation and model development still are critical for research. He noted that this principle spans the fields of both physics and biology. Big data is necessary, but not sufficient, for scientific discovery. Computational language has enabled data sorting and annotation, and the connectivity revolution has facilitated data sharing. Algorithmic abstractions are needed to link inputs, outputs, data, and computational models. He shared data to illustrate that data visualization at various levels allows researchers to pursue different scientific questions. Additionally, computational annotation using ML can be applied to biology's big data. To illustrate a cautionary point about the importance of validation, Dr. Honavar recounted an example of using ML to highlight the dynamics of protein

phosphorylation. The example demonstrated how a minor mistake in coding can create errors that can be amplified in the literature; confirmatory experiments are needed to minimize the likelihood of such errors. Better protocols and tools are needed for metadata, algorithm testing and validation, consistency checks, and workflow reproducibility. In summary, Dr. Honavar outlined the following recommendations: (1) facilitate integration via computational abstractions of biological entities, (2) enhance cross-disciplinary collaboration mediated by computational abstractions, (3) support ontology development and ML for establishing associations across species and across scales, (4) establish computational workflows that document every analytical step, and (5) require computational validations and cross-validations using different data sources.

Illuminating the Genome Using Protein Trap Mutagenesis
Stephen Ekker, Ph.D., Mayo Clinic

Dr. Stephen Ekker, Co-Chair, presented the results of a collaborative effort to develop the "vertebrate genomic codex" and better understand previously uncharacterized genes. The genome contains more than 20,000 components (e.g., gene sequence, expression patterns, protein product behavior and function, interactions and networks). About 90% of genes are uncharacterized, and tools are needed to annotate their expression and function in both biological and pathological processes. Researchers are using random insertional mutations for reporter-tagged alleles to detect vector reading frames for maximum genome coverage. Dr. Ekker emphasized the importance of developing revertible mutant alleles. He described an example of a reversible mutagenesis system with a gene-breaking transposon containing a reversible protein trap, called pGBT-RP2 (RP2), for the creation of disease models for molecular mechanisms and phenotypes. Using this approach, his laboratory generated zebrafish models for 64 human orthologs with human-disease associated pathogenic alleles; of these, 40 alleles have shown potential as new models for human disease. Additionally, the system has illuminated new proteins, and about 90% of cloned genes show novel expression patterns. Dr. Ekker emphasized that (1) *RP2* mutagenicity shows more than 99% knockdown and is the most effective gene-trap insertional mutagen, (2) the *RP2* system traps and disrupts a diverse set of proteins and produces a variety of new potential models for human disease, (3) reproducibility of *RP2* insertion enables the elucidation of molecular mechanisms of phenotypes and diseases associated with loss of function of the trapped gene products, and (4) RP2 protein traps illuminate novel protein expression through at least 5 days of development. Dr. Ekker stated that he envisions a future targeted knock-in of highly mutagenic cargo to maximize genome coverage and achieve comprehensive mutagenesis in model organisms. He encouraged the participants to consider validation at all levels—from the whole genome to the system of interest.

Group Discussion
Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Stephen Ekker, Ph.D., Mayo Clinic

Dr. Alan Attie asked whether the described approaches have been used in large-scale genetic screens. Dr. Cheng responded that high-throughput capacity for histotomographic screening is not yet available but can be developed. Dr. Schimmenti responded that large-scale screens would be beneficial and that a team science approach would benefit further development in this area.

Dr. Fraser commented that one of the advantages of meta-modeling would be the identification and prioritization of new data. He wondered how AI approaches could be harnessed in that effort. Dr. Honavar stated that analytical approaches could be leveraged for scientific discovery.

In response to a question about the cost per generated mutant, Dr. Hugo Bellen commented that different organisms would cost different amounts and that mutant flies would cost approximately $1,000 per gene.

With current funding, 12,000 to 14,000 genes per year could be analyzed and stored in stock centers for data sharing. Dr. Bellen asked Dr. Fraser for an estimate of these costs in zebrafish. Dr. Fraser noted that phenotype characterization would be key and would incur additional costs that must be considered. Dr. Bellen replied that many genes have not yet been characterized; phenotypic characterizations could be enhanced and streamlined. In later discussion, it was noted that comprehensive phenotyping of all cell types—even in the fly—is not yet possible for either larvae or adults but could be developed.

Dr. Fraser suggested combining resources to coordinate data analysis. He stated that team science often is underappreciated within the research community (i.e., in terms of academic recognition). Dr. Ekker agreed and emphasized the importance of supporting collaborative efforts. Dr. Honavar added that supporting teams with a variety of expertise benefits the entire research community.

Dr. John Liechty recommended that biologists should not develop their own infrastructure for data automation but instead should prioritize research. Dr. Fraser agreed, noting that robust and professional tools are needed. Dr. Liechty suggested that the NIH play a role in this effort. Dr. Cheng also commented that this issue has been discussed within the zebrafish community; he suggested that the continued development of computational workflow systems would need to be developed in parallel with computational phenotyping.

Dr. Carole LaBonne stated that such model systems as *Xenopus* are valuable because lateralized CRISPR enables identification of subtle phenotypes. She also noted that these organisms contain important organs that fish lack and also are more closely related to humans. Dr. Fraser agreed that frog models are valuable and often overlooked by researchers.

Dr. Fraser suggested that the research community embrace the use of multiple model systems and noted that a new small frog model is being developed by his colleagues. Dr. Cheng emphasized that his histotomography imaging system is designed for application across model organisms (e.g., large animal models in which the study of tissue samples is important) and humans. Dr. Bellen commented that a pipeline of assays is needed for behavioral phenotyping as well. Dr. Cheng agreed and noted that integrative atlases ideally would incorporate behavior across organisms.

Dr. Sridhar Sivasubbu pointed out that the tools described would be useful for discovering and understanding non-protein-coding RNAs, which far outnumber protein-coding genes. He added that zebrafish provide an ideal model platform for studying noncoding functional DNA elements. Dr. Liechty asked whether the NIH should fund scientific support infrastructure to address this topic. Dr. Cheng agreed that funding in this area offers potential for contributing valuable knowledge about noncoding DNA. He noted that Dr. John Postlethwait has studied noncoding elements conserved between spotted gar and humans using the zebrafish.

Practicing pathologist Dr. Joshua Warrick emphasized the importance of tool building and knowledge sharing across disciplines, citing the example of a bladder cancer zebrafish model that was shown to be incorrect simply by comparing the pathologies, which indicated that a different cell type was cancerous in the model than in humans. Several participants agreed with the importance of comparative pathology, including the recommendation to consider the importance of including humans as a model for understanding vertebrate diseases.

Dr. Fraser commented that vocabulary disparities often are present; better engagement among scientists is needed. Dr. Richard Zaino noted that interdisciplinary collaborations are common, but the proposed team development for data science will be very challenging. New funding mechanisms will be needed to support these efforts. Dr. Bellen noted that vertical integration will be addressed in Session IX.

Dr. James Amatruda stated that the need for data coordination is relevant to clinicians, who observe variation among patients. Computational models should capture diversity and heterogeneity among humans. He suggested assessing whether animal models emulate human disease. Dr. Fraser stated that variance represents a study tool, but better computational tools are needed to better understand it. An analytical pipeline would help researchers explore covariance.

Dr. Liechty stated that computational models can be constructed around existing data. Dr. Fraser cautioned against constraining models to fit narrow ranges of data. Dr. Honavar agreed, noting that the approach could limit the predictive value of models. Dr. Cheng commented that the use of multiple models ideally would yield predicted associations that inform one another.

Dr. Fraser noted that the National Science Foundation (NSF) funds projects to address data science questions. He proposed that the NIH and NSF establish a bridge program to fund the development of computational tools needed to address biomedical research questions. Dr. Honavar noted that the management of such programs is challenging. Dr. Liechty emphasized the importance of marketing tools and skillsets to the research community.

Dr. Ekker stated that genome studies have yielded data on the association of human variants and disease. A large, centralized database would allow investigators to refine existing data and enable data transparency and reproducibility. He emphasized that this infrastructure represents a critical component of validation.

Dr. Cheng suggested that the NIH supports systems-level approaches. Dr. Fraser agreed and emphasized that the community would benefit from a flexible and coordinated effort for data and knowledge sharing across the research community. Several participants agreed. Dr. Bellen noted that the NIH's organizational structure likely would create challenges for this approach that will need to be addressed.

Additional Comments

In the Zoom chat and follow-up conversations through phone and email, many participants—including different model organism researchers, comparative pathologists, and medical pathologists—supported the extension of comparative pathology resources, based on virtual slides, for validation. They emphasized that those resources have yet to be fully developed. Notably, a zebrafish atlas previously supported by ORIP includes some human histology and pathology data and has been modified to allow contributions from comparative pathologists working across model systems.

Drs. Fraser and Cheng agreed on the importance of maintaining transparency in multiscale integrative research, as was outlined in Dr. Fraser's presented example of pancreatic islet function.

In response to questions about the availability of histotomography to the research community, Dr. Cheng indicated that the development of a national resource for histotomography is technologically feasible. Inquiry about the possibility of a synchrotron-based national resource for micro-CT, including X-ray histotomography, is being pursued; institution-based instrumentation is being tested for its potential this year. Dr. Cheng emphasized that X-ray histotomographic samples are permanent because they are embedded in plastic, which makes them available to be scanned in the future as imaging technology improves.

Dr. Amatruda wondered about criteria for the credentialing of models for human disease. He stated that deep phenotyping would uncover new and unexpected consequences of gene inactivation, potentially revealing important new aspects of the human disease. Alternatively, the consequences could reflect artifact or characteristics specific to the nonhuman model.

Dr. Honavar pointed out that automation eliminates human errors but can introduce systematic errors. He emphasized the importance of reproducible and validated computational pipelines and noted that discovery of errors necessitates reanalysis. He conveyed that mistakes play a critical role in ML. Additionally, Dr. Honavar noted that interdisciplinary efforts require cross-training between individuals. He recounted internal sabbatical exchanges such as one he engaged in with a molecular biologist colleague; through this experience, Dr. Honavar learned the vocabulary and tools used in molecular biology, and his colleague developed skills in ML.

Summary and Suggestions

Technology, deep phenotyping, deep integration, and data science (e.g., ML, AI) will play new key roles in advancing the use of model systems for understanding human biology and disease. Phenomics will enrich genetic and molecular studies across length scales and enhance discovery and translation for the improvement of human health. The participants discussed and provided the following areas that require new or continued support from ORIP and the NIH:

- Advancement of cell- and tissue-oriented computational phenomic imaging technologies—especially those for comprehensive phenotyping that includes organismal context—emphasizing tools that are applicable across model systems to facilitate cross-validation
- Broadened availability of imaging technology and related tool development to enhance and integrate genetic, disease, and chemical phenomics
- Enhancement of quantitative tools for tissue phenotyping using ML and AI
- Creation of comparative pathology tools for validation of the similarity of tissue phenotypes between human and model system forms of disease, inclusive of linkages between 2D and 3D data
- Creation of mechanisms for adding tissue and organismal context to -omics data (e.g., single-cell transcriptomics, proteomics, metabolomics)
- Enhancement of real-time analysis of metabolic and physiological processes and integration across scales and imaging by requiring sharing of data, analytical tools, and processes
- Creation of cloud-based links between genotype and phenotype across length scales and -omics, (e.g., user-friendly computational workflow systems that implement collaboration and data integration)

Appendix A: Meeting Agenda

Session VIII. Technologies, Phenotyping, and Data Science for Animal Models
2:00–4:00 p.m. EST
January 5, 2021

Chairs
Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Stephen Ekker, Ph.D., Mayo Clinic

2:00–2:05 p.m. **Opening Remarks**

Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine, Office of Research Infrastructure Programs (ORIP)
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

2:05–3:30 p.m. **Presentations**

Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Pan-cellular, Computational, and Integrative Tissue Phenomics as a Framework for Cross-species, Multiscale Multi-omics

Scott Fraser, Ph.D., University of Southern California
Multiplex and Intravital Imaging for Model Validation

Bo Zhang, Ph.D., Peking University
Real-Time Genotyping and Phenotyping in Live Embryos for Disease Modeling and Validation

Lisa Schimmenti, M.D., Mayo Clinic
Clinician and Patient Roles in Validating Animal Models of Human Disease

Vasant Honavar, Ph.D., The Pennsylvania State University
The Promise and Potential of Artificial Intelligence, Machine Learning and Data Science in Integrating Data and Models Across Modalities, Scales, and Model Systems

Stephen Ekker, Ph.D., Mayo Clinic
Illuminating the Genome Using Protein Trap Mutagenesis

3:30–4:00 p.m. **Group Discussion**

Appendix B: Discussants List

Session VIII. Technologies, Phenotyping, and Data Science for Animal Models
2:00–4:00 p.m. EST
January 5, 2021

Kristin Abraham, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases
Lola Ajayi, Office of Research Infrastructure Programs (ORIP)
James Amatruda, M.D., Ph.D., University of Southern California
Alan Attie, Ph.D., University of Wisconsin–Madison
Hugo Bellen, Ph.D., Baylor College of Medicine
Jason Berman, M.D., Children's Hospital of Eastern Ontario Research Institute
Rochelle Buffenstein, Ph.D., Calico Life Sciences
Michael Chang, Ph.D., ORIP
Marc Charette, Ph.D., National Heart, Lung, and Blood Institute (NHLBI)
Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Miguel Contreras, Ph.D., ORIP
Stephen Ekker, Ph.D., Mayo Clinic
Lynne Fieber, Ph.D., University of Miami Rosenstiel School of Marine and Atmospheric Science
Craig Franklin, D.V.M., University of Missouri
Scott Fraser, Ph.D., University of Southern California
Vasant Honavar, Ph.D., The Pennsylvania State University
Carole LaBonne, Ph.D., Northwestern University
John Liechty, Ph.D., The Pennsylvania State University
Lisa Schwartz Longacre, Ph.D., NHLBI
Calum MacRae, M.D., Ph.D., Harvard Medical School
Kathryn Milligan-Myhre, Ph.D., University of Connecticut
Manuel Moro, D.V.M., National Institute on Aging
Stephanie Murphy, V.M.D., Ph.D., ORIP
Peter Nghiem, D.V.M., Ph.D., Texas A&M University
David O'Connor, Ph.D., University of Wisconsin–Madison
Norbert Perrimon, Ph.D., Harvard Medical School
John Postlethwait, Ph.D., University of Oregon
Randall Prather, Ph.D., University of Missouri
Crystal Rogers, Ph.D., University of California, Davis
Rebecca Roof, Ph.D., National Institute of Neurological Disorders and Stroke
Susan Sanchez, Ph.D., The University of Georgia
Manfred Schartl, Ph.D., University of Würzburg, Germany
Lisa Schimmenti, M.D., Mayo Clinic
Leonard Shultz, Ph.D., The Jackson Laboratory
Jessica Sieren, Ph.D., The University of Iowa
Julie Simpson, Ph.D., University of California, Santa Barbara
Sridhar Sivasubbu, Ph.D., Council of Scientific and Industrial Research Institute of Genomics and Integrative Biology
William Talbot, Ph.D., Stanford University
Han Wang, Ph.D., Soochow University
Meng Wang, Ph.D., Baylor College of Medicine
Joshua Warrick, M.D., Penn State Cancer Institute
Jill Weimer, Ph.D., Sanford Research
Monte Westerfield, Ph.D., University of Oregon

Richard Zaino, M.D., The Pennsylvania State University
Bo Zhang, Ph.D., Peking University
Xiaoli Zhao, Ph.D., National Institute of General Medical Sciences
Sige Zou, Ph.D., ORIP