U.S. Department of Health and Human Services
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Office of Research Infrastructure Programs
Division of Comparative Medicine

Thirteenth Comparative Medicine Resource Directors Meeting
Innovating, Adapting, and Sustaining Resources for a Dynamic Biomedical Landscape

August 3–4, 2021
Virtual Meeting

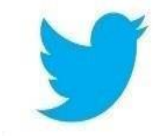
Meeting Report

Thirteenth Comparative Medicine Resource Directors Meeting

August 3 and 4, 2021

Purpose of the Meeting: The biennial Comparative Medicine Resource Directors (CMRD) Meeting is intended to provide a forum for exchange of new information, advances, and ideas; facilitate the development of synergistic working groups, interactions, and collaborations among resources, as well as with National Institutes of Health (NIH) Institutes, Centers, and Offices; and offer opportunities for sharing experiences, strategies, and best practices to optimize access, use, and administration of resources. The thirteenth CMRD Meeting was held virtually on August 3–4, 2021. The purpose of the 2021 meeting was to form and strengthen new and existing connections, disseminate information about new resources and opportunities to collaborate, expand networks, share COVID-19 experiences, learn about new NIH strategic plans and policies, and reinforce the important roles the CMRD community plays in driving biomedical research.

Overview of the Meeting: The 2021 meeting included several of the features of previous meetings—such as a Keynote Address—but also leveraged the virtual format to increase participation of community members through video presentations and breakout sessions that relate to larger group discussions.



ORIP Tweets! The Office of Research Infrastructure Programs (ORIP) has a Twitter account (@ORIP_NIH) that is used to announce information about ORIP resources, funding opportunities, conferences, workshops, and more. ORIP published live tweets throughout the CMRD Meeting, and participants were encouraged to follow along and participate.

Organizing Committee Members

S. Randal Voss, Ph.D., Chair, University of Kentucky
Miguel Contreras, Ph.D., Division of Comparative Medicine (DCM), ORIP
Diogo Magnani, Ph.D., MassBiologics, University of Massachusetts Medical School
Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP
Katy Murray, D.V.M., Ph.D., University of Oregon
David O'Connor, Ph.D., University of Wisconsin–Madison
Laura Reinholdt, Ph.D., The Jackson Laboratory
Ann Rougvie, Ph.D., University of Minnesota
Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville
Cale Whitworth, Ph.D., Indiana University Bloomington

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Executive Summary

The Thirteenth Comparative Medicine Resource Directors (CMRD) Meeting was held on August 3 and 4, 2021. Dr. S. Randal Voss served as the Organizing Committee Chair for the meeting. CMRD Meetings provide a forum for exchange of new information, advances, and ideas; facilitate the development of synergistic working groups, interactions, and collaborations among resources, as well as with National Institutes of Health (NIH) Institutes, Centers, and Offices; and offer opportunities for sharing experiences, strategies, and best practices to optimize access, use, and administration of resources. The theme of this year's meeting was innovating, adapting, and sustaining resources for a dynamic biomedical landscape. In her Keynote Address, Dr. Deborah Fuller presented on her research on the development of second-generation vaccines for COVID-19 using a nonhuman primate species. Dr. Fuller explained that her team leveraged use of the pigtail macaque—which exhibits similar pathology and viral loads to the more commonly used rhesus macaque—to fill gaps in knowledge. Sessions I and II featured Resource and Research Center (RRC) videos produced by the *Tetrahymena* Stock Center, *Drosophila* Genomics Resource Center, *Caenorhabditis* Genetics Center, National Natural Toxins Research Center, *Ambystoma* Genetic Stock Center, National *Xenopus* Resource, Zebrafish International Resource Center, Synchrotron Micro-Computed Tomography Imaging Resource for Biology, Rat Resource & Research Center, Mutant Mouse Resource & Research Centers, Vervet Research Colony, Specific-Pathogen-Free Baboon Research Resource, Squirrel Monkey Breeding and Research Resource, and Caribbean Primate Research Center. Session III addressed updates on administrative practices at NIH-supported resources, as well as presentations on the development and application of innovative tools and integrative approaches (e.g., multiscale multi-omics, diagnosis, site-directed analysis of gene function, a genotype and phenotype resource). Session IV included open discussion of questions related to recommendations of the NIH Advisory Committee to the Director report titled "Enhancing Rigor, Transparency, and Translatability in Animal Research." Discussion topics included services and research activities; dissemination of specialized knowledge, standard operating procedures, and best practices; support for community outreach; and tools to address extrinsic factors that affect outcomes and reproducibility. Breakout sessions (summarized in Session V) included discussions of diversity in comparative medicine, non-COVID-19 resource hurdles, strategies for collecting and sharing resource information, and examples of and best practices for outreach. Session VI addressed discussions of leveraging genetic complexity for research using various animal models (e.g., canines, felines, mice, swine, flies), as well as the application of precision medicine in research. In Closing Remarks, Dr. Stephanie Murphy, Director, Division of Comparative Medicine, Office of Research Infrastructure Programs (ORIP), commented that the meeting's sessions aligned closely with the four themes listed in ORIP's 2021–2025 Strategic Plan: (1) animal models to advance the study of human disease, (2) innovative instruments and equipment to accelerate research discoveries, (3) specialized research training in animal models and related resources, and (4) awareness of ORIP resources and programs. Dr. Murphy commented on the shared diversity of the RRCs (e.g., species, biospecimens, biological materials, technologies, tools, services) serving the biomedical research community. The discussion also incorporated resource promotion and outreach; tools and technologies at various levels (e.g., molecular, cellular, genetic, organismal); rigor, reproducibility, and translatability; research resources during public health crises; and resiliency in facing day-to-day challenges, as well as unanticipated emergencies.

List of Acronyms and Abbreviations

ABSL-3	Animal Biosafety Level 3
ACD	Advisory Committee to the Director
AD	Alzheimer's disease
AGSC	*Ambystoma* Genetic Stock Center
Animal-GRIN	Animal Germplasm Resources Information Network
ARRIVE	Animal Research: Reporting *In Vivo* Experiments
BBB	blood–brain barrier
Bd	*Batrachochytrium dendrobatidis*
BDSC	Bloomington *Drosophila* Stock Center
Bsal	*B. salamandrivorans*
CGC	*Caenorhabditis* Genetics Center
CMRD	Comparative Medicine Resource Directors
CPRC	Caribbean Primate Research Center
CRIMIC	CRISPR-mediated integration cassette
DCI	Division of Construction and Instruments
DCM	Division of Comparative Medicine
DGRC	*Drosophila* Genomics Resource Center
FFR	federal financial report
HD	Huntington's disease
HTORR	Human Tissue and Organ Research Resource
HVAC	heating, ventilation, and air conditioning
IACUC	Institutional Animal Care and Use Committee
ICOs	Institutes, Centers, and Offices
LION	Lipid InOrganic Nanoparticle
MARRVEL	Model organism Aggregated Resources for Rare Variant ExpLoration
MBL	Marine Biological Laboratory
mGAP	macaque Genotype And Phenotype Database
micro-CT	micro-computed tomography
MMRRC	Mutant Mouse Resource & Research Centers
MU-MMRRC	University of Missouri Mutant Mouse Resource & Research Center
NAGP	National Animal Germplasm Program
NHLBI	National Heart, Lung, and Blood Institute
NHP	nonhuman primate
NHPRR	Nonhuman Primate Reagent Resource
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNTRC	National Natural Toxins Research Center
NOW	Nucleic acids On-demand Worldwide
NXR	National *Xenopus* Resource
ORIP	Office of Research Infrastructure Programs
PD	program director
PI	principal investigator
RCAM	Referral Center for Animal Models of Human Genetic Disease
repRNA	replicon RNA
RGD	Rat Genome Database
RRC	Resource and Research Center
RRID	Research Resource Identifiers
RRRC	Rat Resource & Research Center

SMBRR	Squirrel Monkey Breeding and Research Resource
SOP	standard operating procedure
SP	Strategic Plan
SPFBRR	Specific-Pathogen-Free Baboon Research Resource
TSC	*Tetrahymena* Stock Center
UAS	upstream activation sequence
USDA	U.S. Department of Agriculture
VRC	Vervet Research Colony
ZFIN	Zebrafish Information Network
ZIRC	Zebrafish International Resource Center

Meeting Report

DAY 1: TUESDAY, AUGUST 3, 2021

Session I

Introduction and Welcome
Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine, Office of Research Infrastructure Programs

Dr. Stephanie Murphy, Director, Division of Comparative Medicine (DCM), Office of Research Infrastructure Programs (ORIP), welcomed the participants to Day 1 of the Thirteenth Comparative Medicine Resource Directors (CMRD) Meeting. She stated that for more than 20 years, the goals of the CMRD Meetings have been to (1) provide a forum for exchange of new information, advances, and ideas; (2) facilitate the development of synergistic working groups, interactions, and collaborations among resources, as well as with National Institutes of Health (NIH) Institutes, Centers, and Offices (ICOs); and (3) offer opportunities for sharing experiences, strategies, and best practices to optimize access, use, and administration of resources. The theme of this year's meeting is innovating, adapting, and sustaining resources for a dynamic biomedical landscape. Dr. Murphy thanked the participants on behalf of her ORIP colleagues for their insights, expertise, patience, and flexibility. She also expressed appreciation to Dr. S. Randal Voss, Organizing Committee Chair, for his leadership in organizing the meeting. She acknowledged the Organizing Committee members and thanked the session moderators, presenters, and panelists for their engagement in the meeting's virtual format.

ORIP's 2021–2025 Strategic Plan
Franziska Grieder, D.V.M., Ph.D., Director, ORIP

Dr. Franziska Grieder, Director, ORIP, welcomed the participants and outlined the ORIP Strategic Plan (SP) 2021–2025, which is available on ORIP's website. She stated that ORIP's tagline is "Infrastructure for Innovation." As part of NIH's Division of Program Coordination, Planning, and Strategic Initiatives, ORIP maintains a trans-NIH focus. ORIP funds 450 to 500 individual grants per year and provides services in three areas: (1) supporting research resources (e.g., animal models for human disease, cutting-edge biomedical instrumentation); (2) planning, organizing, and conducting workshops both independently and in collaboration with NIH ICOs to identify and pursue scientific opportunities; and (3) supporting research training opportunities for veterinary scientists to capitalize on their expertise in comparative medicine and insight into animal models. ORIP is composed of DCM and the Division of Construction and Instruments (DCI). ORIP also participates in the Small Business Innovation Research Program and the Small Business Technology Transfer Program, which rely heavily on the strengths of DCM and DCI. Dr. Grieder noted that the Divisions interact in many other ways.

NIH Council of Council members Drs. Terry Magnuson and Michael Lairmore served as Council liaisons for ORIP's strategic planning process. Two internal NIH focus groups were held to provide input on infrastructure needs and opportunities for ORIP resources. Additionally, three extramural community panel discussions were held to gather input on resource challenges, opportunities, and new directions. All input was reviewed carefully and distilled in the development of the SP, which was finalized in January 2021. Four themes were identified in the SP: (1) animal models to advance the study of human disease, (2) innovative instruments and equipment to accelerate research discoveries, (3) specialized research training in animal models and related resources, and (4) awareness of ORIP resources and programs. Strategies for Theme 1 include (1.1) fostering the development of and providing support for animal models and research-related resources that meet emerging public health needs, prevent disease,

promote health, and drive foundational science and (1.2) enhancing access to a broad range of animal models with robust veterinary care and well-defined genomic and phenotypic data. Strategies for Theme 2 include (2.1) supporting acquisition of modern scientific instrumentation and (2.2) modernizing the research infrastructure of laboratories and animal research facilities. Strategies for Theme 3 include (3.1) promoting innovative approaches for training and developing the careers of veterinarians working in biomedical research, (3.2) supporting training and career development programs that promote diversity in health-related research, and (3.3) promoting career development of researchers and support staff skilled in the use and oversight of disease model and research resources. Strategies for Theme 4 include (4.1) fostering collaborative research opportunities between ORIP-supported resources and NIH ICOs and other federal agencies and (4.2) expanding outreach to the biomedical research community to raise awareness and dissemination of ORIP-supported resources and programs. Dr. Grieder concluded by thanking the extramural participants, NIH participants, and ORIP colleagues for their input in the strategic planning process.

Videos Highlighting ORIP Research Resources #1
Moderator: S. Randal Voss, Ph.D., University of Kentucky

Dr. Voss thanked the members of the Organizing Committee for their efforts in planning the meeting. He explained that past CMRD Meetings have featured videos from newly funded Resource and Research Centers (RRCs) and new attendees. This year, all attendees were invited to submit videos.

A. *Tetrahymena* Stock Center
Theodore Clark, Ph.D., Cornell University

Dr. Theodore Clark's video provided an overview of research using *Tetrahymena.* The genus' unique mating process enables a remarkable degree of genomic change. Representatives from the *Tetrahymena* Stock Center (TSC) discussed the advantages of research using ciliate organisms, which includes high flexibility, low cost, and rapid development. They also affirmed their commitment to education and training.

B. *Drosophila* Genomics Resource Center
Andrew Zelhof, Ph.D., Indiana University Bloomington

Dr. Andrew Zelhof's video provided an overview of the *Drosophila* Genomics Resource Center (DGRC). Services include (1) collection, storage, and distribution of *Drosophila* cDNA and plasmid reagents; (2) collection, creation, and distribution of *Drosophila* cell lines; and (3) development and testing of cell culture reagents.

C. *Caenorhabditis* Genetics Center
Ann Rougvie, Ph.D., University of Minnesota

Dr. Ann Rougvie's video provided an overview of the *Caenorhabditis* Genetics Center (CGC), which was established to (1) collect, maintain, and distribute useful *Caenorhabditis elegans* strains; (2) promote basic and biomedical research progress; and (3) generate strains of use to the research community. *C. elegans* is a small, free-living nematode with a simple anatomy and short life cycle and is used for diverse areas of basic and biomedical research (e.g., cell biology, neurobiology, behavior). The CGC maintains more than 23,000 *C. elegans* strains, and about 30,000 strains are distributed per year (prior to the COVID-19 pandemic). About 4,000 working stocks are in use at a time, and the organism can survive long-term cryopreservation. The full collection is maintained in two separate copies on campus, and a third copy is maintained in Colorado.

D. National Natural Toxins Research Center
Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

Dr. Elda E. Sánchez's video provided an overview of the National Natural Toxins Research Center (NNTRC), which houses more than 450 venomous snakes comprising 21 species and 32 subspecies. The NNTRC's mission is to provide snake and venom resources, research, and research training for toxin identification, enabling the development of therapeutics.

E. *Ambystoma* Genetic Stock Center
S. Randal Voss, Ph.D., University of Kentucky

Dr. Voss' video provided an overview of the *Ambystoma* Genetic Stock Center (AGSC), which maintains and distributes the Mexican axolotl for biomedical research. Many researchers study axolotls to understand the basis of their unrivaled regenerative ability. Axolotls can regenerate their limbs, heart, spinal cord, and brain. Insights on this process likely will be valuable in the development of techniques for inducing endogenous tissue repair in humans. The Mexican axolotl thrives in captivity and breeds multiple times per year, each time yielding hundreds of offspring. It has a fully aquatic lifestyle, simplifying animal husbandry. The Mexican axolotl is the only salamander that can provide stocks in sufficient numbers to support a community of researchers.

F. National *Xenopus* Resource
Marko Horb, Ph.D., Marine Biological Laboratory

Dr. Marko Horb's video highlighted the National *Xenopus* Resource (NXR), which prioritizes the generation and distribution of new and transgenic animals for the research community. He briefly outlined the rearing process of homozygous animals to adulthood. These animals can be used by laboratories through the NXR Research Facility Resource or transported to users. Researchers have access to staff support, animal housing, and laboratory space to expedite experiments. Training in husbandry and genome editing is available, and advanced workshops in bioinformatics, imaging, and genome editing are available for students and principal investigators (PIs).

G. Zebrafish International Resource Center
Zoltan Varga, Ph.D., University of Oregon

Dr. Zoltan Varga's video provided an overview of the Zebrafish International Resource Center (ZIRC), which serves as a repository of mutant, transgenic, and wild-type zebrafish. ZIRC provides veterinary services to zebrafish facilities and characterizes and disseminates health and husbandry standards. ZIRC performs larval rearing, fish husbandry, egg *in vitro* fertilization, and cryopreservation of fish lines. Presently, the repository contains 12,845 fish lines (45,869 alleles), 962 expressed sequence tags/cDNAs, and 38 monoclonal and polyclonal antibodies. Since 2000, ZIRC has shipped more than 9 million fish to 45 countries. An upcoming facility expansion and modernization project was funded by an ORIP construction grant awarded in 2019. The design phase has been completed, and preparations for construction began in July 2021. The project will include replacement and modernization of ZIRC's water filtration systems, increases to the cryogenic storage space, the addition of a second quarantine room and laboratory space, and increases in equipment-cleaning space.

H. Synchrotron Micro-Computed Tomography Resource for Biology
Keith Cheng, M.D., Ph.D., The Pennsylvania State University

Dr. Keith Cheng's video provided an overview of the Cheng Lab's work toward a Synchrotron Micro-Computed Tomography (Micro-CT) Resource for Biology, including video and still images of whole-organism imaging in *Daphnia magna* and *Danio rerio* using a new custom camera capable of an unprecedented combination of isotropic voxel resolution of 0.5 µM over a field of view of 5 mm. The images highlighted the gut, embryos, filter plates, and fat (i.e., storage) cells. Micro-CT and light micrograph images also were presented of silver-based staining of pigmented cells of larval zebrafish, highlighting the retinal pigment epithelium of the eye, dorsal stripe, lateral stripes, ventral stripe, and yolk sac stripe.

Discussion

- Dr. Voss asked Dr. Cheng to further describe the images presented in his laboratory's video. Dr. Cheng stated that his team developed the featured technology over the course of a decade; the custom lens system was developed over the past few years. The images depict a new combination of resolution and field of view that now are possible with this technology, which was described in a separate presentation during the meeting. Dr. Cheng invited the participants to email him at kcc2@psu.edu or visit the laboratory website for additional information. He stated that computational analyses of these images will provide a useful resource for the research community, including the anchoring of fluorescence and spatially resolved "-omic" (e.g., transcriptomic, proteomic, metabolomic) data.
- Dr. Voss asked Dr. Clark to describe the production process for the TSC's video. Dr. Clark explained that the video was produced for the 2016 The Allied Genetics Conference. The ciliate community had asked the TSC to produce a video for a session titled "Standing Up for Model Organism Research." Footage from the original video was used to produce the new video. Additional content was added to highlight *Tetrahymena* in an engaging way. Dr. Clark emphasized the importance of professional advertising for scientific research and model organisms.
- In the chat, Dr. Matthew Jorgenson asked whether the videos require approval from institutions and noted that they might present concerns related to animal rights.
- Dr. Voss asked the speakers to reflect on the community-building aspect of video production. Drs. Horb and Varga responded that the other videos inspired them to employ a different approach for future productions. Dr. Clark noted that his video was developed with young audiences in mind.
- Dr. Voss commented that charismatic organisms (e.g., vipers) are well-suited for outreach. Dr. Sánchez agreed but noted that many people have phobias that must be considered.
- In the chat, Dr. Miguel Contreras noted that the videos also could serve as a training tool. Dr. Zelhof responded that his videos have been used for tissue culture training and common procedures. The videos are posted on the DGRC website. Dr. Voss noted that Dr. Horb has developed training videos for sperm cryopreservation in *Xenopus*; these efforts help promote standardization, rigor, transparency, and reproducibility. In the chat, Dr. Horb asked about funding opportunities for workshops.
- Dr. Cheng pointed out that professional videographers are available for scientists who are interested in developing videos representing their work. In the chat, Dr. Cale Whitworth commented that funds can be a limiting factor for laboratories, but the impact of professional videos is a valuable investment. Dr. Clark noted that grants can include funds for video production.

- In the chat, Dr. Bruce Fuchs advised that program officers should maintain relevant Twitter handles. In the chat, Dr. Contreras also advised that ORIP is tweeting "CMRD Cinema" at @NIH_ORIP (https://twitter.com/NIH_ORIP/status/1422580133043474433).
- In the chat, Dr. Elizabeth Bryda asked which of the RRCs have Facebook accounts and how frequently they are used. Drs. Horb, Rougvie, and Zelhof each stated that their RRC does not have a Facebook account but that a Twitter account and a website are maintained. Dr. Horb added that the NXR also uses Xenbase but does not possess sufficient staff for social media. Dr. Sánchez stated that the NNTRC maintains a Facebook page in addition to its website. Dr. Varga commented that ZIRC maintains a website and content and communicates with researchers through the Zebrafish Information Network (ZFIN) news blog. ZIRC also communicates through the International Zebrafish Society NewsSplash. Dr. Voss stated that the AGSC maintains Facebook and Twitter accounts.
- In the chat, Dr. Kent Lloyd asked about progress on cryopreservation of *Drosophila melanogaster*. Dr. Zelhof responded that Dr. Whitworth would address this topic in his presentation.

Keynote Presentation—Preclinical Evaluation of Second-Generation COVID-19 Vaccines in Nonhuman Primates

Deborah Fuller, Ph.D., University of Washington School of Medicine and Washington National Primate Research Center

Dr. Deborah Fuller presented on her research on the development of second-generation vaccines for COVID-19. The use of nonhuman primate (NHP) models was crucial in the rapid development of candidate COVID-19 vaccines. NHPs are susceptible to the same diseases as humans and can provide valuable insight into vaccine development studies. Dr. Fuller explained that her team leveraged use of the pigtail macaque—which exhibits similar pathology and viral loads to the more commonly used rhesus macaque—to fill gaps in knowledge. Dr. Fuller next presented a brief overview of the function of mRNA and viral vector vaccines. Antibody responses induced by COVID-19 vaccines are the primary mechanism of protection, and COVID-19 vaccines provide protection from infection, disease, and transmission. Dr. Fuller noted that surges in newly reported cases have resulted from the emergence of new viral variants. Limited vaccine distribution, particularly in low- and middle-income countries, also presents a challenge. Related issues include political and logistical (e.g., storage, transport) challenges. Even after the pandemic is controlled, SARS-CoV-2 is likely to remain endemic in the population, and new variants likely will continue to emerge. Second-generation vaccines will help prevent another outbreak. These vaccines will address the shortcomings of the initial vaccines (e.g., quickly and safely induced immunity, long-term antibody and T cell responses, equal effectiveness across demographic groups, fast scale-up, stability at room temperature, self-administration). Dr. Fuller's team is developing several second-generation nucleic acid vaccines: replicon RNA (repRNA) vaccines, room temperature–stable DNA and repRNA vaccines delivered to the epidermis by a needle-free gene gun, and pan-coronavirus nucleic acid vaccines. Dr. Fuller briefly outlined the mechanisms of these vaccines.

Presently, *in vivo* delivery creates challenges for vaccines. In collaboration with HDT Bio, Dr. Fuller's team is investigating Lipid InOrganic Nanoparticle (LION) delivery of repRNA. They first examined the vaccine in mice; young and middle-aged mice responded to prime immunization, and aged mice required a booster to develop similar responses. Based on these results, the researchers performed a pilot immunogenicity study in pigtail macaques. In this study, a single dose induced robust binding and neutralizing antibodies. Only modest and transient T cell responses, however, were observed. Dr. Fuller suggested that potency of the spike protein might play a role in this finding; other potential immunogens are being investigated. The vaccines also maintain immunogenicity in simian immunodeficiency virus–infected macaques. Additionally, lower doses induced potent and durable immune responses. Comparable protection, even after antibody responses had waned to undetectable levels, indicates that durable memory

B and T cell responses can recall and mediate protection rapidly. Dr. Fuller provided a summary of the findings in a recent study published in *Science Translational Medicine*: (1) sustained antibody responses for at least 7 months after a single dose, (2) T cell responses, (3) strong responses in aged and immunocompromised animals, and (4) sustained protection for at least 7 months in a preclinical NHP.

Multiple vaccines likely will be needed to stop the COVID-19 pandemic because different vaccines provide different advantages. Dr. Fuller explained that mixing vaccines can increase the magnitude and breadth in specificity of the immune response. Dr. Fuller worked in collaboration with Dr. Neil King, who deployed a computational platform to generate nanoparticle vaccines for SARS-CoV-2. The nanoparticles resulted in a robust immune response, significantly reducing viral replication in the nose and lungs of mice to non-detectable levels. Mixing the nanoparticles with the mRNA vaccine increases immunity against various strains of the virus. Dr. Fuller also recently designed a new hybrid vaccine (repRNA–SHARP) based on an HA2 stem-based immunogen. Use of this vaccine as a booster induces superior neutralizing antibody responses. This vaccine is in development presently, and testing in NHPs is being initiated. Dr. Fuller also stated that LION can be used to deliver multiple repRNA vaccines. SHARP could be used as a dual vaccine for COVID-19 and influenza; the mechanism for this approach is being explored presently.

Dr. Fuller emphasized that mRNA vaccines represent a revolution in modern medicine. Because DNA and RNA vaccines induce distinct immune responses, the advantages of both approaches could be leveraged in a single immunization. Dr. Fuller co-founded Orlance, Inc., and is developing a "supersonic" clinical gene gun that enables needle-free, painless delivery of room temperature–stable RNA and DNA vaccines. She briefly presented data demonstrating systemic and mucosal antibody and T cell responses. The company is involved in Nucleic acids On-demand Worldwide (NOW), a collaborative effort with GE Research and the U.S. Department of Defense that would offer near-immediate vaccine doses and therapeutics to stop worldwide outbreaks within 60 days. She explained that a ring vaccination approach would be employed to identify cases and ensure outbreaks remain localized. Dr. Fuller also spoke on a pan-coronavirus vaccine, which could be used to prevent the emergence of deadly future variants; multiple efforts in this area are underway.

Questions
Moderator: David O'Connor, Ph.D., University of Wisconsin–Madison

In the chat, Dr. Varga asked for clarification of the term "toxicity." Dr. Fuller explained that the term refers to effects on the receiving cell. Toxicity responses could result in side effects after immunization.

In the chat, Dr. Douglas Chalker commented that mRNA vaccines use modified RNA to prevent interferon responses to double-stranded RNA and also prevent mRNA destruction. He asked whether this concept applies to repRNA vaccines. Dr. Fuller responded that similar coding sequences are employed in this approach.

In the chat, Dr. Clark asked how the gene gun compares to those used historically by other companies (e.g., Bio-Rad Laboratories, Inc.). Dr. Fuller responded that she worked previously with a company that developed the gene gun for clinical use. Bio-Rad acquired the rights to develop a gene gun for research purposes, incorporating new design features that alter its performance.

In the chat, Dr. Melween Martinez asked about the role of T cell immunity in unvaccinated individuals who have convalesced from natural infection. Dr. Fuller noted that T cell responses from prior coronavirus infections might help confer protection from severe disease. mRNA and viral vector vaccines, however, were designed to express a spike protein in an optimal way to expose additional

epitopes that might not be exposed during a natural infection, potentially providing more effective immunity.

In the chat, Dr. Cheng asked about whether chronically generating antigens potentially could increase the risk of autoimmunity. Dr. Fuller clarified that the repRNA vaccine does not produce antigens indefinitely.

Dr. David O'Connor asked Dr. Fuller about resources or regulatory changes that would have aided—or would aid—her previous and future research. Dr. Fuller stated that access to NHP models is crucial. The NIH approved an emergency reallocation of funds that allowed her team to begin working on development and testing quickly during the pandemic. She emphasized the need to prepare for future pandemics by providing capabilities for studies using different species of NHPs. Additionally, more Animal Biosafety Level 3 (ABSL-3) facilities are needed at primate centers. She stated that collaboration and data-sharing in real time to determine best approaches will be crucial.

Session II

Videos Highlighting ORIP Research Resources #2
Moderator: Michael Schmale, Ph.D., University of Miami

A. Rat Resource & Research Center
Elizabeth Bryda, Ph.D., University of Missouri

Dr. Bryda's video provided an overview of the Rat Resource & Research Center (RRRC), which is located at the University of Missouri Discovery Ridge Research Park. The RRRC's mission is to provide a unique rat model repository for the biomedical research community by importing, archiving, and distributing rat strains and embryonic stem cells; performing critical rat-related services for investigators; making and refining genetically engineered rat strains; and conducting innovative research that ensures the quality, reproducibility, and availability of rat models. Users include investigators from nonprofit and for-profit institutions working in a variety of scientific disciplines. In addition to expertise in rat model cryopreservation and worldwide distribution capabilities, the RRRC provides specialized services, including cryo-resuscitation and rederivation, genetic characterization, and metagenomics analysis. The RRRC strives to serve as a one-stop resource for biomedical researchers.

B. University of Missouri Mutant Mouse Resource & Research Center
James Amos-Landgraf, Ph.D., University of Missouri
Craig Franklin, D.V.M., Ph.D., University of Missouri

Drs. James Amos-Landgraf and Craig Franklin's video provided an overview of the University of Missouri Mutant Mouse Resource & Research Center (MU-MMRRC), which includes more than 6,000 cryopreserved and live mouse models, including a portion of Knockout Mouse Phenotyping Program lines and the full Mutagenetix collection of Nobel Laureate Bruce Beutler. The MU-MMRRC offers such services as cryopreservation, cryo-resuscitation, model genotyping, and colony management. The MU-MMRRC also performs ABSL-3-level containment work and provides experimental design, collaborative, and contract services. The MU-MMRRC performs research to assess the role of intestinal microbiota in phenotype reproducibility and translatability. These efforts have enabled additional services for researchers, including fecal banking and standardized complex microbiota.

C. Vervet Research Colony
Matthew Jorgensen, Ph.D., Wake Forest School of Medicine

Dr. Jorgensen's video provided an overview of the Vervet Research Colony (VRC), which serves as a national research resource by providing animals, biological samples, data, consultation, and training for researchers interested in studying vervets (i.e., African green monkeys). The colony consists of a large, multigenerational pedigree. The animals are born in captivity, are mother-reared in species-typical social groups, and live under the same dietary and environmental conditions. The VRC supports research in such areas as immunology and vaccine development; aging and Alzheimer's disease (AD); and diabetes, obesity, and metabolism. Wake Forest School of Medicine also provides scientific, pathology, and veterinary expertise; modern surgical facilities; and state-of-the-art medical imaging.

D. Specific-Pathogen-Free Baboon Research Resource
Joe Simmons, D.V.M., Ph.D., The University of Texas MD Anderson Cancer Center

Dr. Joe Simmons' video provided an overview of the Specific-Pathogen-Free Baboon Research Resource (SPFBRR). The SPFBRR began in The University of Oklahoma Health Sciences Center and was moved to the Michale E. Keeling Center for Comparative Medicine Research at The University of Texas MD Anderson Cancer Center in 2017 and 2018. Animals at the SPFBRR are free of many pathogens that are found in wild baboons, making them ideally suited for immunosuppression and xenotransplantation studies. The colony contains about 400 animals, with 150 breeding females who produce about 125 animals per year for use in biomedical research projects. A variety of biological samples are available, including blood bags from ABO genotype virus-free baboons.

E. Squirrel Monkey Breeding and Research Resource
Lawrence Williams, Ph.D., The University of Texas MD Anderson Cancer Center

Dr. Lawrence Williams' video provided an overview of the Squirrel Monkey Breeding and Research Resource (SMBRR), which represents the only self-sustaining national resource of laboratory-born squirrel monkeys. The SMBRR houses about 500 animals, primarily in breeding groups that can produce as many as 100 offspring annually. The research staff and caretakers possess technical skills to assist researchers effectively. The animals are used in the areas of neuroscience, AD, hearing, and vision research. The squirrel monkey serves as an important model in malaria vaccine development, *in vitro* fertilization, transgenic studies, social learning, and cooperation. The SMBRR integrates research among multiple disciplines. The team is interested in understanding the natural biology, reproductive system, and diseases of the squirrel monkey, with an emphasis on models for human disease.

F. Caribbean Primate Research Center
Melween Martinez, D.V.M., Caribbean Primate Research Center

Dr. Martinez's video provided an overview of the Caribbean Primate Research Center (CPRC). She explained that the CPRC was named formally in 1970 but was established in 1938, when 409 rhesus macaques were transported from India. The CPRC contains four facilities. The Sabana Seca Field Station contains a conventional colony and a specific-pathogen-free colony. The Laboratory of Primate Morphology contains about 4,000 skeletons of rhesus macaques of known identity and maternal relationship. Dr. Martinez explained that a portion of the collection has been moved in a collaboration with New York University. The Virology Laboratory serves as a platform for vaccine development studies, immunopathogenesis, and innate immunity protocols. The Cayo Santiago Biological Field Station contains the oldest continuously maintained colony of its kind in the world. The Indian origin macaques have not been mixed with Chinese rhesus macaques or with long-tail macaques. The demographic

database of this colony contains more than 60 years of data and 12,000 individuals—the most complete of any free-ranging population.

G. Mutant Mouse Resource & Research Centers
Andrew Brooks, University of California, Davis

Mr. Andrew Brooks' and Dr. Lloyd's video provided an overview of the Mutant Mouse Resource & Research Centers (MMRRC) Program, which operates a consortium of four archive and distribution centers—as well as an Informatics, Coordination, and Service Center—across the United States. The MMRRC Consortium accepts, distributes, and cryopreserves scientifically valuable genetically engineered mouse strains and mouse embryonic stem cell lines with potential value for the genetics and biomedical research communities. The MMRRC serves as the nation's premier repository of spontaneous and induced mutant mouse models and cell lines. The MMRRC is one of the world's largest noncommercial collections of mouse alleles. High standards of experimental design and quality control are upheld to optimize reproducibility.

Discussion

- In the chat, Dr. Voss asked whether the CPRC's operations have returned to normal following hurricanes and other recent events (e.g., the COVID-19 pandemic). Dr. Martinez stated that the CPRC was granted an NIH award to repair damage caused by Hurricane Maria. Normal operations have resumed, but restoration efforts are ongoing. Vaccination of staff members also is a present concern. Dr. Martinez noted that Cayo Santiago faces unique challenges (e.g., transportation of equipment) as a result of its island location.
- Dr. Michael Schmale asked Dr. Williams about the SMBRR's model for AD. Dr. Williams explained that in the wild, a squirrel monkey's typical lifespan is 16–18 years. In the colony, an animal lives 24–25 years. Cerebral amyloid angiopathy–type plaques begin to form between 17–18 years; studies on lifespan, plaque formation, and therapeutic development are ongoing.
- In the chat, Dr. Clark asked Dr. Bryda about the turnaround time for delivery of transgenic rats. Dr. Bryda stated that reagent preparation can take several weeks. The gestation period is 21 days, and the rats can be weaned and shipped after 28 days.
- Dr. Schmale asked about the distribution of animal usage by users who house the animals in their own facilities, relative to users who maintain animals in-house at the central facility. Dr. Williams estimated that at the SMBRR, about 60% of animals are transported off site. Dr. Simmons estimated that at the SPFBRR, 50–60% of animals are transported off site.
- Dr. Schmale inquired further about mechanisms for in-house research at NHP facilities. Dr. Jorgenson noted that the expertise at the VRC is beneficial for users who lack necessary infrastructure and expertise; a lease fee mechanism is available for in-house studies. Dr. Martinez added that a similar mechanism is in place at Cayo Santiago. At Sabana Seca, most animals are transported to the United States for studies. Dr. Simmons commented that most in-house studies at the SPFBRR involve infants, young animals, and larger animals. Additionally, the in-house model is useful for studies that are not consumptive; this approach maximizes use of the animal.
- Dr. Franklin asked Dr. Simmons whether protocols are in place for users who receive specific-pathogen-free animals. Dr. Simmons stated that he works with users and offers follow-up testing, but confusion on this topic often persists.
- Dr. Schmale asked whether investigators travel to rodent facilities to learn techniques for mating lines or performing cryopreservation. Dr. Bryda stated that the RRRC provides a broad array of support; many investigators are more familiar with mice than rats. The RRRC provides colony management services for investigators who do not possess capabilities for maintaining rats; animals are shipped to the investigators for experiments as needed. Dr. Amos-Landgraf added that the MU-MMRRC has provided similar services for investigators whose laboratories were

closed during the COVID-19 pandemic. Additionally, Dr. Amos-Landgraf noted that the ABSL-3 facilities provide extensive capabilities for researchers interested in COVID-19 research.

- In the chat, Dr. Chalker asked how often mutant mice with different genetic backgrounds are made. Dr. Amos-Landgraf replied that most users are interested in C57BL/6 (B6) mice.

Breakout Sessions

Room 1—Promoting Diversity in Comparative Medicine
Moderator: S. Randal Voss, Ph.D., University of Kentucky

A. The NIH Diversity Administrative Supplement Program
Bruce Fuchs, Ph.D., ORIP

Dr. Fuchs provided an overview of the NIH Diversity Administrative Supplement Program and highlighted the ORIP DCM Training and Career Development webpage. Dr. Fuchs called attention to the ORIP Diversity Supplements Guidelines, which were written to facilitate the application process. He also highlighted the current program announcement: Research Supplements to Promote Diversity in Health-Related Fields. The purpose of these awards is to enhance the diversity of the research workforce by recruiting and supporting students, postdoctoral researchers, and eligible investigators from diverse backgrounds. Individuals from racial and ethnic groups determined by the National Science Foundation to be underrepresented in the health sciences, individuals with physical and mental disabilities, and individuals from disadvantaged backgrounds can apply. PIs and program directors (PDs) of research grants can begin the application process by identifying a suitable candidate for the supplement, contacting ORIP program officers to address questions, and requesting that the candidate prepare a personal statement. Dr. Fuchs encouraged PIs and PDs to complete applications no later than July 3 to be considered for that fiscal year.

B. Control and Impacts of Disease of Zebrafish in Research Facilities
Michael Kent, Ph.D., Oregon State University
Corbin Schuster, Oregon State University

Dr. Michael Kent (mentor) and Mr. Corbin Schuster (awardee) described their experiences with ORIP research supplements to promote diversity in health-related research and discussed their research in zebrafish models. Three of Dr. Kent's students have been supported by diversity supplements. Dr. Kent noted the benefits of the program to his laboratory and Oregon State University, which include learning about diverse cultures, direct recruitment of underrepresented students, identification of challenges of academic and professional success, and funding for graduate studies. Mr. Schuster—who was raised on the Yakama Indian Reservation and is a member of the Yakama Nation, with ties to the Confederated Tribes of the Warm Springs, earned his undergraduate degree from Heritage University in 2018. He was accepted that year for an internship with the National Institute of Diabetes and Digestive and Kidney Diseases. He is pursuing his Ph.D. in microbiology at Oregon State University and is interested in postdoctoral opportunities in molecular diagnostics. Mr. Schuster noted several opportunities and benefits of being a mentee in this program, which include integration of traditional ecological knowledge into coursework and research, a platform to participate in university-wide diversity and inclusion efforts, mentoring and teaching, and research training.

Dr. Kent explained that his group has been supported by an ORIP R24 grant since 2001. Dr. Kent's research focuses on developing adult zebrafish models for infectious diseases, toxicology, oncology, behavior studies, and non-protocol induced variation. From 2000 to 2020, Dr. Kent and his colleagues reviewed health endpoints from more than 18,000 zebrafish across more than 300 laboratories and 1,000 different diagnostic cases. The data showed that *Pseudoloma neurophilia* was the most prevalent

pathogen; more than 50% of laboratories are affected. Mr. Schuster noted the impact of *P. neurophilia* in the zebrafish model (e.g., increased morbidity, decreased fecundity, non-protocol-induced variation) and discussed diagnostic challenges (e.g., lack of symptoms, non-lethal test). Mr. Schuster's project focuses on the development of a novel non-lethal water-based assay to overcome these challenges. The test based on digital PCR is very sensitive and specific, and Mr. Schuster soon will be submitting two papers on results using this test.

C. Implementing Pathogen Monitoring for the Laboratory Axolotl
Mirindi Kabangu, University of Kentucky
S. Randal Voss, Ph.D., University of Kentucky

Dr. Voss (mentor) commented on the benefits of the diversity supplements to his laboratory and undergraduate student, Mr. Mirindi Kabangu (awardee). The supplement has funded a project focused on pathogen monitoring in axolotl within the AGSC. Mr. Kabangu has worked to develop a real-time quantitative PCR–based assay to detect a fungal pathogen. A recent University of Kentucky honors graduate, Mr. Kabangu will continue working in the Voss laboratory for the next year and will begin preparing applications for an M.D./Ph.D. program.

Mr. Kabangu presented his research project that addresses maintaining the health in the AGSC stock. In a 2017 outbreak in the Michigan State University stock traceable to the AGSC, animals revealed clinical signs (e.g., dulling in pigmentation, sloughing of necrotic skin, ulcerations) that since have been attributed to chytridiomycosis, a chytrid fungus of either of two sources: *Batrachochytrium dendrobatidis* (Bd) or *B. salamandrivorans* (Bsal). Mr. Kabangu designed a PCR-based screen to evaluate Bd (the form most reported in stock centers) in the AGSC. He also performed a longitudinal study using real-time PCR. Results revealed that animal housing and age are significant factors for infection. Age trends are related to changes in the skin during development. Mr. Kabangu also conducted a data mining study to identify other microbes; human influenza B–like viral sequences were found to be present. Using transmission electron microscopy, he identified the presence of parvovirus in the axolotl skin. The next steps will be to explore microbes on skin, characterize the axolotl's defense mechanisms, and evaluate microbial effects on regeneration.

D. Novel Immune-Deficient Mouse Models of Huntington's Disease
Peter Deng, Ph.D., University of California, Davis
Jan Nolta, Ph.D., University of California, Davis

Dr. Jan Nolta (mentor) came from a disadvantaged background and is a first-generation professor at an academic institution. As Director of the Stem Cell Program and Gene Therapy Center at the University of California, Davis, her two passions are helping teams develop and validate cell and gene therapy products for clinical trials and helping students from diverse backgrounds advance their careers. Dr. Nolta and her team focus on Huntington's disease (HD) and neurological disorders, especially those that affect children. Diverse training of the next generation of stem cell researchers, including diversity supplement awardees, occurs at the University of California, Davis, Good Manufacturing Practice facility.

Dr. Peter Deng (awardee) spoke on the genetic background of HD. A hallmark feature of HD is acute neurodegeneration in the medium spiny neurons of the caudate-putamen. Xenotransplantation has been of interest in regenerative medicine. HD models that recapitulate the disease have been developed, but issues in immune suppression and cell rejection in transplantation remain. Dr. Deng presented his research consisting of two specific aims: develop an immunodeficient YAC128 HD mouse model to study the impact of putative human stem cell therapies and gene therapies and develop a humanized YAC128 HD mouse model to study the impact of human immune systems on potential therapeutics. The animals demonstrated phenotypical changes characteristic of HD regarding behavior, motor movement, and

striatal atrophy. Future directions include using the YACNSG models in enabling studies of human-specific stem cell products and the humanized model to investigate the effects of the immune system in novel therapeutics.

A first-generation scientist from a disadvantaged background, Dr. Deng reflected on the efforts of his parents and mentors. He emphasized the importance of encouraging systemic changes and providing funding to recruit the next generation of scientists.

Discussion

- In the chat, Dr. Christoph Lossin asked about the possibility of diversity supplements funding for staff positions. Dr. Fuchs explained that the current emphasis of this program is on supporting career development of biomedical researchers through mentorship; laboratory staff are ineligible.
- In the chat, Dr. Clark voiced support for NIH support mechanisms to allow established, well-funded investigators to collaborate with PIs at historically Black colleges and universities or colleges with predominantly underrepresented student populations to help with building diversity into the future medical workforce.
- In the chat, Dr. Clark asked Dr. Kent and Mr. Schuster whether *P. neurophilia* could be transmitted vertically via eggs and whether ZIRC monitors the stock for this pathogen. Dr. Kent clarified this pathogen is transmitted vertically and is monitored thoroughly in the ZIRC stocks.
- In the chat, Dr. Clark also asked whether influenza viruses have been reported previously in amphibians or fish. Mr. Kabangu responded that data mining revealed an Australian research group as the first to report this occurrence in 2020. Dr. Kent noted a viral disease, infectious salmon anemia, that has been linked to an influenza virus.
- Dr. Voss inquired about the next steps for making the YACNSG models available to the research community. Dr. Nolta explained that depositing these models with The Jackson Laboratory is in progress; breeding pairs can be provided to others by request.
- In the chat, Dr. Contreras asked the mentors how they promoted their laboratories to attract diversity supplement candidates. Dr. Nolta actively recruits on the University of California, Davis, social media platforms and uses personal outreach efforts. Dr. Kent credited Dr. Kimberly Halsey, an associate professor in the Department of Microbiology at Oregon State University, with identifying the three diversity supplement candidates to work in his laboratory.
- In the chat, Dr. Contreras next asked the mentees how they found their mentor's laboratory. Mr. Kabangu commented that the University of Kentucky's programs allow undergraduate students to conduct research during their freshman year; he selected Dr. Voss' laboratory after attending his course. Dr. Deng began as a linguistics major; he transitioned to science courses and completed an internship in plant science, which led to research in genetics and animal models. He emphasized having an outreach platform to increase awareness of these types of opportunities available to students.

Room 2—Non-COVID-19 Resource Hurdles
Moderator: Elizabeth Bryda, Ph.D., University of Missouri

A. Challenges of Website Management and Data Curation
Elizabeth Bryda, Ph.D., University of Missouri

Dr. Bryda described two major challenges at the RRRC: data curation and website security. The RRRC website includes information on inventory, strains, services, pricing, and protocols. Multiple data sheets on each strain are maintained with links to the Rat Genome Database (RGD). The RRRC has the advantage of sharing personnel with specialized expertise with the MU-MMRRC, which also is located at the University of Missouri. The RRRC accepts 70 to 80 strains annually and maintains an inventory of

more than 500 strains and 6 embryonic cell lines; data are updated and curated online. Because staff are limited, Dr. Bryda manages website data curation; remaining up to date is challenging. Because the University of Missouri does not have an infrastructure to support the structure of the RRRC website, an outside webmaster is used. Website security remains a concern; in 2014, the website was hacked by an animal rights group. On occasion, users are misdirected to a Canadian pharmaceutical company's webpage. Dr. Bryda reiterated the challenges regarding data curation, funding, specialized expertise, and infrastructure to maintain and protect resource websites.

Discussion

- In the chat, Dr. Cheng asked about similar issues that occur at other RRCs. Dr. Jorgensen noted that at the VRC, the volume of requests is significantly less than the RRRC and can be addressed case by case via email, a request form, and one-on-one discussion.
- In the chat, Dr. Yue Liu asked about the possibility of hiring a part-time technician or student to reduce the cost of website and database management. Dr. Bryda explained the difficulty of identifying candidates with the necessary knowledge and expertise.
- In the chat, Dr. Whitworth asked whether specialized web security or institution-based staff control website security issues. Dr. Bryda noted that a webmaster manages and oversees the RRRC website. The order forms are located behind the university's firewall, and security breaches have been related to the external-facing website only.
- In the chat, Dr. Cook noted that the DGRC faces similar challenges for genetic data management. In the chat, Dr. Lloyd asked about lessons learned from other resources that could inform best practices for rodent resources. Dr. Bryda commented that data curation for a website is not her area of expertise. In the chat, Dr. Cheng suggested establishing a CMRD website managers group to address this topic.
- In the chat, Dr. Kevin Cook asked about connection between the resource and databases. Dr. Bryda clarified that the RRRC links to the RGD and soon will connect to the Research Resource Identifiers (RRID) database.
- Dr. Jorgensen called attention to the National Primate Research Centers Consortium's data-sharing platform as a model for a centralized location for the Resource Directors. Dr. Bryda noted that the MMRRC supports a coordinating committee that addresses these types of issues and maintains a resource website portal.
- In the chat, Dr. Aric Daul commented on the challenge of hiring a programmer to design new databases, an ordering system, and a website for the CGC who also has an understanding of genetic nomenclature. The CGC staff also needs an understanding of programming language.

B. Innovative Technologies to Monitor Animal Behavior and Health
Matthew Jorgensen, Ph.D., Wake Forest School of Medicine

Dr. Jorgensen reported the outcomes of the August 25, 2020, ORIP Modernization of Biomedical Research Facilities Workshop. The workshop participants discussed equipment to improve care and maintenance of research animals. Staging essential and smart equipment and increasing efficiencies of animal care facilities were emphasized. Practical considerations included weighing equipment costs against animal care facility improvement needs. Dr. Jorgensen described examples of essential equipment (e.g., cage wash; heating, ventilation, and air conditioning [HVAC]; environmental monitoring; security systems) and highlighted innovative solutions from multiple NHP facilities. Examples included electronic veterinary records with automated email reports, wireless access, electronic bulletin boards, and computational automation. The NHP facilities were staged with smart housing systems that monitor and maintain environmental conditions, robotic DNA/RNA isolation platforms, automated cleaning of technical equipment, and a camera system for remote viewing. The Yerkes National Primate Research Center has installed automated feeders to monitor colonies, and each animal has an identification chip

implanted, alerting staff to potential feeding, social, and/or clinical issues. Among other advanced equipment upgrades to improve care and maintenance of NHPs in research are caging modifications to facilitate animal training and socialization.

C. Developing Networkable Germplasm Repositories
Terrence Tiersch, Ph.D., Louisiana State University Agricultural Center

Dr. Terrence Tiersch explained that the Aquatic Germplasm and Genetic Resources Center's mission is to assist other groups in the development of their own germplasm repositories. Dr. Tiersch stated that large financial investments in genetic resources for aquatic resources have been established, but germplasm repositories are limited. One issue is the lack of translation from research to repositories. Most research in aquatics is focused narrowly on the protocol level, rather than on needs for real-world applications. In addition, protocol standardization across publications and species is nonexistent. Dr. Tiersch described an approach using pathway development, which could help the RRCs establish repositories and necessary capabilities. High-throughput pathways would be protocol-independent and generalizable. Activities at an RRC would include managing the colony, data, and a germplasm repository. Established RRCs can be combined into a network with additional capabilities incorporated. Dr. Tiersch highlighted ZIRC as a model to emulate as a foundation for developing networkable germplasm repositories. He proposed the creation of an NIH Aquatic Biomedical Germplasm Repository Network through such an approach.

Discussion

- Dr. Bryda asked about the feasibility of considering RRC networks for other animal species (e.g., rodents). Dr. Tiersch noted the advantage aquatic RRCs have of being less structured and amenable to front-end system upgrades.
- In the chat, Dr. Cheng noted how the shared elements of networking common among RRCs, including reference analyst services, and strategies for usability could strengthen all RRCs and ORIP-supported research organism efforts.
- Dr. Jorgensen remarked that the network concept would be helpful to alleviate resource hurdles and suggested an independent funding mechanism for resources outside of a center grant.
- Dr. Tiersch emphasized the importance of a multipronged approach and open-source technologies (e.g., 3D printing) to develop open scientific hardware to perform processes (e.g., cryopreserving) that can be standardized. Dr. Tiersch also recommended funding projects at a network level. Dr. Bryda noted that an animal RRC network could provide investigators with a platform to gain insight into best species to address a specific research question.
- In the chat, Dr. Whitworth asked about the cost differences between off-the-shelf live rodents and cryopreserved animals. He further elaborated on maintaining duplicate copies of a living culture for $13 per year in the Bloomington *Drosophila* Stock Center (BDSC). Dr. Bryda noted that cost differences are relative to the species, size, and the cryopreservation method; at the RRRC, purchase of a live animal is $250, whereas a cryopreserved animal could cost as much as $10,000 to resuscitate.
- Dr. Tiersch highlighted that the U.S. Department of Agriculture (USDA) National Animal Germplasm Program (NAGP) is responsible for maintaining a gene bank for all agricultural species. The NAGP's organizational structure could serve as a model for the RRCs. Dr. Tiersch emphasized funding at a higher level as a common resource, with needs associated with communities rather than individual efforts.

Room 3—Strategies for Collecting and Sharing Resource Information
Moderator: Laura Reinholdt, Ph.D., The Jackson Laboratory

A. Collecting and Managing Genetic Information for Stocks
Laura Reinholdt, Ph.D., The Jackson Laboratory

Dr. Laura Reinholdt's presentation focused on the genetic information of mouse strains donated to and housed in the MMRRC at The Jackson Laboratory. Genetically engineered mutant alleles and the genetic background of the strain must be considered. Additionally, when the donated mouse strain contains a new allele, the allele should be named according to a nomenclature checklist. At the MMRRC, curators work with donors to develop strain nomenclature based on critical genetic information. In addition, the allele must be anchored to a genetic sequence with coordinates on a reference mouse genome. Critical information is contained in MMRRC strain datasheets and—when alleles are approved—in the Mouse Genome Informatics organism database. Strains are assigned an official name and a unique RRID.

The MMRRC must overcome multiple challenges, such as gross or genetic contamination of strains. Because approximately 20% of newly donated strains contain genetic contamination, curators must employ quality control measures. The donors and curators implement technologies and practices to ensure the genetic factors contributing to phenotype are characterized, recorded, communicated, and stabilized. These measures ensure reproducibility and usability. Strain information also must be managed after it has been deposited in the repository; updates must be applied to all genetic coordinates in strain datasheets. Management is aided by automated feeds and integration with data resources, and the MMRRC relies on ongoing curation following community standards. In addition, MMRRC curators are integrating such new data types as microbiome data, alternate genome assemblies, and strain data for mice with genomic backgrounds that do not align with the traditional mouse reference genome.

B. Compiling Antibody Information Across Models and Resources
Diogo Magnani, Ph.D., MassBiologics, University of Massachusetts Medical School

Dr. Diogo Magnani presented plans and actions from the Nonhuman Primate Reagent Resource (NHPRR) regarding the compilation of antibody information and integration with other resources. The NHPRR provides a means of acquiring reagents with a focus on antibodies. Antibodies are precise tools, but biological and experimental factors can lead to unexpected interactions. Thus, proper antibody validation is critical. The NHPRR established a user-contributed reagent reactivity database with data from NHP studies. These data are submitted by investigators and are included on the NHPRR website. The website database indicates the reactivity of therapeutic molecules in NHPs and is connected to information from the ImMunoGeneTics information system.

The NHPRR intends to integrate scientific literature, but doing so is challenging because NHPRR resources often are cited incorrectly or inconsistently. RRIDs were associated with reagents in the most recent update to the NHPRR website, which should improve citations and facilitate the extraction of reagent information from publications. The website is integrated with SciCrunch, which has enabled new reagent citations to be connected to the website's main pages. NHPRR staff will continue implementing similar integrations that will mediate transactions with other entities. For example, they plan to associate antibody reactivity data with the macaque Genotype And Phenotype Database (mGAP) to create new genome-based reagent selection tools. These emerging forms of data integrations across models and resources have the potential to enrich and aggregate research information, assist with correct reporting, and enhance research rigor.

C. The Animal-GRIN Database
Harvey Blackburn, Ph.D., NAGP, Agricultural Research Service, USDA

Dr. Harvey Blackburn's presentation focused on agricultural species and genetic diversity. The Agricultural Research Service of the USDA works with RRCs to back up agricultural species collections, and the NAGP has developed the Animal Germplasm Resources Information Network (Animal-GRIN) to accommodate inventory management. Animal-GRIN consolidates resources among the United States, Canada, and Brazil, with cross-country data sharing. Animal-GRIN is web-based, dynamic, and comprehensive; the database is accessible and searchable.

Animal-GRIN's public interface has increased the use and impact of the NAGP collection. Primary users include data entry management organizations from the United States, Brazil, Canada, Mexico, and Australia, as well as stakeholders (e.g., researchers, livestock producers, industry geneticists, government agencies). This use has increased the return on investment for the NAGP. Greater accountability for Animal-GRIN can be achieved via increased data sharing and more comprehensive databases, as well as reports on how to use samples from the repository. The host website will require constant renovation and periodic redesigns.

Dr. Blackburn concluded his presentation by highlighting the following key thoughts: (1) biologists tend to underestimate the value and effort required to build effective databases, which can impede data sharing and information exchange; (2) data sharing and information exchange also can be impeded by the use of antiquated methods; (3) a highly visible and useable database builds program integrity; and (4) effective strategies for collecting and sharing resources often utilize databases and information systems.

Discussion

- In the chat, Dr. Reinholdt asked about assessments of breed using genotype arrays. Dr. Blackburn stated that multiple methods are in use for genotyping livestock populations, including methods using commercially developed genotyping chips. Genotyping data and samples are stored and made publicly available by the NAGP.
- Dr. Reinholdt asked whether the genotype information stored by the NAGP is anchored to locations in a sequenced genome. Dr. Blackburn responded that all NAGP data have been produced by genotyping the sample using a commercial chip, which enables the anchoring of genetic information to genome features and parts of genes.
- Dr. Reinholdt commented that her team detects gross and genetic contamination using the miniMUGA platform, which facilitates the determination and validation of the strains' genetic backgrounds. miniMUGA provides high-resolution information on the percentage of the genome in a particular animal strain that comes from a specific genetic background.
- In the chat, a participant asked how users can be encouraged to engage in the collection and maintenance of updated information about repository resources. The participant also asked about concerns about the quality of the information submitted by users. Dr. Magnani responded that the quality of the information is bolstered by the display of information, such as the tests with which antibodies were validated.
- In the chat, Dr. Lossin voiced support for a "wiki" curation approach, noting that moderation and engagement would be critical. He also asked about design considerations when developing a user interface for repositories and databases. Dr. Magnani stated that he made the database display as simple as possible for users. He also built the website one component at a time to ensure that the integrated tools would interact properly at each stage of development.
- In the chat, Dr. Lossin emphasized the importance of persistent resource identification. He also noted that combination of genetic backgrounds and legacy nomenclature present challenges for curation.

- Dr. Magnani proposed several ideas to encourage more user engagement, including posting a table with the names of top contributors, creating a vendor category for users, developing a matching game with manuscripts and the reagents used in the manuscript's study, and allowing users to register individual accounts. Dr. Magnani asked participants to send him additional ideas.
- In the chat, Dr. Sam Zheng asked for more information on the use of SciCrunch for searching lists of RRIDs.

Room 4—Outreach: Examples and Best Practices
Moderator: Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

A. The National Natural Toxins Research Center: Engaging the Venomous Community
Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

Dr. Sánchez's presentation focused on the NNTRC. Sophisticated laboratory instrumentation enables the purification and identification of venom molecules, testing to identify the activity of venom molecules, and cloning of important molecules to increase yields for testing and reduce dependence on snakes for venom. Venoms can be a drug source, with some purified venom toxins proving to be therapeutic when prescribed at modest doses. Additionally, venomous snakes are a significant public health concern. Antivenoms can be costly and difficult to acquire, with many causing undesirable side effects. Researchers have been working to improve antivenoms. Strategies in this area include searching for different sources of antivenom molecules, utilizing bacteria phages to produce antidotes, synthesizing antivenom molecules, repurposing drugs, utilizing humanized antibodies, and working with small proteins from animals that are naturally resistant to snake venom. The NNTRC collaborates with other groups, investigators, and projects to study venom and develop antivenoms. The NNTRC also engages the venomous community through publications in journals specializing in toxins or venoms, conferences focused on toxinology, student outreach and training programs at the NNTRC, and social media outreach.

B. The First 10 Years of the National *Xenopus* Resource: How We Reach Our Customers
Marko Horb, Ph.D., Marine Biological Laboratory

Dr. Horb presented on the NXR, which hosts a website through which investigators can order strains and join the *Xenopus* listserv. From 2016–2021, 169 new mutant *Xenopus* strains were engineered, including 109 first-generation mutants and 50 second-generation mutants. NXR staff are engineering additional mutant strains and optimizing the methods by which new mutant strains are generated. NXR is encouraging community engagement and the development of additional mutant *Xenopus* strains by outside investigators. The NXR and Marine Biological Laboratory (MBL) have supported and established long-term collaborations with many researchers. NXR and MBL also host workshops and the *Xenopus* Resources and Emerging Technologies Meeting. NXR participates in the International *Xenopus* Conference, hosts the Xine listserv, and works closely with Xenbase. Challenges include issues related to *Xenopus* distribution. Training workshops include necessary costs that remain prohibitively expensive for many small laboratories. Additionally, the NXR works to reach as many people as possible via conferences and advertises its services through listservs.

C. Making New Connections in the Virtual World
Thomas Bell, Ph.D., National Disease Research Interchange

Dr. Thomas Bell's presentation focused on the work of the National Disease Research Interchange's Human Tissue and Organ Research Resource (HTORR), which was established to provide human biospecimens to advance biomedical research, development, and education. The HTORR has a broad reach, covering many different body systems and supporting researchers with varied research interests. The HTORR enables access to normal and diseased human biospecimens, and the process by which these

donations are acquired is customized to fit each researcher's precise needs. The HTORR finds new investigators through referrals, email blasts, and research conferences. Because most in-person conferences were canceled during the COVID-19 pandemic, HTORR staff members attended virtual conferences. New methods must be established to accommodate the ongoing need to identify new investigators at virtual meetings. The COVID-19 pandemic also has shaped HTORR outreach via the adoption and use of GlobalData. The HTORR promotes new and existing services via websites, Google Ads, social media, electronic advertising at conferences and journals, and press releases. The HTORR also tracks publications through PubMed searches, which identifies approximately 10% of publications citing HTORR resource use, and Google Scholar, which identifies approximately 90%.

Discussion

- Dr. Franklin asked whether the HTORR includes a memorandum describing how to cite products in publications. Dr. Bell said that the HTORR provides this information and emphasizes the importance of proper citations. The products are not always cited properly, and HTORR staff are working to improve this issue.
- In the chat, Dr. Franklin inquired about the use of RRID numbers. Dr. Horb stated that the use of RRID numbers facilitates the citation and search processes. NXR staff include resource citation instructions in emails to users.
- In the chat, Dr. Franklin asked whether a broad-based presentation describing all the ORIP-supported resources should be developed and distributed. Drs. Horb and Bell cautioned that doing so would require a very large presentation or would be very general.
- In the chat, Dr. Schmale asked how resource groups manage the costs of website design and maintenance and whether these costs could be covered by P40 or other ORIP grants. Dr. Sánchez responded that groups must seek other sources but added that they can direct funds from existing grants.

Session III

Administrative Practices at NIH-Supported Resources

Gavin Wilkom, M.I.M., National Heart, Lung, and Blood Institute
Moderator: Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP

Mr. Wilkom presented an update on NIH grants management. He explained that updates to forms (e.g., biosketches, other support pages) support the need for applicants and recipients to provide full transparency and disclosure of all foreign and domestic research activities. A signature is required for all key personnel to clarify accuracy. The updates are preferred and expected immediately and will be required by January 25, 2022. More information is available at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-073.html, and questions about biosketches can be directed to nihosbiosketch@nih.gov.

Investigators can apply for COVID-19 and administrative supplements. Mr. Wilkom explained that most COVID-19 supplements are administered via the CARES Act, which permits automatic carryover authority even if the parent award does not have this same authority. If ORIP—or another NIH ICO—funds the supplement, however, the carryover reflects that of the parent award. Mr. Wilkom stated that NIH staff members have been asked to provide as much flexibility as possible for prior approval requests related to COVID-19 supplements. Administrative supplements, in contrast, follow the same budget period end date as the parent award. No-cost extensions are prohibited, although revision supplements may be requested. The scope of the parent award allows for the supplement research to continue, but carryover of funds must be requested separately.

Changes to the submission of federal financial reports (FFRs) have occurred. Since January 1, 2021, FFR submission has occurred through the NIH Payment Management System. The NIH has acknowledged issues with reporting requirements in the system and has enabled additional flexibility by designating the documents as interim annual reports. Mr. Wilkom explained that the closing of subaccounts after 120 days has caused issues for recipients; a process has been established for requesting submissions on closed accounts.

Mr. Wilkom concluded by sharing additional details of interest. He shared a link for the NIH Strategic Response to COVID-19. He noted that the NIH is providing up to $2,500 in annual childcare costs for fellowship awardees; more information on availability to training grant recipients will be available in early fiscal year 2022. Lastly, he informed the participants of the Prohibition for Covered Telecommunications Equipment or Services.

Discussion

- In the chat, Dr. Zelhof asked whether the FFR should be filed for the competitive segment first when requesting approval for carryover funds from supplement grants. Mr. Wilkom explained that carryover requests must be submitted with an FFR in place; the most recent FFR is preferred, but system issues have necessitated leniency in review of FFRs. An unobligated balance still must be confirmed.

Development and Application of Innovative Tools and Integrative Approaches
Moderator: Keith Cheng, M.D., Ph.D., The Pennsylvania State University

A. How Spatial Context Nucleates Multiscale Multi-omics
Keith Cheng, M.D., Ph.D., The Pennsylvania State University

Dr. Cheng presented the idea of using computational phenomics to measure histological changes for the study of tissues and whole organisms in health and disease across all of phylogeny. Histotomography, a customization of micro-CT, represents a new imaging technology that comprises a critical framework for computational phenomics. Histotomography is aimed at enabling full-volume histological analysis and quantitative analysis. The idea was inspired by the principle that every living thing is composed of cells, and every disease is associated with microscopic 3D tissue change. Visualization of these changes are described but are not yet practical to be sampled more than 1–2% in 2D; further, the changes cannot yet be measured computationally. Small, crowded cells overlap. Additionally, because some cells (e.g., cancer cells) are larger than the typical 5 µm slice thickness, histological representations poorly recapitulate the features of whole cells. The Geometry of Life and Disease Project aims to characterize visually and mathematically every cell, tissue, organism, and life stage in health and disease. Goals of the project are to (1) phenotype every cell type, tissue, organ, and organism; (2) allow that phenotyping to be computational so that it is more accurate, objective, quantitative, and reproducible than current 2D, descriptive phenotyping; (3) make phenotyping 3D and inclusive of cell and tissue volume, shape, and texture; (4) study tiny and deep structures in intact animals that are not as accessible using light-based technologies, such as fluorescence; (5) enable crowd-sourced labeling and discovery; (6) make valuable samples permanent for reimaging; and (7) make it practical to automatically compute complete, quantitative, objective, whole-organism 3D phenotypes across cell types, organ systems, and length scales. Dr. Cheng briefly outlined the process of image acquisition, which is based on synchrotron micro-CT, and presented 3D renderings of zebrafish. He highlighted ways in which histotomography provides capabilities that are not possible using histology. Methods for cell-specific staining are being established presently, and histotomography is being developed in other organisms (e.g., *Daphnia*, for which a video was shown). Dr. Cheng concluded that computational phenomics will yield improved insight into gene function, more rational environmental regulation, and quantitative diagnostics.

B. Fly Tools and Approaches to Diagnose Human Diseases
Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine

Dr. Hugo Bellen presented his research, which is aimed at advancing basic science and medicine by studying human genes associated with diseases in flies. These efforts are important for diagnosis of rare diseases, elucidation of pathogenic mechanisms of diseases, drug discovery, and discovery of gene functions. He explained that the research is driven by definition of orthologous phenotypes for human genes with variants of unknown significance. CRISPR-mediated integration cassette (CRIMIC) technology is used to disrupt genes, excise cassettes, exchange cassettes, and express upstream activation sequence (UAS) constructs. Using this approach, Dr. Bellen's team is developing an "off-the-shelf" library of about 9,000 UAS-human cDNA constructs for expression in *Drosophila*. This approach has been used for identification of *ANKLE2* mutations associated with microcephaly. Since 2016, the technology also has been used for diagnosis through the Undiagnosed Diseases Network. *ACOX1* has been implicated in a progressive metabolic disease; the approach has provided insight into the mechanism of loss- and gain-of-function mutations in this gene.

C. Development of Tools for Site-Directed Analysis of Gene Function
Maura McGrail, Ph.D., Iowa State University

Dr. Maura McGrail presented on the development of tools for site-directed analysis of gene function. She spoke on the use of microhomology-mediated end-joining for precision-targeted integration at DNA double-stranded breaks. Dr. McGrail's team developed a series of vectors for integration and secondary markers that allow for simple visual genotyping of alleles. Her team is applying the GeneWeld integration strategy to advance Cre recombinase genetics in zebrafish and to improve methods for precision gene editing. She explained that robust cell type–specific, spatial, and temporal regulation of gene activity is needed in various organisms. Loss-of-function mutations lead to lethality during embryonic development, which complicates the study of gene function; pleiotropy also complicates phenotypic interpretation. Dr. McGrail's team generated endogenous proneural Cre drivers using GeneWeld. They also developed a Universal Flip vector series for floxed conditional alleles. This approach enabled a simple and universal conditional vector design, a robust and reproducible knockdown of gene expression, and recapitulation of loss-of-function phenotypes at morphological and cellular levels. A conditional gene rescue system allows for targeted integration. The system was validated in zebrafish via conditional gene inactivation. Dr. McGrail's group now is expanding community resources for Cre recombinase genetics. They have distributed vectors to other laboratories from 60 institutes and 15 countries.

D. mGAP: A Broadly Used Macaque Genotype and Phenotype Resource to Expand NHP Research
Betsy Ferguson, Ph.D., Oregon National Primate Research Center

Dr. Betsy Ferguson presented on mGAP, which was inspired by the growing momentum for precision medicine (e.g., gene therapy). She explained that NHPs are well-suited for precision medicine research because of their similar anatomy to humans. Parallel NHP models for human genetic disease are needed. Dr. Ferguson stated that the goals of mGAP were to (1) establish a comprehensive NHP genomic data resource, (2) attract a broad range of investigators and clinicians who are new to NHP research use, and (3) leverage variant data and collaborations to develop and characterize genetically parallel NHP models for human disease. Dr. Ferguson's team thus far has produced, collected, and analyzed 2,329 rhesus macaque genomic data sets. From those data, more than 42 million variants were detected using a consistent analysis pipeline, and about 4,000 associated phenotypes were predicted. Researchers can search mGAP by disease of interest, gene name, or predicted pathogenic variants. Data annotations provide information on allele position, translational effect, pathogenicity, gene–trait association, allele conservation and frequency, and link to animal genotypes. To date, the mGAP has been accessed by 410 registered users from about 130 institutions; these numbers continue to increase. The mGAP data are

used for comparative, population, and functional studies. The data also have been used to support other NIH resources and to support NHP disease model discovery (e.g., Bardet-Biedl syndrome). Future plans for mGAP include continued expansion of genomic sequence data, continued user base growth, and multi-center efforts to identify and study new disease models.

Discussion

- In the chat, Dr. Clark asked whether the effects of large-molecule drugs can be tested in *Drosophila*. Dr. Bellen responded that this capability is dependent on the ability of the drugs to cross the blood–brain barrier (BBB), as well as their water solubility. He commented that the drug concentrations for humans are applicable to flies.
- Dr. Cheng asked about large-molecule drugs in other organisms (e.g., fish, NHPs). Dr. McGrail stated that the BBB of fish allows for screening drugs for their ability to cross the BBB in humans. Drs. Bellen and Ferguson agreed that similar applicability is available for flies and NHPs.
- In the chat, Dr. Voss asked whether the vectors are being applied to animal models other than zebrafish. Dr. McGrail stated that the vectors are being used in mammalian cells (e.g., pig cells). Researchers from the cavefish community also have requested the vectors. She stated that the approach should work in other model systems.
- Dr. Cheng asked Dr. Bellen for his insight on when to move from "fast" models (e.g., *Drosophila*) to other models. Dr. Bellen stated that he begins working with *Drosophila* or zebrafish and moves to mice after pathogenicity of the mutations has been demonstrated. The experiments in mice progress from knock-out to knock-in to gene therapy.
- Dr. Bellen commented that CRISPR technology provides insight on gene and protein functions and understanding of disease processes. He expressed interest in including NHP data in the Model organism Aggregated Resources for Rare Variant ExpLoration (MARRVEL) database.
- Dr. Ferguson noted that CRISPR-based models are being pursued presently in NHPs but stated that natural models continue to provide benefits for researchers (e.g., speed, availability).
- Dr. Cheng inquired about resources (e.g., molecular, imaging, physiological) needed for integration across model organisms. Dr. Ferguson commented that this topic should be given consideration in the future. She suggested pursuing development of resources similar to the germplasm collection. Dr. Bellen emphasized the importance of performing transcriptomics, single-cell sequencing, phenotyping (e.g., behavior), and metabolomics to produce signatures that can be crossed between different organisms. Dr. Cheng commented that spatially resolved RNA sequencing represents an area that will provide powerful capabilities for research.
- Dr. Chalker asked about heterozygous advantages for variants in NHP populations. Dr. Ferguson stated that population diversity should be maintained. Specific advantages of heterozygosity, however, have not yet been detected. She noted that some carriers appear to be prolific breeders.

DAY 2: WEDNESDAY, AUGUST 4, 2021

Session IV

Introduction

Franziska Grieder, D.V.M., Ph.D., Director, ORIP

Dr. Grieder welcomed the participants to Day 2 of the meeting. She stated that the participants were asked to comment on four discussion questions related to the NIH Advisory Committee to the Director (ACD) report titled "Enhancing Rigor, Transparency, and Translatability in Animal Research." The recommendations in this report, if approved, would affect the biomedical research community and animal RRCs. ORIP is working to address the recommendations. The present discussion will focus on

Recommendations 3.2 and 4.3. She suggested generating a list of action items for strategic engagement opportunities, with a focus on broad questions.

Group Discussion—Rigor, Reproducibility, and Translatability
Moderators: Malgorzata Klosek, Ph.D., Director, DCI, ORIP
Kent Lloyd, D.V.M., Ph.D., University of California, Davis
Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP

Dr. Murphy reminded the participants that ORIP supports RRCs for a broad array of animal models; the RRCs specialize in animal model acquisition, validation, creation, preservation, maintenance, and distribution. The RRCs serve as intellectual infrastructure for the research community.

Questions A and B focused on developing research-related expertise, standard operating procedures (SOPs), and best practices in response to Recommendation 3.2: "The NIH should establish or identify venues for the exchange of information related to animal model design and characterization, study design, and general best practices." Questions C and D focused on improving methodological documentation and reporting of results in response to Recommendation 4.3: "The NIH should encourage and support work to better understand, monitor, record, and report important extrinsic factors related to animal care that might impact research results."

A. What types of services and research activities are being, or should be, provided by RRCs relative to assistance with study design, statistical analysis, phenotyping, feasibility, utility, and pilot studies for proof of principle?

Dr. Cook stated that in the *Drosophila* community, the complexity of the model organism presents challenges for investigators. Many researchers are unaware of experiments and appropriate stocks. Dr. Cheng suggested developing a mechanism for discussions with clinicians on experimental design. Study designs should be adaptable to new knowledge and circumstances, and statistics should consider such issues as sampling and comprehensive phenotyping. Dr. Cheng also emphasized the importance of developing technologies for complete phenotyping.

In the chat, Dr. Rougvie commented that for RRCs with smaller staffs, providing experimental design services is challenging. In the chat, Dr. Amos-Landgraf added that the MU-MMRRC is unequipped to provide these services. He emphasized the importance of statisticians as a resource for RRCs and users. Dr. Sánchez agreed on the need for guidance from statisticians on study design and interpretation. Dr. John Postlethwait suggested that the NIH develop statistical modules for animal models; the RRCs could make the modules available through their websites. In the chat, Dr. O'Connor suggested providing examples of exemplar manuscripts that have used RRCs successfully.

In the chat, Dr. Chang inquired about whether Directors promote their RRCs at national meetings. Drs. Bryda, Cheng, Daul, Franklin, Horb, Sánchez, and Zelhof affirmed that they are involved in these efforts. In the chat, Dr. Ferguson commented that outreach presentations at conferences can help show how RRCs address unique needs for users and allow for integration. In the chat, Dr. Cheng suggested launching a YouTube channel; approaches to maintain high standards should be discussed. Dr. Cook responded that coordination with model organism databases also should be considered for phenotyping efforts.

In the chat, Dr. R. Balfour Sartor noted that he has also presented at national meetings and meets with investigators to discuss study design and feasibility. Pilot proof-of-principle studies can help conserve time and resources. He added that he works with investigators to phenotype mice more efficiently.

Dr. Bellen underscored the importance of supporting resource databases. In the chat, Dr. Rougvie echoed support for databases. In the chat, Dr. Blackburn stated that phenotyping databases can serve as a resource for investigators. In the chat, Dr. Chalker expressed support for resources to integrate data across databases and stock centers. Dr. Reinholdt noted that the mouse genome database includes a tool to identify models with an allele of interest through different repositories. In the chat, Dr. Jack Koch suggested developing a centralized portal that includes all biomedical models; community interaction is crucial. In the chat, Dr. Daul stated that the CGC works with WormBase to ensure data remain updated between databases.

B. What are the needs and challenges for RRCs to disseminate their specialized knowledge, standard operating procedures, and best practices related to animal model design, characterization, and use to researchers and among RRCs?

Dr. Lloyd noted that several participants submitted responses to this question prior to the meeting. Needs included assistance with and greater emphasis on dissemination (e.g., for consistency in formats), tabulation (e.g., best practices, unanswered questions), and epigenetic components of phenotype. In the chat, Dr. Franklin commented that the MU-MMRRC offers study design consultation for genomic research (e.g., sample size). Analysis and interpretation are offered as part of collaborative studies. Dr. Lloyd stated that collaboration is crucial for the dissemination of knowledge.

Dr. Postlethwait stated that some general principles apply to phenotyping for all model organisms; other principles are more specific. The principles ultimately must relate to humans. He suggested undertaking a general effort to identify these principles. Dr. Lloyd noted that the Monarch Initiative and MARRVEL pursue similar efforts; he wondered whether strategies should be employed to better engage these resources. In the chat, Dr. Westerfield stated that the Alliance of Genome Resources is pursuing similar efforts but is reliant on model organism databases.

Dr. Cheng added that reference atlases for human disease are important to allow current and potential users of model systems to compare their model with actual human disease. Dr. Bellen stated that model organism databases compile lists of genes related to human disease. He emphasized the importance of considering the interplay between databases and stock centers. Dr. Lloyd asked about approaches for this effort. Dr. Bellen stated that all NIH ICOs must provide a coordinated support system for a long-term vision plan. In the chat, Dr. Koch stated that clear documentation of unique identifiers and adherence to communication standards are crucial.

Dr. Reinholdt stated that the MMRRC is assessing and revising SOPs as needed; these are made available online. She noted that different RRCs likely will require slightly different protocols. Additionally, effective dissemination of this information and guidance must be ensured. She suggested organizing workshops at conferences. She added that the MMRRC actively assesses study designs based on new models and user feedback; that information can be applied for establishment of best practices.

In the chat, Dr. Sartor emphasized the importance of documenting and sharing SOPs to eliminate redundancies and improve protocols. Challenges for reaching consensus include different environments and ingrained procedures. In the chat, Dr. Amos-Landgraf commented that the MMRRC has established committees to review SOPs, which are available on the MMRRC website; a centralized website involving all resources would be beneficial for fostering community interactions. In the chat, Dr. Koch suggested disseminating information for SOPs to RRC websites, social media, and listservs. In the chat, Dr. Jorgenson noted that publication of SOPs can be challenging. In the chat, Dr. Rougvie suggested using micropublications to provide a broader reach.

In the chat, Drs. Clark and Jorgenson stated that they work with users directly to provide support and guidance. Dr. Clark added that teaching sessions (e.g., workshops, videos) would be useful.

In the chat, Dr. Franklin noted that investigators' schedules often make dissemination through real-time webinars and Zoom conferences a challenge. He suggested developing a series of short courses on the topic, noting that they could be tied to the grant application process as a benefit for investigators.

C. How can you support outreach to the research community about the importance of accounting for extrinsic factors (e.g., ambient temperature, microbiota, lighting levels) in animal-based research?

Dr. Murphy noted that several participants submitted responses to this question prior to the meeting. One commenter stated that the NIH can support community-based efforts to raise awareness. Another commenter stated that this concern should be communicated to veterinarians and colony managers.

Dr. Martinez stated that all members of the community share responsibility for this topic. Knowledge-sharing and broad awareness is crucial. She noted that this topic could be incorporated into Institutional Animal Care and Use Committee (IACUC) training, and the NIH could develop a short course for IACUC members. Additionally, IACUCs can develop questions on this topic for investigators to consider. Information should be shared among research groups when it is acquired. In the chat, Dr. Horb suggested that ORIP fund workshops for information sharing. In the chat, Dr. Chalker noted that the NIH supports many conferences; he suggested supporting workshops centered on extrinsic factors.

In the chat, Dr. Horb noted that the *Xenopus* community has raised concerns about factors for husbandry. Integrating NXR data into Xenbase is important, but funds for this effort are limited. In the chat, Dr. Varga noted that the zebrafish community faces similar issues; husbandry standardization efforts have been beneficial for reproducibility. Another commenter stated that water quality and temperature are crucial, but these variables rarely are reported in publications. In the chat, Dr. Bryda commented that requirements by journals for description of extrinsic factors would be helpful. Dr. Sánchez asked how often the Animal Research: Reporting *In Vivo* Experiments (ARRIVE) guidelines 2.0 are employed by investigators. Dr. Murphy noted that this issue was raised in the ACD report's discussion about another recommendation; presently, requirements are at the journals' discretion. In the chat, Dr. Allison Rogala stated that these guidelines should be emphasized.

In the chat, Dr. Koch stated that open-source scientific hardware offers opportunities to provide widespread reproducibility and monitoring abilities among communities. Dr. Tiersch added that interdisciplinary teams provide value for this effort. In the chat, Dr. O'Connor asked whether extrinsic factors represent an additional area of complexity in resources; he emphasized the importance of providing awareness for investigators. Dr. Reinholdt noted that extrinsic factors are understood, but the consequences often are unclear. Additionally, investigators often are unsure how to control for or address these factors. Dr. Reinholdt suggested focusing on factors with larger amounts of associated data. Dr. Murphy noted that the ACD report is focused on identifying extrinsic factors.

Dr. Murphy shared additional comments that were submitted in advance. One commenter stated that at their RRC, these issues are included in the methods sections of manuscripts and discussed with investigators. Their RRC's Co-Director is trained in comparative medicine and is involved in these discussions.

D. Beyond additional funding or financial resources, what tools does your Center need to improve monitoring, controlling, recording, and documenting extrinsic factors that affect research outcomes and reproducibility?

Dr. Lloyd noted that several participants submitted responses to this question prior to the meeting. One commenter stated that the zebrafish centers use circulating systems that monitor water conditions automatically. Data loggers with remote access, monitoring software, autoclaves, advanced caging systems, and video equipment would be beneficial across the RRCs.

In the chat, Dr. O'Connor stated that monitoring, controlling, and documenting are staff-intensive activities; automated recording would be beneficial, but personnel still are needed for processing and analysis. In the chat, Dr. Rogala suggested that ORIP fund small grants to support studies of extrinsic factors. Dr. Tiersch noted that recent advances in technology have extended biologists' capabilities for use of monitoring and controls. He emphasized that this hardware could serve as a form of outreach. In the chat, Dr. Michael Tyers noted that human-based monitoring and analysis is not scalable for large data sets and data streams; he suggested implementing artificial intelligence–based approaches to address extrinsic factors. In the chat, Dr. Chalker noted that the topic of extrinsic factors underscores the importance of coordination between databases and stock centers. In the chat, Dr. Lossin emphasized the importance of user-friendly online interfaces and considering reproducibility at the onset of studies.

Dr. Postlethwait noted that the monitoring of microbiota is beneficial, but this metric is challenging to assay. Support for RRCs in this area, as well as specialized expertise for interpretation and application, would be beneficial. Dr. Lloyd added that microbiome analysis involves several technical areas for consideration; he suggested that the RRCs work collaboratively in this area. In the chat, Dr. Cheng commented that microbiota analyses could be complemented by other molecular analyses of the environment that they create; standardization of these analyses would enable cross-comparisons of results. In the chat, Dr. Daryl Gohl suggested genotyping stock collections to confirm unexpected contamination.

In the chat, Dr. Chalker noted that this issue underscores the importance of communication between stock centers and databases. In the chat, Dr. Clark raised concern that many users might be apprehensive about the implications of microbiome data for their research. Dr. Cheng responded that these data help users anticipate issues or gain insights on unexpected results. In the chat, Dr. Sartor stated that standardization and validation of microbiota present an opportunity for RRCs to expand their value for the research community. In the chat, Dr. Clark agreed but noted that the standards must be agreed on. In the chat, Dr. Lloyd added that the RRCs should be considered an extension of users' laboratories, and their ability to provide experimental services should be emphasized.

E. General Discussion

Dr. Lloyd invited the panelists to discuss other aspects of the report. Dr. Cheng emphasized that phenomics studies must acknowledge existing technological limitations for phenotyping.

COVID-19: Lessons Learned
Moderator: Cale Whitworth, Ph.D., Indiana University Bloomington

A. Learning to Fly Again: Lessons from the COVID-19 Pandemic at the Bloomington *Drosophila* Stock Center
Cale Whitworth, Ph.D., Indiana University Bloomington

Dr. Whitworth presented lessons from and impacts of the COVID-19 pandemic at the BDSC. He first provided a brief overview of the BDSC, which maintains strains in duplicate copies. At the beginning of the pandemic, large- and small-scale cryopreservation of *Drosophila* was infeasible, requiring maintenance of live strains. These efforts require manual labor within a small space. An active research program also is in place at the BDSC. During the first several months, activities were limited to maintenance of live strains. Dr. Whitworth emphasized the importance of being as proactive as possible; these efforts included designating essential staff in advance, ordering extra supplies as needed, and developing a formalized plan for curtailing operations (e.g., ranking fly stocks). He noted that the BDSC's productivity decreased during the pandemic; managerial staff spent time and resources on responding to the pandemic that normally would be directed at other aspects of operations. Additional challenges included financial impacts; increased expenses for maintenance of fly stocks were combined with decreased program income. Dr. Whitworth noted that a funding mechanism within the P40 program for financial disaster plans would be beneficial in the future.

B. JAX Mouse Models of COVID-19: New Models and Applications
Cathleen Lutz, Ph.D., The Jackson Laboratory

Dr. Cathleen Lutz presented on the challenges and opportunities of the COVID-19 pandemic at The Jackson Laboratory. She began by acknowledging that depopulation of laboratories across the research community led to marked decreases in mouse distribution. The Jackson Laboratory worked with investigators during this time to ensure flexibility for orders. Additionally, the demand for cryopreservation increased in response to depopulation. Service requests for breeding and efficacy testing also increased as biotechnology and pharmaceutical companies worked to preserve their investment programs. The Jackson Laboratory also worked quickly during the pandemic to identify ACE2 models for the community. The team implemented an unprecedented scale-up of mice using *in vitro* fertilization to meet the research community's demand for these models; full-scale production to demand was in place by June 2020. The model now is being distributed globally, and new models are in development. Because COVID-19 presents a broad array of symptoms, development of animal models is challenging. Dr. Lutz briefly outlined efforts to develop mouse models for COVID-19 that mimic human variation. She also highlighted the establishment of a COVID-19 testing center at The Jackson Laboratory. She concluded by emphasizing the importance of ensuring employees' safety, continuing to serve the scientific community, and providing additional services as needed during challenging times.

C. COVID-19 Lockdown and Recovery at the Zebrafish International Resource Center
Zoltan Varga, Ph.D., University of Oregon

Dr. Varga presented on the impact of the COVID-19 pandemic at ZIRC. He highlighted ZIRC's core functions as a repository, diagnostic center, and health resource for users. He explained that an existing preparedness plan—involving pre-emergency planning, crisis management, and post-emergency/recovery planning—was in place through the University of Oregon at the onset of the pandemic. Key programmatic functions (i.e., cryorepository, live animals, database) were identified. Potential scenarios were developed with reference to the SARS-CoV-1 and MERS outbreaks. Other scenarios include earthquakes and fires. Dr. Varga noted that this process involves staff cross-training and annual plan revisions. In March 2020, only critical ZIRC staff were allowed to access the facility to perform animal

care and monitoring. Staff increases and resumed activities were initiated in a phased approach between May 2020 and June 2021. Challenges of the pandemic have included loss of business and revenue, staff reductions and layoffs, slow recovery of business, backlogs (e.g., fish lines, routine cryopreservation, health services), declines in colony health, remote work for staff, and sourcing of materials. The Holiday Farm Fire in September 2020 created additional challenges for air quality. Dr. Varga emphasized the value of support from the community (e.g., resource sharing), improved preparedness planning for future emergencies, increased resiliency, support and guidance from the university, supplementary funds from the NIH and ORIP, and new tools that will provide additional capabilities moving forward (e.g., Zoom/Microsoft Teams, cross-training, rotation of tasks). He emphasized the importance of resource resilience in dealing with unexpected challenges.

Discussion

- In the chat, Drs. Bryda and Daul commented on the challenges of domestic and international shipments during the pandemic. Dr. Lutz explained that The Jackson Laboratory uses its own domestic courier system, but overseas shipments continue to present a challenge. Dr. Varga agreed and noted that shipping delays must be anticipated. Dr. Whitworth also agreed, noting that the BDSC has continued to recommend using a courier system. He added that the withdrawal of the United Kingdom from the European Union ("Brexit") also created challenges for some international shipments. Dr. Varga emphasized the importance of open communication with investigators.
- In the chat, Dr. Daul stated that maintaining a large supply of critical non-perishable supplies has been beneficial. Dr. Whitworth noted that the BDSC's greatest need has been ingredients for fly food. He noted that space can impose limits for long-term backlog storage, but areas for long-term storage now are being established within the BDSC. Dr. Varga stated that food supplies were not limited at ZIRC, but cryovial shortages have imposed issues. Dr. Varga added that other reagents have been delayed at various points; proactivity is crucial. Dr. Lutz noted that surgical and N95 masks represented the greatest supply issue at The Jackson Laboratory; alternative arrangements were implemented to address this issue.
- In the chat, Dr. Rashida Moore asked whether the pathogen issues at ZIRC resulted from the decrease in staffing. Dr. Varga agreed that this might have been the case; the fish were maintained in a single water system during the time, and the system might have been overburdened.
- Dr. Whitworth underscored the value of connecting with other emergency preparation teams to develop connections in anticipation of future emergencies. Dr. Varga suggested that RRCs share their emergency preparedness plans in future meetings. Dr. Lutz added that her facility holds drills for various scenarios; these exercises are valuable for emergency preparedness.

Session V

Breakout 1 Summary—Promoting Diversity in Comparative Medicine

S. Randal Voss, Ph.D., University of Kentucky

Breakout Session 1 was focused on promoting diversity through the Diversity Administrative Supplement Program, which was established to increase the number of biomedical researchers from underrepresented groups. Dr. Fuchs oversees the diversity supplement program for ORIP. Three mentor–mentee pairs shared their perspectives on the diversity supplement program. Dr. Kent and Mr. Schuster elaborated on their research work developing an assay to quantify and assess the impact of *P. neurophilia*, a persistent pathogen in zebrafish facilities. Mr. Kabangu and Dr. Voss developed tests monitoring pathogens, such as the chytrid fungus, that could impact the health of axolotls at the University of Kentucky stock center and in the larger axolotl community. Dr. Nolta discussed the training environment at the University of

California, Davis, and Dr. Deng described how he integrated a mutant form of the HD gene in an immunodeficient mouse strain, which made the mouse strain suitable for the transplantation of foreign mesenchymal stem cells, allowing for therapeutic research. Discussions following these three talks included scientific and research topics, as well as conversations centered on the formation of the mentor–mentee relationships.

Key ideas from Breakout Session 1 are as follow: (1) the ORIP Diversity Supplement mechanism is successful; (2) applicants and applications are evaluated rigorously, fairly, and constructively during the review process; (3) the application requires a strong research plan and a feasible career development plan; (4) the mechanism is providing excellent research opportunities for early-stage scientists from underrepresented groups; and (5) it will be important and rewarding to track the career trajectories of Mr. Schuster, Mr. Kabangu, and Dr. Deng. Dr. Voss noted that women from underrepresented groups should be included in discussions at the next CMRD meeting.

Discussion

- Dr. Fuchs clarified his answer to a question he was asked during Day 1 of the meeting. He noted that although most diversity supplement recipients are working toward a doctoral degree, this is not required for the supplement award. However, the diversity supplement is not intended to support staff members who are not otherwise focused on honing a career in biomedical research.
- In the chat, Dr. Lossin commented that this restriction prevents underrepresented bioinformatics staff members from receiving support.
- Dr. Chalker asked whether RRC Directors can connect with diversity research programs in undergraduate programs to discuss alternative careers in biomedical research.
- Dr. Deng discussed his career aspirations. He would like to participate in stem cell therapies and next-generation gene therapies with genome modification. Dr. Deng seeks to benefit society with his work and continue his outreach work advocating for positive change in the biomedical field.
- Mr. Schuster's career aspirations include the pursuit of a postdoctoral position involving work in molecular diagnostics. During the pandemic, Mr. Schuster enjoyed his work on studying prevalence of COVID-19 infection in Oregon communities. He would like to participate in the development of a more effective national emergency preparation plan.
- Dr. Voss asked Dr. Fuchs whether a plan exists for the long-term assessment of diversity supplement awardees. Dr. Fuchs stated that he has been tracking the awardees informally, and a formal plan is in development.
- In the chat, Dr. Clark asked Dr. Fuchs about funding mechanisms facilitating collaborations between investigators at large academic research centers and faculty at smaller teaching colleges with underrepresented populations. Dr. Fuchs answered that this was an interesting proposition. He stated that the diversity supplement can be used to fund applicants who are investigators developing independent research careers from institutions that are focused on underrepresented minorities, allowing awardees to work with investigators from more research-intensive institutions and develop their research skills.
- Dr. Voss asked whether Dr. Fuchs felt that the diversity supplement was being utilized adequately by funded investigators. Dr. Fuchs responded that the diversity supplement often is not utilized fully. He is working on promoting the diversity supplement to more people who can use it. Dr. Kent added that this diversity supplement is a mutually beneficial award, aiding both investigators who serve as mentors and students serving as mentees.

Breakout 2 Summary—Non-COVID-19 Resource Hurdles
Elizabeth Bryda, Ph.D., University of Missouri

Dr. Bryda first discussed the challenges of website management and data curation. Maintaining strain curation documentation is a major task requiring experts who fully understand the type of data that needs to be captured in these documents. Dr. Jorgensen discussed the different technologies that can be used to monitor animal behavior and health. He also emphasized the importance of developing innovative animal care and husbandry solutions. The implementation of innovative techniques and equipment must be balanced with the cost of these new technologies. Dr. Tiersch's talk centered on developing networks. He discussed the coordination of resources both horizontally and vertically. Dr. Tiersch also discussed the idea of using industrial engineering tools (e.g., process mapping, modeling) to improve efficiency, identify unnecessary waste and cost, and scale activities.

Discussion

- Dr. Jorgensen asked the participants whether they use automated technologies for monitoring behavior and health. In the chat, Dr. Horb stated that the NXR uses Iwaki aquatic controllers with a web-based interface for monitoring water quality parameters. He noted that this is beneficial during power outages and other emergencies.
- In the chat, Dr. Liu asked about costs associated with the feeding and monitoring systems. Dr. Jorgenson explained that the systems involve up-front and maintenance costs.
- In the chat, Dr. Lossin stated that the expertise of data curators should be given greater support.
- Dr. Tiersch emphasized the value of generalization across model organisms to share solutions among communities. He added that harmonizing work from a collaborative group can be challenging because some centers have very sophisticated facilities and technologies that other participants in the group cannot afford or maintain.
- In the chat, Dr. Horb added that linking to model organism databases would be beneficial but would require funds for curation. Dr. Tiersch responded that providing extra services to help RRCs and the research community in a revenue-neutral format is a considerable challenge. RRCs possess expanded social media and internet capabilities, which can facilitate interactions and build a strong interface with investigators.
- Dr. Tiersch commented that low-cost 3D printers allow investigators to access technologies that previously would have been out of reach for them. By sharing hardware development files, facilities can use the same hardware, facilitating harmonization across different communities.

Breakout 3 Summary—Strategies for Collecting and Sharing Resource Information
Laura Reinholdt, Ph.D., The Jackson Laboratory

The goal of Breakout Session 3 was to address challenges with data collection and data sharing experienced by resource centers. The presenters talked about information around genetically engineered alleles, genetic background, breeding and husbandry, metagenomic data, health information, and phenotypes. Discussions around protocols and validation methods were centered around reagent resources. When presenting on the sources of resources, the speakers touched on identifying donors, tracking reagents' sources, identifying publications citing the resource, and the acquisition of the resource. Resource information is dynamic, with living resources changing physically and non-living reagents and information changing with increasingly sophisticated technologies and methods. User feedback could be collected and distributed via a wiki curation strategy. The NHPRR has provided a model for this strategy.

This breakout session also focused on the importance of unique identifiers for strains and resources. Community standards are set by nomenclature committees, which also assign and approve the

nomenclature for unique identifiers. Databases are optimized to streamline data collection, but they also must have accessible user interfaces and be interoperable. Because the information around resources is dynamic, RRCs rely on ongoing curation by experts, such as trained biologists and geneticists. Repositories also rely on integrated data resources and community standards for information management.

Discussion

- Dr. Lossin stated that the research community must be encouraged to adopt standards and identifiers to facilitate the development of tools. Dr. Reinholdt responded that MMRRC curators help users adopt standards and identifiers. This information is required to make strains available in the repository and populate associated strain datasheets.
- In the chat, a participant asked about the challenges associated with the integration of genetic information tied to organisms that already are housed in repositories. Dr. Blackburn responded that repositories require long-term support to implement changes. In the chat, Dr. Lossin added that these interfaces must be carefully designed and optimized for users. Dr. Reinholdt added that some resources recruit users or advisory board members to test functionalities and provide feedback.
- Dr. Reinholdt noted that some have responded negatively to the idea of wiki curation for resources, citing concerns about the contribution of incorrect or overrepresented data. She noted that such a strategy could be helpful for collecting information. In the chat, Dr. Westerfield noted that the zebrafish community is eager to pursue efforts in this area and previously established a wiki system through ZFIN. In the chat, Dr. Chalker noted that the *Tetrahymena* Genome Database uses a wiki format; SOPs for curation and integration would be useful.

Breakout 4 Summary—Outreach: Examples and Best Practices
Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

Breakout Session 4 addressed common approaches for community outreach, which include the use of publications, conferences, press releases, websites, investigator referrals, electronic advertising, workshops, and webinars. The session presenters also addressed new approaches to community outreach, such as Google Ads, social media, GlobalData, and virtual presentations. Dr. Horb added that the NXR performs community outreach via the *Xenopus* listserv and Xenbase. Community outreach challenges include difficulty tracking publications, particularly when resources are not cited properly by investigators; maintaining resource inventory; providing workshops at an affordable cost; building collaborations during the COVID-19 era when in-person conferences were canceled or postponed; and maintaining resource websites and social media accounts.

Discussion

- In the chat, Dr. Koch stated that an additional form of outreach that should be explored further is the production of open hardware, which can provide devices for potential users. This strategy can be accompanied by use-case videos and documentation to facilitate hardware use, and a plan could be employed to capture feedback and make improvements to the devices.
- Dr. Reinholdt asked how the effectiveness of outreach can be measured. Dr. Sánchez responded that success is measured by the number of customers using a resource. Dr. Horb answered that effectiveness can be seen by indirect measures (e.g., responses to listserv emails). In the chat, Mr. Brooks added that the conversion rate could be determined using Google Analytics.

Session VI

Harnessing Genetic Complexity and Diversity to Advance Disease Research
Moderator: Charles Vite, D.V.M., Ph.D., University of Pennsylvania

A. Canine and Feline Models of Neurological Diseases
Charles Vite, D.V.M., Ph.D., University of Pennsylvania

Dr. Charles Vite presented on discovery of naturally occurring canine and feline models for disease, with a particular focus on neurological disorders. He first provided an overview of the Referral Center for Animal Models of Human Genetic Disease (RCAM), which identified and characterized naturally occurring genetic diseases through the Penn Vet Ryan Veterinary Hospital; Metabolic and Molecular Laboratory; and collaborations with veterinary specialists, researchers, and institutions. The goals of the RCAM are to (1) identify hereditary metabolic diseases with the cat and dog populations, (2) develop precise diagnostic tests to carrier and affected animals, (3) recommend informed breeding of carrier and normal animals to preserve gene pools, (4) maintain breeding colonies of hereditary disorders in cats and dogs to better understand disease pathogenesis and to develop therapies, and (5) provide tissue samples and large-animal models for human genetic disease to investigators to better understand disease pathogenesis and as preclinical models for potential human clinical trials. He presented an organization chart depicting the RCAM's workflow and procedures. The RCAM maintains breeding colonies for lysosomal storage diseases, dermatologic diseases, cardiovascular diseases, nervous and muscular system diseases, and hematological and immunological system diseases. Dr. Vite explained that naturally occurring large-animal models allow for the advancement of small-molecule therapy, enzyme-replacement therapy, and gene therapy into clinical trials. He outlined recent efforts to develop therapies for feline Niemann–Pick disease, type C1. Cyclodextrin therapy was found to delay the onset of the disease. Dr. Vite noted that the RCAM examines various levels of drug toxicity in the animals (e.g., peripheral nerve conduction velocity, hearing levels), and the drug has been tested in clinical trials. Efforts in gene therapy for Niemann–Pick disease in feline models are being pursued presently.

Discussion

- Dr. Cheng asked whether histological slides from large-animal models could be shared for comparison with humans and other model systems. Dr. Vite stated that he would be happy to pursue this effort.

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

Dr. Catherine Cook Kaczorowski presented on the development of a reproducible model for cognitive aging and AD and highlighted implications for personalized medicine. She explained that classically, animal models for AD have been produced from single inbred strains that are poorly validated. Additionally, cognitive and pathological tests must be developed and validated, and environmental effects must be considered. Further, the value, rigor, and reproducibility of animal studies are crucial. Cognitive aging is a complex process with broad variation among individuals. This variation is partly heritable, but the involved genes are not understood fully. Additionally, protective genetic factors lead to asymptomatic AD, which is challenging to study in human populations. Animal models are valuable for screening and testing treatments. Dr. Cook Kaczorowski's team developed a genetically diverse panel of mice with human mutations that cause AD. They combined an established classical inbred strain with a reference panel, introducing a controlled, trackable level of genetic variation. Using a detailed phenotyping pipeline, the team can identify modifiers of AD at early and late timepoints. They found that genetic background modifies age at onset of working memory deficits, as well as short- and long-term memory.

The C57BL/6J (B6) background appears to be resilient, and DBA/2J (D2) alleles confer susceptibility to disease. They found that genetic background is related to the degree of human amyloid-beta accumulation, but amyloid load does not correlate with cognitive function. Using these data, Dr. Cook Kaczorowski's team developed a genetic risk score to assess sensitivity to variation in AD risk loci and predict AD-related cognitive decline.

Discussion

- In the chat, a participant asked about variation and genetic mapping of the strains. Dr. Cook Kaczorowski stated that on average, the sample size of each strain is 3–5. Heritability was 0.7, and each strain has replicates across the panel. Additional strains are being added for fine mapping, and CRISPR validation is being performed at select loci.

C. Swine as Models of Human Disease: Opportunities and Challenges
Randall Prather, Ph.D., University of Missouri

Dr. Randall Prather presented on opportunities and challenges of swine models for human disease. Various factors should be considered in the selection of a model (e.g., availability, phenotype, physiology, xenobiotic metabolism, immune response, literature, size, genome, acceptability as a preclinical model). The reproductive characteristics of the selected species (e.g., adult body size, litter size, age to puberty, generation interval, time to produce experimental units) must be considered for the experimental design. Many investigators desire to work with miniature pigs to ensure sufficient housing space; these animals, however, often exhibit poor reproductive performance. Intellectual property represents an additional area of concern with commercial suppliers. The University of Missouri has begun construction of a facility to house more than 100 domestic-sized pigs for biomedical research. He explained that lack of atlas material creates challenges for validation. Using CRISPR technology, Dr. Prather's team developed a swine model for congenital heart disease. Presently, they are working on combining genetic models to develop a model for hypoplastic left heart syndrome. Additional efforts to develop atlases for the kidney and brain are in progress. Dr. Prather stated that recent challenges have included laboratory closures during the COVID-19 pandemic. Because the team was unable to source ovaries using established protocols, research activities were reduced during this time. He concluded by stating that challenges for validation include lack of housing for domestic and miniature pigs, lack of atlas material, limited capabilities for cryopreservation, extended timelines (e.g., gestation interval), and limited biological material (e.g., ovaries).

Discussion

- In the chat, a participant asked about examination of expression and morphogenesis using virtual reality technology. Dr. Prather agreed that the concept would be interesting to explore in a pilot grant.
- Dr. Cheng asked whether a pilot program of supplements to companies that supply ovaries would be beneficial. Dr. Prather noted that demand in this area might be limited. He explained that a member of his group collected ovaries from a local slaughterhouse twice per week.

D. Harnessing the Power of Genetic Variation: Modifiers of Rare Disease
Clement Chow, Ph.D., The University of Utah

Dr. Clement Chow presented on the use of genetic variation for studies of rare diseases using *Drosophila* models. Genetic variation creates a complex problem for biomedical research. The Precision Medicine Initiative is aimed at better understanding individual factors in disease outcomes and therapy responses. Dr. Chow said that typically, researchers fail to account for genetic variation. Dr. Chow's group is working to harness the power of genetic variation to identify novel elements of cell and disease pathways. During the past decade, the concept of rare diseases has gained new attention; patients are identified daily,

and patient groups are growing. New technologies have enhanced capabilities for rapid diagnosis. Additionally, new model organism tools are being developed. Dr. Chow emphasized the importance of understanding the phenotypic spectrum in rare disease. His group uses the *Drosophila* Genetic Reference Panel, which was developed using a natural population in Raleigh, North Carolina. The model is tested on 200 backgrounds; this panel can provide insight on pathogenesis and genetic disease modifiers. Dr. Chow outlined recent efforts using this approach to better understand *NGLY1* mutations, which lead to a congenital disorder of deglycosylation. The team identified a human ortholog that interacts with *NGLY1*, helping explain variability of disease symptoms among patients. The approach is being applied to other diseases, such as retinitis pigmentosa, Parkinson's disease, and flavivirus infection. Dr. Chow concluded by stating that *Drosophila* serves as a powerful tool for rare disease precision medicine.

Discussion

- In the chat, a commenter asked whether Dr. Chow examined larval phenotypes of *NGLY1* mutants and cause of lethality. Dr. Chow stated that the cause of lethality still is unknown, although genetic rescue has been performed. He noted that he has not examined larval phenotypes; another study reported that the mutant larvae are smaller. His group is focused on adult phenotypes, which he stated are more applicable to human biology.
- In the chat, a commenter asked about different cell types. Dr. Chow stated that preliminary data suggest that the genetic interaction affects secretory cells and neurons.
- In the chat, Dr. Clark asked about genetic modifiers that promote survival. Dr. Chow explained that one allele promotes survival, and another promotes lethality. Enhancement of NKCC1 activity in flies should promote survival.

Online Survey and Acknowledgments
S. Randal Voss, Ph.D., University of Kentucky

Dr. Voss reminded the participants to complete the meeting survey, which is available through the registration site. He thanked several staff members at the University of Kentucky for their assistance during the meeting. He also thanked representatives from Event Technologies for providing support in planning the meeting's virtual platform. Dr. Voss concluded by announcing that Dr. Sánchez would serve as the new CMRD Meeting Organizing Committee Chair.

2023 CMRD Meeting
Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

Dr. Sánchez introduced herself and stated that she would be responsible for writing and submitting an R13 grant for the 2023 CMRD Meeting. She encouraged the participants to contact her via email for information on serving on the Organizing Committee.

Closing Remarks
Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP

Dr. Murphy stated that she has participated in the past three CMRD Meetings, each of which has addressed a different topic footprint. She noted that all three meetings have adapted to incorporate emerging topics of relevance to the biomedical research community.

Dr. Murphy summarized key highlights and themes from the meeting. She remarked that the meeting's sessions aligned closely with the four themes listed in ORIP's SP. Theme 1—animal models to advance the study of human disease—relates to the resource videos (Sessions I and II), as well as to discussions of genetically relevant animal models (Session VI) and resource descriptions (Breakout Session). Theme 2—innovative instruments and equipment to accelerate research discoveries—relates to

discussions of tools and technologies (Session III) and identification of instrumentation and equipment needs (Session IV). Theme 3—specialized research training in animal models and related resources—relates to the diversity supplement program (Breakout Session) and was referenced across multiple sessions addressing RRC training opportunities for users, investigators, and staff members. Theme 4—awareness of ORIP resources and programs—relates to the resource videos (Sessions I and II); dedicated outreach discussions (Breakout Session); and discussions of rigor, reproducibility, and translatability (Session IV).

Several additional themes emerged during the meeting. Dr. Murphy commented on the shared diversity of the RRCs (e.g., species, biospecimens, biological materials, technologies, tools, services) serving the biomedical research community. She also highlighted resource promotion and outreach, which were featured in the resource videos and virtual discussions, as well as in Breakout Room 4. Session III addressed tools and technologies at various levels (e.g., molecular, cellular, genetic, organismal). Breakout Room 2 also addressed technologies for monitoring animal behavior and health. She stated that rigor, reproducibility, and translatability represent important emerging topics within the biomedical research community. This topic was addressed in Session IV, Breakout Room 3, several resource videos, and Session VI. Dr. Murphy noted that the topic of research resources during public health crises represented an important area of discussion. Session IV addressed the impact of the COVID-19 pandemic on the operations of RRCs. She noted that in this session, lessons learned and opportunities (e.g., altered strategies, enhanced research directions, new animal models) from the pandemic also were discussed. She noted that the keynote speaker highlighted the contributions of the RRCs to new research relevant to the pandemic. Dr. Murphy also emphasized the importance of resiliency in facing day-to-day challenges, as well as unanticipated emergencies.

Dr. Murphy concluded by thanking Dr. Voss for his leadership in planning the meeting during the COVID-19 pandemic and adapting to a virtual platform. She applauded him for incorporating new components of the meeting (e.g., the breakout sessions) and accommodating participants from different time zones to ensure that all were able to participate. She reminded the participants that engagement in completing the meeting survey is crucial for planning future meetings. She also encouraged participants to continue communicating with Dr. Sánchez, particularly regarding emerging technologies and topics.

Meeting Agenda

DAY 1: TUESDAY, AUGUST 3, 2021

Session I

11:00 a.m.–11:10 a.m.	**Introduction and Welcome** *Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine (DCM), Office of Research Infrastructure Programs (ORIP)*
11:10 a.m.–11:30 a.m.	**ORIP's 2021–2025 Strategic Plan** *Franziska Grieder, D.V.M., Ph.D., Director, ORIP*
11:30 a.m.–12:00 p.m.	**Videos Highlighting ORIP Research Resources #1** *Moderator: S. Randal Voss, Ph.D., University of Kentucky*
12:00 p.m.–12:45 p.m.	**Keynote Presentation—Preclinical Evaluation of Second-Generation COVID-19 Vaccines in Nonhuman Primates** *Deborah Fuller, Ph.D., University of Washington School of Medicine and Washington National Primate Center*
12:45 p.m.–1:00 p.m.	**Questions** *Moderator: David O'Connor, Ph.D., University of Wisconsin–Madison*
1:00 p.m.–1:15 p.m.	Break

Session II

1:15 p.m.–1:45 p.m.	**Videos Highlighting ORIP Research Resources #2** *Moderator: Michael Schmale, Ph.D., University of Miami*

Breakout Sessions

1:45 p.m.–3:00 p.m. **Room 1—Promoting Diversity in Comparative Medicine**
Moderator: S. Randal Voss, Ph.D., University of Kentucky

This breakout session showcases ORIP diversity supplement awardees and their mentors.

- The NIH Diversity Administrative Supplement Program
  Bruce Fuchs, Ph.D., ORIP

- Control and Impacts of Disease of Zebrafish in Research Facilities
  Michael Kent, Ph.D., Oregon State University
  Corbin Schuster, Oregon State University

- Implementing Pathogen Monitoring for the Laboratory Axolotl
  Mirindi Kabangu, University of Kentucky
  S. Randal Voss, Ph.D., University of Kentucky

- Novel Immune-Deficient Mouse Models of Huntington's Disease
  Peter Deng, Ph.D., University of California, Davis
  Jan Nolta, Ph.D., University of California, Davis

Room 2—Non-COVID-19 Resource Hurdles
Moderator: Elizabeth Bryda, Ph.D., University of Missouri

This breakout session identifies barriers and solutions to everyday resource problems independent of COVID-19.

- Challenges of Website Management and Data Curation
  Elizabeth Bryda, Ph.D., University of Missouri

- Innovative Technologies to Monitor Animal Behavior and Health
  Matthew Jorgensen, Ph.D., Wake Forest School of Medicine

- Developing Networkable Germplasm Repositories
  Terrence Tiersch, Ph.D., Louisiana State University Agricultural Center

Room 3—Strategies for Collecting and Sharing Resource Information
Moderator: Laura Reinholdt, Ph.D., The Jackson Laboratory

This breakout session tackles issues associated with data collection and sharing.

- Collecting and Managing Genetic Information for Stocks
  Laura Reinholdt, Ph.D., The Jackson Laboratory

- Compiling Antibody Information Across Models and Resources
  Diogo Magnani, Ph.D., MassBiologics, University of Massachusetts Medical School

- The Animal-GRIN Database
  Harvey Blackburn, Ph.D., National Animal Germplasm Program, Agricultural Research Service, U.S. Department of Agriculture

Room 4—Outreach: Examples and Best Practices
Moderator: Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

This breakout session explores innovative outreach approaches to impact user communities.

- The National Natural Toxins Research Center: Engaging the Venomous Community
  Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

- The First 10 Years of the National *Xenopus* Resource: How We Reach Our Customers
  Marko Horb, Ph.D., Marine Biological Laboratory

- Making New Connections in the Virtual World
  Thomas Bell, Ph.D., National Disease Research Interchange

Session III

3:00 p.m.–3:20 p.m. **Administrative Practices at NIH-Supported Resources**
Gavin Wilkom, M.I.M., National Heart, Lung, and Blood Institute
Moderator: Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP

3:20 p.m.–4:40 p.m. **Development and Application of Innovative Tools and Integrative Approaches**
Moderator: Keith Cheng, M.D., Ph.D., The Pennsylvania State University

Investigators working with different animal models will share information about cutting-edge technologies and approaches.

- How Spatial Context Nucleates Multiscale Multi-omics
  Keith Cheng, M.D., Ph.D., The Pennsylvania State University
- Fly Tools and Approaches to Diagnose Human Diseases
  Hugo Bellen, D.V.M., Ph.D., Baylor College of Medicine
- Development of Tools for Site-Directed Analysis of Gene Function
  Maura McGrail, Ph.D., Iowa State University
- mGAP: A Broadly Used Macaque Genotype and Phenotype Resource to Expand NHP Research
  Betsy Ferguson, Ph.D., Oregon National Primate Research Center

DAY 2: WEDNESDAY, AUGUST 4, 2021

Session IV

11:00 a.m.–11:05 a.m. **Introduction**
Franziska Grieder, D.V.M., Ph.D., Director, ORIP

11:05 a.m.–12:05 p.m. **Group Discussion—Rigor, Reproducibility, and Translatability**
Moderators: Malgorzata Klosek, Ph.D., Director, Division of Construction and Instruments, ORIP
Kent Lloyd, D.V.M., Ph.D., University of California, Davis
Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP

This session will discuss recommendations from the June 11, 2021, Advisory Committee to the NIH Director (ACD) Report.

12:05 p.m.–1:05 p.m. **COVID-19: Lessons Learned**
Cale Whitworth, Ph.D., Indiana University Bloomington

Investigators talk about challenges and opportunities that COVID-19 presented to their resources.

- Learning to Fly Again: Lessons from the COVID-19 Pandemic at the Bloomington *Drosophila* Stock Center
  Cale Whitworth, Ph.D., Indiana University Bloomington
- JAX Mouse Models of COVID-19: New Models and Applications
  Cathleen Lutz, Ph.D., The Jackson Laboratory
- COVID-19 Lockdown and Recovery at the Zebrafish International Resource Center
  Zoltan Varga, Ph.D., University of Oregon

1:05 p.m.–1:15 p.m. Break

Session V

1:15 p.m.–1:35 p.m.	**Breakout 1 Summary—Promoting Diversity in Comparative Medicine** *S. Randal Voss, Ph.D., University of Kentucky*
1:35 p.m.–1:55 p.m.	**Breakout 2 Summary—Non-COVID-19 Resource Hurdles** *Elizabeth Bryda, Ph.D., University of Missouri*
1:55 p.m.–2:15 p.m.	**Breakout 3 Summary—Strategies for Collecting and Sharing Resource Information** *Laura Reinholdt, Ph.D., The Jackson Laboratory*
2:15 p.m.–2:35 p.m.	**Breakout 4 Summary—Outreach: Examples and Best Practices** *Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville*
2:35 p.m.–2:50 p.m.	Break

Session VI

2:50 p.m.–4:10 p.m. **Harnessing Genetic Complexity and Diversity to Advance Disease Research**
Moderator: Charles Vite, D.V.M., Ph.D., University of Pennsylvania

This session will address challenges and opportunities in developing genetically relevant animal models.

- Canine and Feline Models of Neurological Diseases
  Charles Vite, D.V.M., Ph.D., University of Pennsylvania
- Concept for Reproducible Animal Models for Complex Human Disease: Implications for Personalized Medicine
  Catherine Cook Kaczorowski, Ph.D., The Jackson Laboratory
- Swine as Models of Human Disease: Opportunities and Challenges
  Randall Prather, Ph.D., University of Missouri
- Harnessing the Power of Genetic Variation: Modifiers of Rare Disease
  Clement Chow, Ph.D., The University of Utah

4:10 p.m.–4:15 p.m.	**Online Survey and Acknowledgments** *S. Randal Voss, Ph.D., University of Kentucky*
4:15 p.m.–4:20 p.m.	**2023 CMRD Meeting** *Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville*
4:20 p.m.–4:40 p.m.	**Closing Remarks** *Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP*

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