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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 IX. Vertical Integration Approach for Preclinical Research

Tuesday, January 12, 2021
Virtual Meeting

Workshop Report

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Executive Summary

The ninth of 10 sessions of the Virtual Workshop on Validation of Animal Models and Tools for Biomedical Research was held on January 12, 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 IX focused on strategies for vertical integration of various animal models for human disease. Topics of discussion included data integration for gene variant prioritization and validation, integrative cross-organism approaches, machine learning (ML), and translational tools. The speakers outlined resources needed for vertical integration: tools to knock down and tag genes; documentation of gene expression in tissues; systematic documentation of phenotypes at molecular, developmental, and behavioral levels; approaches for database mining across species; artificial intelligence (AI) for data mining to predict associated biochemical and signaling pathways; proof-of-concept studies in animal models and humans; a quantitative translation toolbox for the use of animal models; new partnerships with drug-discovery leaders in academic, government, and industry sectors; promotion of vertical integration among researchers; and education on the strengths and limitations of different model organisms. The participants voiced their support for stock centers; data standardization and integration; and collaboration among basic science researchers, clinicians, and bioinformaticians. Several participants emphasized the inclusion of different areas of expertise to maximize productive outcomes.

Session Co-Chairs
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Calum MacRae, M.D., Ph.D., Brigham and Women's Hospital

Presenters
John B. Hogenesch, Ph.D., Cincinnati Children's Hospital Medical Center
Zhandong Liu, Ph.D., Baylor College of Medicine
Peter Robinson, M.D., The Jackson Laboratory
Rada Savic, Ph.D., University of California, San Francisco
Olga Troyanskaya, Ph.D., Princeton University

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Sige Zou, Ph.D., Coordinator, Program Official, Office of Research Infrastructure Programs (ORIP)

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Alan Attie, Ph.D., University of Wisconsin–Madison
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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, 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 ninth 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. Dr. Calum MacRae, Co-Chair, introduced the speakers.

Modeling Human Variants in *Drosophila* and Other Model Organisms and the Integration of Data from Numerous Sources for Variant Prioritization
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Zhandong Liu, Ph.D., Baylor College of Medicine

Dr. Hugo Bellen, Co-Chair, presented on the use of model organisms for rare disease diagnosis and therapeutic development through vertical integration. He explained that vertical integration requires validation between and across the species of interest. Dr. Bellen described his work with the Undiagnosed Diseases Network (UDN), which enables collaborative efforts among clinicians and scientists across the United States for the study of rare diseases. Identified variants are sent through the UDN to a screening center for analysis. Dr. Bellen emphasized that information on gene variants can be generated from multiple model organisms. Integration of these data often is challenging for researchers. Model organism Aggregated Resources for Rare Variant ExpLoration (MARRVEL) (marrvel.org) was established to integrate genetic and genomic information from humans and model organisms to aid in human variant prioritization and experimental design for rare diseases research.

MARRVEL is an open-access website for clinicians, genome scientists, and model organism researchers that provides a snapshot of information that is distributed across different websites with a simple input and output. Users can access a summary of gene function, disease and trait associations; reported pathogenic and other types of alleles; and information from other human databases. Additionally, MARRVEL contains ortholog candidates in model organisms, tissue expression data, gene ontology, and links to PubMed and other model organism databases. From this information, researchers can determine the most suitable model organism(s) for a disease of interest. Dr. Bellen briefly outlined his research using CRISPR and CRISPR-mediated integration cassette technologies to study gene function in flies, leading to novel disease diagnoses and drug testing. Next steps for MARRVEL include the use of AI to streamline manual data processing through integration.

Dr. Zhandong Liu outlined the MARRVEL AI system. His team developed a hybrid knowledge-based system, which enables diagnosis with limited sample sizes. After preliminary filtering, the variants are sorted into six modules based on biological questions: (1) prior curation in disease databases and symptom matching, (2) molecular evidence for pathogenicity, (3) variant type classification, (4) pathogenicity prediction, (5) phenotype comparisons among associated genes, and (6) model organism phenotype matching. Next, a supervised learning approach (e.g., support vector machine) is used to

determine optimum weights to combine these modules into a single priority score for each candidate variant. This AI system is trained and tested on solved cases at Baylor Genetics Laboratories and within the UDN. Dr. Bellen outlined several tools and resources that are necessary for vertical integration: gene knockdown and tagging; documentation of gene expression in tissue; systematic documentation of phenotypes at the molecular, developmental, and behavioral levels; approaches for data mining across species; AI for data mining to predict associated biochemical and signaling pathways; promotion of vertical integration among researchers (e.g., UDN); and education on the strengths and weaknesses of different model organisms.

Data Integration and Validation of Candidate Variants Regulating Sleep and Rhythms in Cells and Mice

John B. Hogenesch, Ph.D., Cincinnati Children's Hospital Medical Center

Dr. John B. Hogenesch discussed his group's work on data integration for studies of sleep and rhythms at cellular and organismal levels. The group is using ML approaches to identify sleep regulators. This approach requires prior knowledge of sleep genes in three classes: (1) "gold standard" (i.e., with support from both human and animal models), (2) "highly likely" (i.e., with support from nonhuman mammalian models), and (3) potential sleep regulators (i.e., with fly model support only). The researchers built an ML model to identify genetic regulators of sleep and found that protein–protein interactions and circadian expression were the most informative determinants of the model. They tested a suite of ML models and found that the random forest method outperformed other classifier algorithms for analysis. They then identified candidate sleep regulators and associated pathways. Dr. Hogenesch outlined his work on Smith-Kingsmore syndrome (SKS), which is associated with abnormal sleep patterns. His group developed a mouse model for SKS to establish molecular links to observed phenotypes. They then developed a treatment model for SKS using mammalian target of rapamycin (mTOR) inhibitors. In a study of SKS patients, the group greatly expanded natural history data, comparing observed phenotypes to those recorded previously in the literature. In interventional studies, they noted behavioral improvements (e.g., enhanced verbal skills, decreased self-aggression, increased attention span, stabilized mood, improved hyperphasia, decreased seizure frequency). Dr. Hogenesch listed the following conclusions: (1) new methods and technologies have made researchers far better at defining new diseases than treating them, (2) therapeutic proof-of-concept studies in animal models and humans can help bridge this gap, (3) new partnerships are needed with drug-discovery leaders in academic, government, and industry sectors, and (4) sleep is important but often overlooked in health studies.

From Genomes to Networks—Integrative Cross-Organism Approaches to the Study of Human Disease

Olga Troyanskaya, Ph.D., Princeton University

Dr. Olga Troyanskaya presented on cross-organism research for human disease studies. She argued that the mapping of genomes and phenomes is crucial for understanding human disease. Model organisms are necessary for understanding relevant biological mechanisms. Genomes can be decoded using AI to answer the following questions: (1) how genome variants affect gene regulation and expression, (2) which variants are functional and cause disease, (3) how these variants can be tested experimentally, (4) how complex molecular circuits work in human cells and tissues, (5) how the dysregulation of circuits causes disease, (6) how model organisms can enable these studies, and (7) whether these computational approaches can be combined with experiments that are integrated across species to enable mapping of genotype–phenotype relationships in human disease. Dr. Troyanskaya explained that because most regulatory disease mutations likely are rare, an approach to predict the biochemical and phenotypic effects of any mutation—even rare or never-before-seen variants—is needed. Deep learning models have enabled such predictions at single-nucleotide resolution. For example, this approach has been used to

identify significant non-coding regulatory mutation burden at the transcriptional and post-transcriptional levels in autism spectrum disorder. These variants appear to drive differential expression in cell culture, but organism-level experimental data from model systems are needed for further validation. DeepArk (deepark.princeton.edu/about) was developed for prediction of regulatory logic in model organisms and across species. Additionally, data integration can be applied to regulatory network prediction, mapping the network structure of cell types and tissues in specific environmental or developmental contexts. Dr. Troyanskaya also emphasized the importance of mapping the network basis of biological processes and phenotypes. For example, vertical integration could be applied to elucidate the basis for neuronal vulnerability and functional mapping in Alzheimer's disease. She stated that key future insights for vertical integration include genome decoding, data-driven mapping across organisms, understanding of cellular complexity and cell type evolution, and precision medicine. Key challenges for vertical integration include data availability, tighter integration between computation and experiments and between human and model system studies, and the need for computational and experimental technical innovations.

Knowledge Graphs for Data Integration and Machine Learning in Cross-Species Disease Research
Peter Robinson, M.D., The Jackson Laboratory

Dr. Peter Robinson discussed the use of ML and knowledge graphs for vertical integration. He explained that the Monarch Initiative (monarchinitiative.org) supports ontology-driven representation of biomedical data (i.e., knowledge graphs). Knowledge graphs allow expressive and efficient queries and can be used in various ML algorithms. The Monarch Initiative connects human phenotypes with animal models in a standardized database for diagnosis. Dr. Robinson explained that future challenges require the integration of ever-increasing amounts of data. His group is developing ML algorithms for large, highly heterogenous knowledge graphs. Their goal is to provide an ontology-driven framework to generate testable hypotheses about disease biology, based on a heterogenous knowledge graph that comprises all relevant data for major model systems. Dr. Robinson explained that ML algorithms leverage existing knowledge for predictions. ML uses "node walks," which involve random sampling for the generation of vectors based on different parameters. Using this approach, his group has completed a detailed bio-curation to assemble the largest collection of published synthetic lethal injections as a basis for ML. They then developed a family of algorithms to "rebalance" the walk. Cross-validation with random forest predictions from the vectors derived from the random walk show a substantial and significant performance gain from the heterogenous walk. Dr. Robinson conveyed that ML on knowledge graphs allows a systematic exploration of hypotheses in many different areas of biology (e.g., semantic modeling and integration, deep-learning algorithm development, assessment by systematic experimental validation, design of knowledge graphs to model emerging precision medicine questions).

Translational Tools and Cross-Species Data Integration Approaches for Multi-Drug Regimen Development for Infectious Diseases
Rada Savic, Ph.D., University of California, San Francisco

Dr. Rada Savic presented on cross-species integration approaches in drug development for infectious diseases. She highlighted tuberculosis (TB)—the leading cause of death due to infectious diseases—as a case example. *Mycobacterium tuberculosis* can survive in diverse environments, and the current treatment strategy is prone to failure and relapse. A four-drug combination has been successful in controlled settings but has limitations (e.g., low effectiveness, long duration, adverse events, resistance) in uncontrolled settings. Researchers are interested in developing a shorter-duration treatment. To date, efforts in this area have been unsuccessful. TB Reanalysis of Fluoroquinolone Clinical Trials was initiated to redefine the drug development process through data integration and translation, expert review meetings, a novel drug development pathway, and a new regimen development initiative. Data have been shared from *in vivo*

clinical experiments using animal models (e.g., rodents, rabbits) and preclinical studies. Dr. Savic explained that clinical trials collect different endpoints at different phases. This approach creates challenges for data sharing and integration with animal models. From these efforts, researchers determined that a five-item risk score can help stratify patients for tailored treatment approaches. Additionally, they determined that current drugs fail to reach the site of action. Dr. Savic also explained that rabbit models are an ideal translational model for drug penetration because they have a larger body size than mice and develop necrotic lesions during TB infection. Early monotherapy clinical trials can be predicted from mouse studies using an integrated immunology–disease approach. Additionally, Phase III combination trials can be predicted effectively when accounting for lesion penetration and clinical phenotypes. Dr. Savic emphasized that the path to clinical translation is highly complex; additional tools are needed to draw connections between various components of disease phenotypes and treatment regimen. She proposed a quantitative translation toolbox, developed using AI approaches, for animal models for human disease. Dr. Savic also emphasized that novel trial designs should be linked to a Bayesian adaptive platform.

Group Discussion
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Calum MacRae, M.D., Ph.D., Brigham and Women's Hospital

Dr. David Adams commented that the interface between clinical cases and model organism expertise represents a barrier for many clinicians. ML technologies therefore could reasonably be used in some aspects of this process. These technologies, however, would need to be evaluated continually for sensitivity and specificity. Dr. Adams recommended specific, long-term support for improving the transition from clinical observation to engagement of the model organism community. Dr. MacRae agreed and encouraged researchers to consider the impact of throughput and scalability in all approaches to vertical integration.

Dr. Shinya Yamamoto highlighted the value of collaborations between clinicians and basic science researchers to better understand disease genes and phenotypes. He noted that the UDN is developing ModelMatcher (modelmatcher.net) to facilitate these interactions. Dr. Hogenesch commented that collaborative efforts and resource sharing between institutions impose significant delays for researchers. He conveyed the need for NIH support to bridge this gap. Dr. Yamamoto highlighted the importance of stock centers for the collection and distribution of community resources. Dr. Lilianna Solnica-Krezel also noted that many zebrafish researchers lack cryopreservation capabilities.

Dr. Daniel Rader asked about existing information and tools related to model evaluation and selection. Dr. Rolf Stottmann suggested studying questions in the simplest and most accessible model that exhibits the physiology of interest. Additionally, Dr. Bellen suggested first considering the simplest organism with the fastest genetics to better understand the function of a gene of interest; based on the resulting data, more complex models then can be considered. Dr. Bellen emphasized the importance of considering common signaling pathways for therapeutic application.

Dr. Jessica Whited asked whether tools for vertical integration could be used for validation of organisms that model novel advantageous traits, rather than diseases. Dr. Hogenesch replied that technological advances have enabled the use of genomic tools that previously were unavailable to researchers. For ML and data integration, training data in these organisms are needed. Dr. MacRae asked whether set perturbations are needed for an organizing framework in drug development. Dr. Hogenesch suggested considering drugs that are either approved or nearly approved.

Dr. Dan Roden encouraged the participants to consider the importance of human data for genotype and phenotype studies. He also emphasized the need for ongoing NIH-wide support for model organism

databases. Dr. Keith Cheng commented that the heterogeneity and frequency of lesions observed in various diseases should be compared between model organisms and humans using ML algorithms. Dr. Cheng voiced his support for vertical integration of phenotype in addition to genotype. Dr. Bellen noted that systematic and centralized phenotypic characterization (e.g., histology, behavior) is possible when genotypic data are established. Dr. MacRae noted that these efforts would require standardized data collection. Dr. Cheng agreed, affirming that tissue phenotype data must be systematized and cross-referenced to human data.

Dr. Rader asked whether a systematic approach should be employed for saturation mutagenesis of clinically relevant genes and relevant phenotyping to generate comprehensive libraries of functional missense variants. Dr. Bellen noted that this need spans different model organisms, and individual laboratories are employing these methods. He stated that a centralized approach would benefit the entire research community.

Dr. Stottmann wondered about mechanisms to publish negative data. Dr. Bellen agreed on the importance of the issue and noted that bioRxiv (biorxiv.org) supports efforts in this area. Dr. Monte Westerfield added that microPublication (micropublication.org) also publishes negative results.

Additional Comments

In the Zoom chat, Dr. Yamamoto explained that ModelMatcher is being built with Canadian researchers from the Rare Diseases: Models & Mechanisms Network project (rare-diseases-catalyst-network.ca), which is an open registry of scientists, including model organism scientists, who wish to collaborate with clinicians. The developers hope to begin advertising ModelMatcher to the model organism community with the help of the Alliance of Genome Research databases. They are working with MatchMaker Exchange databases (e.g., GeneMatcher, PhenomeCentral) for integration into clinical matchmaking databases.

Dr. Cheng noted that tissue structure can be critical for studies of lesion heterogeneity. He highlighted an example of a high-profile publication stating definitively that herpes simplex virus causes cervical cancer. An examination of the pathology of the mouse, however, indicated that the lesions were simply hypertrophic as a result of irritation. Thus, actual lesions must be available for further inspection in disease studies. He emphasized that variations in cell type, reactive cytology, and fibrosis should be presented in pathogenesis study and treatment.

Dr. Craig Franklin wondered whether efforts to integrate the metagenome into the discussed strategies (e.g., coupling genome with metagenome with phenotype) have been pursued.

Summary and Suggestions

The following general questions have been identified for vertical integration: (1) What data are missing? (2) How can the gaps be filled in a directed fashion? (3) Should all NIH-funded model organism experiments require the collection of exome or genome data to leverage all experiments for genome annotation? (4) Which of these efforts should be aligned through mandates across certain types of NIH research? (5) How can efforts be coordinated to ensure vertical integration? (6) What is the ideal unit or use case for vertical integration to occur? (7) How can the best approaches be defined quickly? The participants discussed and provided the following areas that require new or continued support from the NIH:

- Infrastructure to change the scale of data collection (e.g., genomes to alleles, individuals to populations), including new tools in genetics, genomics, proteomics, cell biology, and cell physiology and new approaches to data collection
- Infrastructure to optimize all data collection and data management across the NIH and beyond, including standard data collection requirements for genotypes, phenotypes, and perturbations (i.e., metadata); standard formats and documentation; formal testing of discrete analytic approaches against empiric outcomes; and long-term support for integrated databases and stock centers
- Infrastructure to align data collection around common goals (e.g., decoding genomes, decoding biological circuits, creating discrete platforms and approaches to connect investigators and data)
- Infrastructure to support the development of a skilled workforce and ongoing creative research paradigms (e.g., cross-disciplinary communities, cross-disciplinary education)

Appendix A: Meeting Agenda

Session IX. Vertical Integration Approach for Preclinical Research
2:00–4:00 p.m. EST
January 12, 2021

Chairs
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Calum MacRae, M.D., Ph.D., Brigham and Women's Hospital

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**

Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Zhandong Liu, Ph.D., Baylor College of Medicine
Modeling Human Variants in Drosophila *and Other Model Organisms and the Integration of Data from Numerous Sources for Variant Prioritization*

John B. Hogenesch, Ph.D., Cincinnati Children's Hospital Medical Center
Data Integration and Validation of Candidate Variants Regulating Sleep and Rhythms in Cells and Mice

Olga Troyanskaya, Ph.D., Princeton University
From Genomes to Networks—Integrative Cross-Organism Approaches to the Study of Human Disease

Peter Robinson, M.D., The Jackson Laboratory
Knowledge Graphs for Data Integration and Machine Learning in Cross-Species Disease Research

Rada Savic, Ph.D., University of California, San Francisco
Translational Tools and Cross-Species Data Integration Approaches for Multi-Drug Regimen Development for Infectious Diseases

3:30–4:00 p.m. **Group Discussion**

Appendix B: Discussants List

Session IX. Vertical Integration Approach for Preclinical Research
2:00–4:00 p.m. EST
January 12, 2021

Kristin Abraham, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases
David Adams, M.D., Ph.D., National Institutes of Health Intramural Program
Lola Ajayi, Office of Research Infrastructure Programs (ORIP)
Bree Aldridge, Ph.D., Tufts University
Rami Al-Ouran, Ph.D., Baylor College of Medicine
Dustin Baldridge, M.D., Ph.D., Washington University in St. Louis
Lindsey Barske, Ph.D., Cincinnati Children's Hospital Medical Center
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
Greg Carter, Ph.D., The Jackson Laboratory
Hannah Carter, Ph.D., University of California, San Diego
Stephen Chan, M.D., University of Pittsburgh School of Medicine
Michael Chang, Ph.D., ORIP
Keith Cheng, M.D., Ph.D., Penn State College of Medicine
Francis Sessions Cole, Ph.D., Washington University School of Medicine in St. Louis
Miguel Contreras, Ph.D., ORIP
Gerald Downes, Ph.D., University of Massachusetts Amherst
Lynne Fieber, Ph.D., University of Miami Rosenstiel School of Marine and Atmospheric Science
Garret FitzGerald, M.D., Perelman School of Medicine at the University of Pennsylvania
Craig Franklin, D.V.M., University of Missouri
Scott Fraser, Ph.D., University of Southern California
William (Bill) Gahl, M.D., Ph.D., National Human Genome Research Institute
John B. Hogenesch, Ph.D., Cincinnati Children's Hospital Medical Center
Carole LaBonne, Ph.D., Northwestern University
Andrew Liu, Ph.D., University of Florida College of Medicine
Zhandong Liu, Ph.D., Baylor College of Medicine
Kent Lloyd, Ph.D., D.V.M., University of California, Davis
Lisa Schwartz Longacre, Ph.D., National Heart, Lung, and Blood Institute
Cathleen Lutz, Ph.D., The Jackson Laboratory
Grant MacGregor, Ph.D., University of California, Irvine
Calum MacRae, M.D., Ph.D., Brigham and Women's Hospital
Dongxue Mao, Ph.D., Baylor College of Medicine
D.P. Mohapatra, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)
Manuel Moro, D.V.M., National Institute on Aging
John Morrison, Ph.D., University of California, Davis
Stephanie Murphy, V.M.D., Ph.D., ORIP
Peter Nghiem, D.V.M., Ph.D., Texas A&M University
Norbert Perrimon, Ph.D., Harvard Medical School
Elsje Pienaar, Ph.D., Purdue University
John Postlethwait, Ph.D., University of Oregon
Daniel Rader, M.D., University of Pennsylvania
Vida Ravanmehr, Ph.D., The Jackson Laboratory
Justin Reese, Ph.D., Lawrence Berkeley National Laboratory
Peter Robinson, M.D., The Jackson Laboratory
Dan Roden, M.D., Vanderbilt University

Crystal Rogers, Ph.D., University of California, Davis
Rebecca Roof, Ph.D., NINDS
Susan Sanchez, Ph.D., The University of Georgia
Rada Savic, Ph.D., University of California, San Francisco
Timothy Schedl, Ph.D., Washington University School of Medicine in St. Louis
Lilianna Solnica-Krezel, Ph.D., Washington University School of Medicine in St. Louis
Angelike (Angela) Stathopoulos, Ph.D., California Institute of Technology
Paul Sternberg, Ph.D., California Institute of Technology
Rolf Stottmann, Ph.D., Cincinnati Children's Hospital Medical Center
Natasha Strydom, Ph.D., University of California, San Francisco
William Talbot, Ph.D., Stanford University
Olga Troyanskaya, Ph.D., Princeton University
Douglas Wallace, Ph.D., Children's Hospital of Philadelphia
Michael Wangler, M.D., Baylor College of Medicine
Kathryn (Nicole) Weaver, Ph.D., Cincinnati Children's Hospital Medical Center
Jill Weimer, Ph.D., Sanford Research
Monte Westerfield, Ph.D., University of Oregon
Jessica Whited, Ph.D., Harvard University
Hari Yalamanchili, Ph.D., Baylor College of Medicine
Shinya Yamamoto, Ph.D., Baylor College of Medicine
Xiaoli Zhao, Ph.D., National Institute of General Medical Sciences
Leonard Zon, M.D., Harvard Medical School
Sige Zou, Ph.D., ORIP