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Division of Comparative Medicine

Fourteenth Comparative Medicine Resource Directors Meeting

Advancing Biomedical Research: Integrative Approaches and Innovations

August 6–7, 2024

Rockledge II, Room 160

6701 Rockledge Drive

Bethesda, MD

Meeting Report

Fourteenth Comparative Medicine Resource Directors Meeting

August 6 and 7, 2024

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 fourteenth CMRD Meeting was held August 6 and 7, 2024. The purpose of the 2024 meeting was to form and strengthen new and existing connections, disseminate information about new resources and opportunities to collaborate, expand networks, 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 2024 meeting included presentations, breakout sessions, poster sessions and video sessions that highlighted recent research developments and collaborative opportunities. It provided a platform for discussing innovative approaches in comparative medicine and exploring future directions for resource management and development.

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

Scientific Advisory Board for the R13 Conference Grant to Texas A&M University–Kingsville

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Elda E. Sánchez, Ph.D. (Texas A&M University–Kingsville)
Biao Tian, Ph.D. (NIH/OD)
S. Randal Voss, Ph.D. (University of Kentucky)
Sige Zou, Ph.D. (NIH/OD)

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Executive Summary

The Fourteenth Comparative Medicine Resource Directors (CMRD) Meeting was held on August 6 and 7, 2024. Dr. Elda E. Sánchez 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 exchanging advances, fostering collaborations, and sharing best practices to enhance the administration and utilization of resources within the CMRD community. The theme of this year's meeting was advancing biomedical research, integrative approaches, and innovations. In his Keynote Address, Dr. David Liu presented recent work on cutting-edge technologies in gene editing, including base editing and prime editing. These methods facilitate precise DNA modifications to address genetic disorders and enhance therapeutic approaches.

Session I featured emerging complementary models, technologies, and methodologies and videos highlighting resources, including the Center for Precision Animal Modeling, Aquatic Germplasm and Genetic Resources Center, *Ambystoma* Genetic Stock Center, An Integrated Platform for Diploid Germplasm Conservation in Zebrafish from the Zebrafish International Resource Center, *Drosophila* RNAi Screening Center and Transgenic RNAi Project, *Drosophila* Cryopreservation at the University of Minnesota, Neotropical Primate Reagent Resource, Human Tissues and Organs for Research Resource, and Building a Wide-Field, High-Resolution Histotomography Resource for Biology. Session II explained how to create an effective NIH Data Management and Sharing Plan with a review of the NIH policy and expectations, and Session III discussed impact factors for animal models and related resources. Session IV consisted of breakout groups that discussed strategic planning needs for comparative medicine resources on the themes of animal models, instrumentation, training, and outreach, followed by additional videos from the Mouse Peroxisome Research Resource, A Community Resource for Germline and Somatic Genetic Disease Modeling in Zebrafish, the Precision Medicine Nonhuman Primate Resource, the JAX Center for Precision Genetics, A Comprehensive Resource for the *Drosophila* 4th Chromosome, the New World Monkey Immunoreagent Resource, the *Xenopus* Cell Atlas, and the *Xiphophorus* Genetic Stock Center. Session V outlined administrative practices at NIH-supported resources, and Session VI consisted of poster presentations. In Session VII, attendees summarized the breakout discussions, and a video from the National *Xenopus* Resource was shown. In Session VIII, presenters discussed key considerations when adding a curation and informatics component to a comparative medicine resource, and Session IX highlighted important factors in planning for the expected and unexpected.

In the closing remarks, Dr. Stephanie Murphy, Director, Division of Comparative Medicine, Office of Research Infrastructure Programs (ORIP), noted the common themes of the day: precision medicine models and technologies, new approaches and complementary methodologies, data management and sharing, reproducibility and transparency, policy and regulations, and preserving and protecting resources and people.

List of Acronyms and Abbreviations

ACD	Advisory Committee to the Director
AGGRC	Aquatic Germplasm and Genetic Resources Center
AGSC	*Ambystoma* Genetic Stock Center
AI	artificial intelligence
AOR	Authorized Organization Representative
ATP-Bio	Advanced Technologies for the Preservation of Biological Systems
C-PAM	Center for Precision Animal Modeling
CAST	CRISPR-associated transposase
CDC	Centers for Disease Control and Prevention
CMRD	Comparative Medicine Resource Directors
Complement-ARIE	Complement Animal Research In Experimentation
CPAs	cryoprotective agents
CPRC	Caribbean Primate Research Center
CRIMIC	CRISPR-mediated integration cassette
DCI	Division of Construction and Instruments
DCM	Division of Comparative Medicine
DMS	Data Management and Sharing
DOC	U.S. Department of Commerce
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DRSC	*Drosophila* RNAi Screening Center
DSPI	Data Sharing Policies Implementation
ESI	early-stage investigator
FAIR	findable, accessible, interoperable, and reusable
FFR	federal financial report
GREI	Generalist Repository Ecosystem Initiative
HTORR	Human Tissue and Organ Research Resource
HVAC	heating, ventilation, and air conditioning
ICs	Institutes and Centers
ICOs	Institutes, Centers, and Offices
ICSC	Informatics, Coordination, and Service Center
IP	intellectual property
iPSC	inducted pluripotent stem cell
IUB	Indiana University Bloomington
JAX	The Jackson Laboratory
MAGIC	mosaic analysis by guide-RNA-induced crossover
mGAP	Macaque Genotype and Phenotype
MMRRC	Mutant Mouse Resource & Research Centers
MOU	memorandum of understanding
MPRR	Mouse Peroxisome Research Resource
NAMs	new approach methodologies
NCATS	National Center for Advancing Translational Sciences
NHLBI	National Heart, Lung, and Blood Institute
NHP	nonhuman primate
NHPRR	Nonhuman Primate Reagent Resource
NIH	National Institutes of Health
NOFO	notice of funding opportunity
NOSI	notice of special interest
NXR	National *Xenopus* Resource

ODSS	Office of Data Science Strategy
OER	Office of Extramural Research
ONPRC	Oregon National Primate Research Center
ORIP	Office of Research Infrastructure Programs
ORRA	Office of Research Reporting and Analysis
PACE	phage-assisted continuous evolution
pegRNA	prime editing guide RNA
PI	principal investigator
RRC	Resource and Research Center
RRID	research resource identifiers
SDS	strain data sheet
SQL	structured query language
TRiP	Transgenic RNAi Project
TRUST	transparency, responsibility, user focused, sustainability, and technology
UAS	upstream activating sequence
UPR	University of Puerto Rico
USDA	U.S. Department of Agriculture
XGSC	*Xiphophorus* Genetic Stock Center
ZIRC	Zebrafish International Resource Center

Meeting Report

DAY 1: TUESDAY, AUGUST 6, 2024

Introduction and Welcome

Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine (DCM), Office of Research Infrastructure Programs (ORIP)

Dr. Stephanie Murphy, Director, DCM, ORIP, welcomed the participants to Day 1 of the Fourteenth 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 the 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 advancing biomedical research, integrative approaches, and innovations. Dr. Murphy thanked the participants on behalf of her ORIP colleagues for their insights, expertise, patience, and flexibility. She also expressed appreciation to Dr. Elda E. Sánchez, Organizing Committee Chair, for her leadership in organizing the meeting. She acknowledged the Scientific Advisory Board members and thanked the session moderators, presenters, and panelists for their engagement in the meeting.

Keynote Presentation—Continuous Directed Evolution of Next-Generation Genome Editing Agents

David Liu, Ph.D., Harvard University

Dr. David Liu, Harvard University, outlined recent work on technologies for performing gene correction and large-gene integration at targeted sites in cells, animals, or humans. Base editing and prime editing are technologies developed to enable efficient installation or correction of mutations in living systems. These technologies are not known to exist in nature and involve engineered proteins. Base editors use deaminases evolved in the laboratory to efficiently convert one target base to another and then guide the cell through DNA repair processes on both strands. Base editing has been used *ex vivo* and *in vivo* to treat animal models for human genetic diseases, such as by converting a defective copy into a healthy version.

Base editing studies in animal models for human disease have paved the way for the clinical application of base editing. At least nine base editing clinical trials are currently underway, and at least three have already reported clinical outcomes. Only 6 years have passed since the first publication on base editing and the first positive readout, and the first *in vivo* base editing clinical trial reported results in late 2023. *In vivo* base editing demonstrates the potential not only to treat serious diseases but also to lower future disease risk, which Dr. Liu speculated would become increasingly commonplace as these trials continue to yield positive results.

Although base editors can correct translation mutations, Dr. Liu and his team were interested in developing ways of correcting all other types of mutations. Prime editors are fusions of programmable nickases with engineered reverse transcriptases. An engineered prime editing guide RNA (pegRNA) specifies the target site and encodes the desired edit; after the prime editor nicks the target site, the nicked DNA strand forms a complex with the pegRNA that allows the reverse transcriptase to copy the desired edit directly onto the end of the strand, encouraging the cell to repair the DNA using the edited strand as a template and permanently correcting both strands. Encoding the edit in the pegRNA allows researchers to perform almost any insertion, substitution, or deletion—currently up to about 200 base pairs in length.

Although prime editing has advanced significantly in recent years, the reverse transcriptase at its heart has

been challenging to improve. Phage-assisted continuous evolution (PACE) uses a phage containing proteins or gene variants with the desired activity; the speed of the phage life cycle enables evolution campaigns of thousands of generations on a practical timescale. To link prime editing to phage propagation, cells were equipped with defective RNA polymerase chains that require prime editing to restore their function, forcing the phage to encode the active prime editor to perform its life cycle. PACE was used to evolve compact reverse transcriptases with an improved ability to perform prime editing in human cells, including options well suited for longer and more complicated prime edits on highly structured templates. These have proven particularly important for challenging edits in challenging cell types, which are critical for challenging therapeutic edits, such as precise correction of a three-base-pair deletion that is the predominant cause of cystic fibrosis. Prime editing has also been applied both *ex vivo* and *in vivo* to rescue a number of animal models for human disease.

Base editing and prime editing have rapidly been translated into clinical trials and are ideally suited to treat genetic diseases that arise from a small number of mutations or to install edits in wild-type genes that reduce disease risk, but one major challenge is the allelic diversity of many genetic diseases, some of which may be caused by more than 500 known mutations. Gene complementation therapy has been used for many years, but its drawbacks limit its use. A newer form of gene complementation therapy uses programmable nucleases to cut the chromosome and stimulate repair, but this method also has drawbacks. Ideally, an entire healthy gene could be integrated efficiently into the endogenous site of pathogenic gene loss or a well-established safe harbor locus. In 2021, a combination of prime editing and site-specific recombinase enzymes was used to perform targeted integration into human cells to integrate a large gene- or exome-sized DNA into a newly installed landing site. Using the PACE platform, more efficient recombinases were evolved and engineered.

After developing more evolved recombinases and prime editors that can provide efficient results in many contexts, Dr. Liu's team focused on developing ways to evade cellular and immune responses to the introduction of large DNA donors. CRISPR-associated transposases (CASTs) mediate targeted gene integration in a single process with no double-strand breaks, which results in a very efficient, very specific process with minimal byproducts. However, the CASTs at that time showed zero or very low activity in mammalian cells. Dr. Liu's team used PACE to evolve CASTs in a way that improved activity and minimized dependence on cytotoxic bacterial proteins. After changes in all CAST protein components, integration efficiencies of 10% to 30%, with an average of 13%, were observed at therapeutically relevant loci, an improvement of more than 350-fold over the wild-type CAST. Dr. Liu commented that although his team remains optimistic about improving evolved and engineered CAST systems further, these efficiencies are already sufficient, if translated into therapeutic contexts, to offer potential benefits to patients with a variety of loss-of-function genetic disorders that can now be addressed with a single treatment. Evolved and engineered CAST systems show tolerance of large DNA payloads up to 15 kilobases and preserve many key features of naturally occurring CASTs.

Dr. Liu emphasized that the efforts of many researchers in this community enabled the rapid development of base and prime editing. He hoped these developments could address the long-standing challenge of precisely inserting healthy genes or gene fragments into chosen genomic sites efficiently, without generating double-stranded breaks, and with minimal byproducts.

Discussion

- An attendee asked about the percentage of cells needed for clinical improvement in cystic fibrosis; Dr. Liu replied that these experiments are in progress in animals. A drug cocktail considered effective at rescuing the symptoms of cystic fibrosis corrects 20% to 30% of ion channel function, which suggests that a minority of tissue functions can rescue symptoms. Small molecules partially rescue all cells, whereas gene editing fully rescues a portion of cells, and each method may have different benefits. However, a growing body of data suggests that editing a modest fraction of cells can offer partial or complete rescue to animals.

- Dr. Liu was asked about the best strategy for addressing large structural variants. He noted that although the largest section replaced so far was 15,000 base pairs, many thousands of base pairs can be deleted, so base and prime editing can be used to delete many repeats by targeting a pegRNA to the sequences before and after the repeats.
- Another attendee asked whether PACE can evolve CASTs to handle very large cargo. Dr. Liu replied that this project is good but high risk because the size-limiting determinants of recombinase or CAST function remain unknown. He pointed out that his laboratory is actively working to optimize these systems in animals.

Session I: Emerging Complementary Models, Technologies, and Methodologies

Moderators: Sige Zou, Ph.D., DCM, ORIP, and S. Randal Voss, Ph.D., University of Kentucky

Microphysiological Systems: *In Vitro* Tools for Safety, Efficacy, and Precision Medicine Studies

Danilo Tagle, Ph.D., National Center for Advancing Translational Sciences (NCATS)

Dr. Danilo Tagle, NCATS, explained that NCATS works to move basic discoveries into the clinical realm, including by developing better predictive tools. Microphysiological systems are biological devices that seed human-derived cells and tissues proportionally onto "chips" to capture the microenvironment of tissues in the body. Microfluidics, stem cell biology, and bioengineering technologies are used to develop microphysiological systems that illuminate drug metabolism and organ crosstalk. These systems also can be used to investigate organs and systems that are difficult to model. Over the course of the program, NCATS focused on developing microphysiological systems to study safety and toxicity issues and then pivoted to modeling human diseases on chips. The current focus is modeling clinical trials on a chip by representing a diverse patient population and stratifying for the best responders. NCATS has built confidence in this technology by collaborating with the U.S. Food and Drug Administration and the pharmacological industry, operating independent testing centers, and offering a microphysiological systems database that is free and open to the public. NCATS has also supported a number of startup companies in this growing market and hosted a workshop on the potential of animal cells on chips, which can help bridge animal and human data. Dr. Tagle demonstrated how microphysiological systems can be used to predict drug response and develop precision medicine strategies.

Dr. Tagle introduced the Complement Animal Research In Experimentation (Complement-ARIE) Program, an NIH-wide Common Fund program aimed at combining recent technological advances in multiple fields to develop more powerful predictive tools for *in vitro*, *in silico*, and *in chemico* studies. The notice of funding opportunity (NOFO) will be released in October and will focus primarily on comprehensive technology development centers, a data coordinating center, and a public–private partnership for the validation and quantification of new approach methodologies (NAMs). Complement-ARIE will include community engagement and training activities and a set-aside to capitalize on emerging scientific opportunities. A key feature of the program will be a validation and quantification network involving regulatory partners from industry, federal agencies, and nonprofit organizations.

Defining New Cancer Biology and Therapeutic Opportunities Using Zebrafish

David Langenau, Ph.D., Harvard Medical School

Dr. David Langenau, Harvard Medical School, outlined current processes used in zebrafish to study cancer biology. One of the major models is adult immune-deficient zebrafish. Dr. Langenau's team has developed processes to improve growth and deliver clinically relevant dosing, which expands the scale of experiments in ways not always possible in the mouse model. In a model for rhabdomyosarcoma, for example, the combination of temozolomide and poly(ADP-ribose) polymerase inhibitors was effective at eliminating the tumor in fish; this combination is now in an open Phase 1 clinical trial. A subset of tumors was nonresponsive, and the zebrafish model was used to show that these tumors evolved resistance by affecting the expression of a wide array of drug efflux pumps. Adding a drug that inhibits the relevant

pathway allows cells to become responsive to therapy even in very aggressive models. Using the zebrafish model for these studies allows researchers to treat many animals in a short time with very few staff. These models have also been used to define new classes of drugs, such as antibody peptide epitope conjugates, which can use highly specific targeting to degrade cancerous cells.

Dr. Langenau's team has also addressed challenges in maintaining zebrafish with ablated immune systems, thus improving experimental throughput without needing to genotype every fish. Although the techniques are in the early stages, initial experiments showed that fish injected with rhabdomyosarcoma cells developed tumors, so these techniques may lead to innovations in short-term assays.

The Monarch Initiative: Using Multi-Species Genotype-Phenotype Data for Diagnostics and Discovery
Melissa Haendel, Ph.D., The University of North Carolina at Chapel Hill

The Monarch Initiative works to understand the phenotypic diversity of life and its relationship to genotypes and environmental influences to inform human health and care. Monarch aims to inventory and collect genotype-phenotype correlation data for use in diagnostics and mechanistic discovery. Data must be deeply integrated to be usable for mechanism discovery, but many model organism communities create their own ontologies that are not designed for interoperability. Semantic structures are required to outline the relationships between data points and types in ways that are amenable to machine learning applications. Phenotyping terminology for humans often differs from clinical terminology, and patients' electronic health records usually do not identify the biological characteristics described in model systems, which are necessary for connecting human phenotypes to model systems. Monarch has worked with a number of databases and ontologies to map semantic similarities across species, allowing phenotypic characteristics correlated to disease mechanisms to be identified. Large language models are also used to harmonize data and find evidence in the literature to support phenotypic characterization. The Monarch Initiative received the NIH DataWorks! Prize for data reuse, and its tools and standards have been adopted by most NIH institutes and many resources.

Upgraded MAGIC Tools for More Reliable and Versatile Mosaic Analysis in *Drosophila*
Chun Han, Ph.D., Cornell University

Dr. Chun Han, Cornell University, explained that his team has developed two CRISPR-based technologies for use in *Drosophila*. In mosaic analysis by guide-RNA-induced crossover (MAGIC), CRISPR-Cas9 cuts DNA at a specific locus, allowing each arm to cross and exchange chromosomes. Using guide-RNA transgenes creates one cell carrying two copies of the transgene and the other homozygous mutant. MAGIC has several advantages over traditional *Drosophila* mosaic analysis techniques, including flexible crossover sites and the ability to be used on existing mutations or in wildly derived chromosomes and other species. Some accomplishments to date include developing more efficient guide-RNA designs and improving markers for visibility and detection. Dr. Han's team also developed anti-CRISPR techniques, which enable the simultaneous use of both guide-RNA and Cas9 in the same fly, enhancing the versatility of their genetic research.

Use of Somatic Cell Nuclear Transfer for Germplasm Conservation
Jose Cibelli, Ph.D., Michigan State University

Dr. Jose Cibelli, Michigan State University, outlined the use of somatic cell nuclear transfer combined with cryopreservation, allowing exact phenotypes to be preserved across laboratories and reducing the loss of zebrafish within laboratories. After eggs are collected, the DNA is ablated, and cells are implanted through the micropyle before the eggs are reactivated. Current experiments focus on standardizing the procedure and testing donor cell types to optimize the process. Progress is possible in the chromatin modifier, where many failures in cell reprogramming occur—by erasing the memory of several

methylation types from genes related to somatic cells, the cells can be made more plastic to improve cloning. Dr. Cibelli's team is assessing zebrafish cells to identify those with the lowest amount of H3K9 methylation to use as donor cells. Improving parameters for identifying ideal chromosomes for the cryopreservation of zebrafish is also in progress.

Videos Highlighting ORIP Research Resources #1
Moderator: Desirée von Kollmar, ORIP

Center for Precision Animal Modeling (C-PAM)
Bradley Yoder, M.D., The University of Alabama at Birmingham

C-PAM's video introduced its role in providing critical infrastructure for precision diagnostics and therapeutics for the wider biomedical community using animal models. C-PAM addresses human variants of uncertain significance and the lack of therapies after a genomic diagnosis, with the common solution of precision disease modeling. A precision disease model is constructed from the specific molecular characteristics of a patient to become an avatar for that patient. C-PAM has a variety of animal and cell models and aims to eventually translate a specific diagnosis into precision therapeutics. The diagnosis often identifies variants of uncertain significance rather than a specific problem genotype. Variants of very high suspicion can be used to construct precision disease models, which can resolve the diagnostic odyssey if they meaningfully recreate the patient phenotype. These precision disease models can be used to determine the applicability of precision therapeutics.

Aquatic Germplasm and Genetic Resources Center (AGGRC)
Terrence Tiersch, Ph.D., Louisiana State University Agricultural Center

AGGRC's video emphasized the importance of protecting the vital genetic resources of incredibly diverse aquatic species. AGGRC partners with communities to develop tailored solutions for preserving and using genetic resources. Cryopreservation allows genetic samples to be stored and remain viable for decades, protecting valuable genetic traits and reducing the number of live animals needed, minimizing cost and resources. AGGRC has helped create the NIH Aquatic Biomedical Model Repository Network and acts as a centralized hub for repository development, community services, training, and open-source hardware, and it collaborates with other NIH and federal stock and genetics preservation resources.

Ambystoma *Genetic Stock Center (AGSC)*
S. Randal Voss, Ph.D., University of Kentucky

AGSC maintains and distributes stocks from a unique population of laboratory axolotls to laboratories and classrooms throughout the country and abroad. AGSC staff curate and make available information that is useful to the axolotl community. They also perform outreach to introduce students to research and the essential role of axolotls. Axolotls have an unrivaled ability to regenerate organs, including the brain and spinal cord. Understanding the cellular mechanisms of this regeneration could have clinical significance for treating human trauma, disease, and aging. AGSC axolotls—genetically distinct from axolotls currently facing extinction in Mexico—are descended from a hybrid strain founded in the laboratory in 1962, resulting in complex hybrid genomes for all AGSC axolotls, which have hindered attempts to assemble a genome map. AGSC recently used material from a wild tiger salamander to perform *in vitro* fertilization on an AGSC axolotl and then sequenced the genomes of both parents and the hybrid offspring. The Vertebrate Genomes Project made a tool to help assemble the DNA sequences into the correct order, and two highly accurate and complete genome assemblies were made for the axolotl and salamander. The axolotl assembly was recently submitted to the National Center for Biotechnology Information for gene annotation to facilitate research efforts in the axolotl community.

An Integrated Platform for Diploid Germplasm Conservation in Zebrafish
Jose Cibelli, Ph.D., Michigan State University

The Zebrafish International Resource Center (ZIRC) is developing a platform for diploid germplasm conservation in zebrafish for several reference strains. The strategy involves isolating, culturing, and cryopreserving cells for long-term storage. When rederivation of a zebrafish line is needed, cells are thawed and used as donors for cloning. Clones can then be used as progenitors to recreate the line through natural mating. AGGRC and ZIRC collaborate with other partners to develop an integrated platform for isolation, culture, genotyping, and cryopreservation of diploid cells; standardized zebrafish cloning procedures generating homozygous lines; and promotion, dissemination, and training of resource center personnel. Scientists will have access to stable diploid genomes of reference lines—including homozygous zebrafish—and the possibility of eliminating recalcitrant pathogens from contaminated lines.

Drosophila *RNAi Screening Center (DRSC) and Transgenic RNAi Project (TRiP)*
Norbert Perrimon, Ph.D., Harvard Medical School

DRSC and the Transgenic RNAi Project (TRiP) aim to provide cutting-edge molecular genetic technologies to *Drosophila* researchers and other communities. The facility offers start-to-finish in-house support for the engineering of *Drosophila* stocks, such as building Split-GAL4 system stocks to allow community members to perturb genes in discrete cell types. Another project focuses on visualizing mitochondria to support human mitochondrial disease studies in *Drosophila*. Also unique is the support for CRISPR pooled screens in insect cells. The facility offers many opportunities for collaboration, such as community nominations for stock engineering and training for genome-wide CRISPR cell screens. The TRiP toolbox, RNAi, CRISPR, and other fly stocks are directly distributed by the Bloomington *Drosophila* Stock Center. The facility has developed a number of engineered cell lines. These technologies help researchers use more precise fly models for human diseases, apply technologies to insect disease vector species, and mine and integrate model organism data.

Drosophila *Cryopreservation at the University of Minnesota*
John Bischof, Ph.D., University of Minnesota

This center works to establish assets to be used by individual researchers, laboratories, and stock centers for cryopreservation of *Drosophila melanogaster*. Cryopreservation of *Drosophila* strains prevents genetic drift and strain loss. The resource aims to optimize resources for *Drosophila* embryo cryopreservation at the laboratory scale, develop techniques for stock centers, and disseminate resources to the community. A dedicated laboratory space has been established to train scientists, with multiple stations to demonstrate key steps in the procedure. Kits have been designed to ship to individual laboratories, and a website has been established for resource sharing. As the protocol is developed, the center is eager to collaborate to determine how cryopreservation can help meet the community's needs.

Neotropical Primate Reagent Resource
Kathleen Engelman, Ph.D., University of Massachusetts Chan Medical School

The mission of the Neotropical Primate Reagent Resource is to develop and validate monoclonal antibodies required for studies featuring marmosets, squirrel monkeys, or owl monkeys. The availability of immunological reagents specifically tailored for neotropical primates has not kept pace with the growth of this research. The resource has created several new agents to support current studies and open new areas of research previously restricted due to a lack of tools, including species-matched monoclonal antibodies. All *in vivo* antibodies pass rigorous testing for purity, quality, and specificity to ensure safety and reliability. Validated antibody selection for cell population identification includes species cross-reactivity from commercial sources and novel monoclonal antibody discovery for unidentified targets. Anti-IgG antibodies with high reactivity to neotropical monkey IgG and defined monoclonal antibodies

for assay controls are also offered.

Human Tissues and Organs for Research Resource (HTORR)
Thomas Bell, Ph.D., National Disease Research Interchange

HTORR works to provide human biospecimens from all body systems to support the advancement of biomedical research. It uses a prospective procurement model to collect samples, allows the investigator to customize the collection process and preservation method, and provides access to a diverse range of donor populations and sample types with pathology reports. A pilot award program was just launched with 2-year awards that provide up to 10 biospecimens as well as technical support, letters of support, and budgets for future grant applications. This program focuses on individuals from underrepresented populations in the U.S. biomedical workforce, early-stage investigators, and established investigators transitioning to the use of human biospecimens. Applications were due on October 1, 2024.

Building a Wide-Field, High-Resolution Histotomography Resource for Biology
Keith Cheng, M.D., Ph.D., The Pennsylvania State University

Histotomography is synchrotron micro–computed tomography with sub-micron resolution optimized for soft tissue differentiation of centimeter-scale organs and tissue samples. It allows for the digital recreation of histology-like virtual sections and can be used to study micron- to millimeter-scale phenotypes characterized by convoluted or branched structures. The central goal of this technology is to enable quantitative histopathological analysis that facilitates the objective, reproducible study of the volume, shape, and texture of cells across organisms and tissue types. Custom-designed optics combine high resolution with a wide field of view, and experts across disciplines will use this technology, still under development, to collaborate and accelerate discoveries.

Session II: Creating an Effective Data Management and Sharing Plan
Moderator: Biao Tian, Ph.D., DCM, ORIP

Review of NIH Policy and Expectations
Cindy Danielson, Ph.D., Office of Research Reporting and Analysis (ORRA), Office of Extramural Research (OER), and Julia Slutsman, Ph.D., Data Sharing Policies Implementation (DSPI), OER

Data sharing helps enable validation of research results, availability of high-value data sets, acceleration of research, increased collaboration, public trust in research, accountability, stewardship of taxpayer funds, maximized participant contributions, and appropriate data protections. NIH requires all NIH-funded research generating scientific data to have a Data Management and Sharing (DMS) Plan. This requirement would not apply to grant programs that support infrastructure if no research question is proposed, but if core facilities support research that generates data, a single DMS Plan should be submitted with each application. A comprehensive list of activity codes generally subject to the policy is available, but each funding opportunity will identify whether a DMS Plan is required.

NIH's policy has an expectation of maximized data sharing as the default practice. However, not all data generated over the course of a project will be scientific data, and not all data will be appropriate to share. Sharing may be limited for ethical, legal, or technical reasons, but NIH generally will not accept assertions that the data set is too small, unlikely to be reused, or not aligned with a suitable repository. Scientific data underlying a peer-reviewed journal article should be shared no later than when the article is published, and additional scientific data should be shared no later than the end of an award. NIH does not set a specific time frame for how long shared data should be available, but a time frame may be specified by the chosen repository.

NIH offers many resources on the DMS Plan website to help applicants, such as a framework for

assessing repositories, sample plans, webinars, and FAQs. Allowable costs in budget requests include resources for curating, preserving, or sharing data but not costs associated with infrastructure or routine conduct of research. Changes to DMS Plans can be requested off-cycle using the prior approval method or when reporting plan results in the Research Performance Progress Report. The majority of applicants submit the optional format page, but reviewers have noticed that plans often include repetitive or inconsistent information, so applicants are encouraged to review submissions carefully.

Discussion

- The presenters were asked how the DMS Plan resources on the website are kept up to date. The National Library of Medicine has a process for gathering information from ICOs to update the list of NIH-supported repositories periodically, and the Office of Data Science Strategy (ODSS) maintains a list of generalist repositories.
- One attendee pointed out that many institutions did not receive thorough information on the requirement before its implementation and that many questions on the form are redundant. He also asked how NIH defines sharing, noting that researchers often request a co-author credit in exchange for sharing older data. The presenters responded that NIH worked to conduct community outreach before implementation. They agreed that the form could be improved and noted that a pilot with the Federal Demonstration Project is in progress and will use a streamlined form. Sharing means making data available more broadly outside the project, which may be controlled or public access. The policy aims to ensure that limitations are appropriate, but a culture change is required and takes time.
- Another participant asked about plans for data persistence. The presenters replied that generalist repositories are available if an appropriate repository does not exist.
- Drs. Danielson and Slutsman were asked whether NIH plans to offer training in outdated formats so researchers can continue to use older data. They replied that NIH ODSS Generalist Repository Ecosystem Initiative (GREI) discussions have touched on the topic of repositories maintaining a long-term preservation mechanism and/or policy. The ODSS GREI webpage is updated with additional resources as they become available.
- Another question was asked about the conflict between an institution's desire for data security and NIH's desire for data sharing. A session attendee pointed out that Penn State is developing a way to store data in a preapproved location with a single pipeline, which could allow researchers to access it in ways that meet an institution's security requirements.
- The final question focused on expectations for authorship and intellectual property (IP) for reused data. The presenters directed the attendee to IP information in the FAQ on the website and noted that no specific guidance on acknowledgment of secondary use of controlled access data in publications is available except for data subject to the genomic sharing policy.

Session III: Impact Factors for Animal Models and Related Resources

Moderators: Bettina Buhring, Ph.D., DCM, ORIP, and Matthew Jorgensen, Ph.D., Wake Forest University School of Medicine

Lost in Translation: Extrinsic Factors in Animal Research

Claire Hankenson, D.V.M., University of Pennsylvania

Dr. Claire Hankenson, University of Pennsylvania, explained that the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training," first published in 1985, remain relevant. Animal research should prioritize animal welfare and minimize pain and discomfort at all costs. Revision of the guide is in progress and likely will include many changes, possibly including increased flexibility, performance-based measures that depend on species, and additional data behind the recommendations. One important consideration is the role of Institutional Animal Care and Use Committees, which have been criticized for their lack of consistency, but Dr. Hankenson pointed out

that standardization of groups of people is almost impossible. Similarly, she emphasized that aiming for 100% reproducibility of studies is an impossible standard given the variability in extrinsic factors related to animal care, particularly because animal care is provided by humans, who cannot be completely standardized. Even very basic variables, such as the sex of a researcher or how a mouse is handled, can affect the animal's experience and the research results. Workplace behavior has also changed in recent years, with many people reporting more distractions and less focus than before the COVID-19 pandemic, which affects the results of a high-focus task like animal care. In response to these challenges, a working group of the Advisory Committee to the Director (ACD) of NIH reviewed extrinsic factors related to rigor, reproducibility, and transparency in animal care. The ACD working group recommended evaluating all aspects of research design and improving the reporting of methodological details, including information on the environment and animal care. Dr. Hankenson stressed that the research community should shift from aiming for 100% reproducibility to focusing on generalizability and applicability across different research settings.

Do Mice Need an Impact Factor? A Look Across the Scientific Literature to Find How Authors Describe and Validate Key Biological Resources
Anita Bandrowski, Ph.D., SciCrunch

Dr. Anita Bandrowski, SciCrunch, pointed out that many authors of journal articles do not include full, correct information on the source of the model organism strain used, which affects rigor and reproducibility of the studies. The Mutant Mouse Resource and Research Centers (MMRRC) consortium led an initiative in 2016 to reduce nontransparent practices through such efforts as including the research resource identifiers (RRID) for each mouse used in the published paper, which improves the transparency of manuscripts and allows stock centers to track their impact. RRIDs are persistent unique identifiers assigned at the stock centers in collaboration with the Model Organism Database. They also are machine-readable publications. These efforts have significantly increased the findability of mouse resources. Good practices also have increased, although less dramatically, in other model organisms. RRIDs can also optimize research studies or resources by showing the community the available resources for a given disease state.

Another way to assess good practices in scientific research reporting is the SciScore tool, which scores a manuscript on the inclusion of elements required for rigor. This tool has significantly increased the use of RRIDs in some journals, and some increases have been seen in the percentage of publications sharing code. Dr. Bandrowski emphasized that the small improvements noted reflect the start of a culture change in best practices, but the MMRRC's efforts can be studied and applied more widely to drive improvements in transparency across the board.

Artificial Intelligence–Enabled Mouse Genetic Discovery for Improving Human Health
Gary Peltz, M.D., Ph.D., Stanford University

Dr. Gary Peltz, Stanford University, pointed out that major barriers to genetic discovery include limited information on the pattern of genetic variation and many false positives in genetic association studies. Dr. Peltz outlined a study of opioid addiction in mice that led to a study in adult volunteer humans; that study had high success rates. However, a clinical trial for addressing neonatal opioid withdrawal syndrome showed a decrease in symptom scores but no change in incidence or length of hospital stay. Dr. Peltz pointed out that the Mouse Phenome Database contains many traits and data points, but few have been identified and used effectively for disease modeling. Conventional filtering strategies are not practical and result in many false positives. Artificial intelligence (AI)–assisted genetic analysis and literature search can be used to narrow down candidate genes that can be tested experimentally, accelerating mouse genetic discovery.

Structural variants occupy far more of the genome than single-nucleotide polymorphisms. A murine

structural variant database could significantly improve knowledge of disease correlations, but many papers use older sequencing or poor tools. Combinations of high-quality long sequencing and simulations have improved the knowledge of structural variants. Dr. Peltz explained that the SJL mouse, a long-established model, develops spontaneous B-cell lymphomas. AI was used to assess structural variants and identify a gene difference in a specific tissue. Human Hodgkin's disease is also a B-cell lymphoma, so this knowledge may translate to improvements in human health.

Session IV: Strategic Planning for Comparative Medicine Resources

Moderators: Miguel Contreras, Ph.D., DCM, ORIP, and Kent Lloyd, D.V.M., Ph.D., University of California, Davis

Attendees were asked to select one word that characterizes the essential role of DCM in NIH-sponsored biomedical research using Slido word clouds; "support" and "resources" were equally the most popular selections, distantly followed by "animals."

Room 1—Animal Models

Moderators: Oleg Mirochnitchenko, Ph.D., DCM, ORIP, and Bradley Yoder, M.D., The University of Alabama at Birmingham

Discussion

- The group discussed several emerging areas where animal models could be expanded or refined.
  - Humanization around mouse loci would allow direct testing of therapeutics, but any humanized models must consider where the materials come from and whether they represent diverse populations. Patient-specific models are also needed.
  - Models for aging are lacking and should be developed further.
  - Better tools are needed to compare human tissue phenotypes with the microanatomy of animal models.
  - Patient-derived induced pluripotent stem cells (iPSCs) are critical to translating between human and animal research.
  - The microbiome affects therapeutics but has not been controlled; humanizing the mouse microbiome is needed.
  - Looking for new models should be balanced with refining existing models.
  - An inventory of investigative possibilities in naturally occurring species is needed.
  - The best model should be chosen based on histopathology and phenotype specifics.
  - Most studies use inbred lines, but outbred lines or models for diverse backgrounds could provide better results.
  - Invertebrate models that can be humanized are needed.
  - Publishing white papers will help justify the need for new models.
  - The infrastructure of existing facilities needs improvement.
  - Characterizing and maintaining existing models would help researchers use current resources more effectively. Tissue phenotypes for every cell and tissue could be obtained, and computing power could be increased to support projects related to the entire organism.
  - Wider use of the animal models on different genetic backgrounds is needed.
  - More research on mitochondrial diseases is needed.
- The second question was related to emerging services that resource centers should provide.
  - *In vivo* mammalian models for long-term toxicology other than the rat are needed.
  - More data analytics training is needed for typical biologists, and expert analysts should be included in research teams. Data scientists should be added to projects early in their development.
  - Bioinformatics around phenomics is needed. User-friendly interfaces that can be viewed are needed, but bioinformaticians need to focus their efforts to translate the information.

  - A resource's website should be considered part of the resource.
  - Transparency and training are needed to introduce a model, and teaching models for invertebrates are needed at earlier educational stages.
  - Optimizing CRISPR processes for reproductive biology is challenging.
  - Different biological fields use different languages, and identifying and filling the gaps in communication is required.
  - New data science schools are needed to support early training in both data science and biological research. People with interests in both fields are needed.
  - Single-cell technology is needed to compare across species and diseases.
  - Additional suggestions included creating and distributing cell lines relevant to the center, websites of global resources, training videos for all levels of experience, increased phenotyping capacity, support for sharing techniques, and trainee programs at centers.
- The third question was related to challenges and opportunities for maintaining the utility of resource centers.
  - The landscape of products not derived from animals needs to be assessed, and a method for validating such products must be determined. Complementary approaches are needed to address areas where animal models are not translatable, but scoping and prioritization of translatability are needed.
  - Pathologists are needed in environmental toxicology.
  - The lack of integration across subspecialties reflects the tendency of training programs to emphasize specialization.
  - Personnel will be a challenge in the future; NIH budgets are not keeping up with the cost of living, making hiring and retaining personnel challenging. Capped budgets also affect the centers' ability to keep up with research.
  - In some cases, specific pathogens may not be known or managed, which complicates the use of specific pathogen–free animals.
  - Personnel with varied skills and flexibility are needed, as is research housing with separate biosecurity for animal transportation.
  - Expectations for publication often are not relevant to resource centers.
  - Increasing resource center offerings requires expanding or adding centers.
- The group also discussed major factors that resources should consider related to emergencies.
  - Inflexibility regarding using funds is challenging and prevents resources from planning for contingencies. The ability to plan ahead should be built into the grant structure. This is especially difficult for P40 grants, which must zero out their yearly budget.
  - Cryopreservation of all models should be supported, and redundant support systems for websites and databases are needed. Supplies also should be able to be stockpiled.
  - The inflexibility of bureaucracies is challenging; NIH can encourage institutions to maintain support during emergencies.
  - In industry, validation is less important than patterns across models. Consistency across a phenotype could be considered a validation metric, but the difference between consistency and accurate representation of disease should be assessed. The balance between the need for validation and the need for diversity also must be considered.
- Responses to the fifth question, related to new approaches for comparison between model organisms and humans, were submitted by email and referenced genetic synteny studies, common tools for microbiome studies, and the need for comparative atlases for most phenomena.
- A response submitted by email to the sixth question, which focused on NIH high-priority areas, emphasized the need for animal resource centers to proactively address community needs, potentially in response to NIH priorities rather than researcher requests.

Room 2—Physical Infrastructure
Moderators: Yong Chen, Ph.D., Division of Construction and Instruments (DCI), ORIP, and Diogo Magnani, Ph.D., University of Massachusetts Chan Medical School

Discussion

- The group reviewed the opportunities to fund instruments and facilities for participants' institutions. Construction is a unique funding mechanism at NIH because it requires an annual appropriation from Congress. The program is very competitive, and 25% of the budget is allocated to institutions of emerging excellence.
- Although instruments are valuable, one of the recent challenges is the high cost of service contracts, which increasingly makes them inaccessible. The expectation is that the instrument will sustain itself through support from instrumentation fees or user fees. However, it is difficult for many lesser-resourced institutions.
- Meeting the requirement of three major users for an instrument award can be difficult for smaller institutions. A "major user" of an instrument is any researcher with funding from a research project grant.
- The funding caps are adjusted to compensate for rising instrumentation costs; the most recent adjustment was in 2023.
- Users indicate that service vendors are adding surcharges to their costs.
- Awareness of the available programs remains a challenge, and the group recommended that ORIP expand efforts to raise awareness and understanding of these funding opportunities.
- Institutions with co-funding resources can support more instrumentation than lesser-resourced institutions, so increasing funding for the instrument programs would allow more institutions to apply for grants.
- Funding is needed for the service contract to continue running the instrument. Service contract fees are increasing significantly. Users could be asked to share their instruments more widely in exchange, but some institutions may not charge users, and users may not be able to pay, so sustainability models may need to be addressed. A transactional model is not appropriate for all instruments or users.
- One future need is centralized cage washing, which is critical for research programs but requires new equipment, automation, and facilities support.
- C06 grant funding often covers only part of the necessary cost of major new construction.

Room 3—Training
Moderators: Ritesh Tandon, Ph.D., DCM, ORIP, and Craig Franklin, D.V.M., Ph.D., University of Missouri

Discussion

- ORIP is exploring the need for training veterinarians as part of its next strategic plan.
- Interdisciplinary careers and integrated teams are becoming increasingly important. The distinction between cross-disciplinary, interdisciplinary, and transdisciplinary also should be considered. Being interdisciplinary is a skill in itself.
- Cross-training in computational science will be important in planning for the future. Some institutes offer courses on this topic, but more integration would be beneficial.
- Some training programs pull trainees into specialty areas, which can be limiting. ORIP is a home for veterinarians who offer unique expertise and skills for biomedical research. However, other researchers can offer unique perspectives for animal research. Training non-D.V.M.s could be valuable.
- Significant changes to training paradigms will be needed in the future. Bridging the gap between basic research and clinical care is becoming increasingly important. Vertical and horizontal

integration are both critical. This convergence is occurring across many industries.

- The participants' responses to the word cloud were focused on translational science, highlighting the importance of this topic at NIH. Collaboration between physicians and scientists will be important for progress in this area.
- Academic researchers often focus on publications in high-impact journals, but the NIH mission ultimately focuses on translation. More work could be done to bridge the gap between these two approaches.
- Specific expertise is necessary for comparative studies. Additionally, training is needed to meet expectations associated with science research. This can be challenging but is important for moving forward. Diverse perspectives add value to research teams. Diversity encompasses various categories. This information is included in NOFOs, but it was suggested that more efforts be made to convey this information to the research community.
- NIH institutional training grant applications for due dates on or after January 25, 2025, will now include "Training in the Responsible Conduct of Research" and "Recruitment Plan to Enhance Diversity" as items that contribute to the overall impact score. These items will move from "Additional Review Considerations" and will be included as "Additional Review Criteria." As such, reviewers will evaluate the "Training in the Responsible Conduct of Research" and the "Recruitment Plan to Enhance Diversity" while determining scientific and technical merit and providing an overall impact score.
- Training can encourage researchers to think about business perspectives, focusing on the end user. ORIP could consider a similar approach for its training programs. ORIP's current programs do not address all these topics, but it is important to understand the needs fully.
- Broad impact requires team science, but this approach is not supported by current NIH funding mechanisms. This change in perspective reflects overall changes in the world.
- Communication is key to breaking down silos in science. Training in improving workflows and integrating people will be essential. Training is now needed not only for improving technical skills but also for identifying approaches for collaboration and communication. Interdisciplinary collaborations are now expected across the entire scope of a researcher's work.
- ORIP's goals are ultimately focused on the development of animal models for human disease. NAMs also may become important in the future. ORIP's training programs, however, offer training in various scientific areas outside of model development. Veterinarians offer unique scientific skills.
- ORIP's training programs are currently not aligned with its comparative medicine resources; efforts in this area could be beneficial. ORIP's resource grants do include a training component. Resources could work with their institutional leadership to promote training, but institutional barriers are present.
- Cost-benefit analysis should also be considered when developing training programs; certain scientific topics can have a broad impact on the scientific community. A new funding mechanism might be needed to progress in this area. A balance exists between individual trajectories and overall community benefits. The computational science community can serve as a model for this topic.
- The T32 programs are designed to train individuals to become independent researchers, which is rare among veterinarians. Broader criteria for evaluating the success of T32 trainees could be considered.
- Veterinary trainees often do not have sufficient time to develop their academic careers. Protected time is essential for success. Protected time before application would be beneficial but is likely impractical.
- ORIP could help promote interdisciplinary diversity among faculty members involved in its training programs. ORIP's partnerships could serve as a model for such programs.
- ORIP could consider other training avenues focused on nimble approaches for nontraditional topics (e.g., statistics, industry). A certificate program or apprenticeship could be considered for a fast-track approach. This approach is currently being implemented in manufacturing. Stagnant salaries for postdoctoral researchers remain an issue. Addressing this concern would help improve retention.

- NIH's current focus is on early-stage investigators (ESIs). However, team science should still be considered. Additionally, training will be needed as ESIs replace current resource directors; this is a long-standing issue across various areas.
- Fostering diversity remains a challenge across the field. Introducing diversity early in education is essential. Investments in summer programs (e.g., high school, college) could offer long-term benefits.
- Two years of support is often not sufficient for retaining individuals in academia. Long-term diversity support could help address this challenge. Grants for minority-serving institutions can also help foster diversity.

Room 4—Outreach
Moderators: Bettina Buhring, Ph.D., DCM, ORIP, and Marko Horb, Ph.D., Marine Biological Laboratory

Discussion

- Outreach may be considered as occurring within the biomedical community or to the general public. Themed events, such as research animal demonstrations and poster competitions judged on accessibility, can be tailored to the general public. Other outreach activities include events like Take Your Child to Work Day and maintaining an active social media presence to engage a broader audience.
- Reaching lay people is important because the public opinion of research among medical personnel informs their clinical decisions. Driving medicine and education requires the knowledge, support, and engagement of the public.
- To reach others within the same field, Google ads are often cheaper than conferences and reach more people. NIH supports a Slack channel for zebrafish researchers. Local events can improve the engagement of the local scientific community, and smaller conferences can be held to complement large conferences.
- Referrals to biomedical research resources are a critical way to improve community outreach. Conferences often help, but many institutions need to be selective with their conference budgets and have scaled back or diversified their outreach efforts. Sending early-career staff members to conferences can be effective because experienced researchers often already know many people in the field; early-career researchers can also enthusiastically engage with contacts.
- Support for outreach is needed in grant mechanisms themselves, reflecting the importance of outreach.
- Possible metrics for tracking the success of outreach include the number of people who attend facility tours or request pilot projects, as well as the number of letters of support or inquiries. Tracking the usage of reagents is difficult, but sending a logo or boilerplate language that users can apply to their presentations or papers is helpful. Some resources use a memorandum of understanding (MOU) to ensure their resource is acknowledged in publications and meetings. Submission templates could be designed with a field for the source of the resource. A resource acknowledgment request also can be added to email signatures.
- Careful wording is crucial when discussing animal research, particularly in informal settings. Researchers should receive training on how to speak about animal research responsibly and how to engage with activists. Each request for access to resources should be assessed with care to ensure it aligns with ethical and operational guidelines.
- PBS or local news segments may help with outreach, but researchers should review the content to ensure the research been represented accurately.
- ORIP can make additional efforts to publicize NIH, its mission, and details about resource programs.

Videos Highlighting ORIP Research Resources #2
Moderator: Desirée von Kollmar, ORIP

Mouse Peroxisome Research Resource (MPRR)
Joseph G. Hacia, Ph.D., University of Southern California

Peroxisomes are metabolic organelles critical for eukaryotic cell functions and the development and functions of all mammalian organ systems. MPRR aims to promote basic and translational research in peroxisome biology based on community feedback. MPRR uses the Jackson Laboratory (JAX) methodology for producing, phenotyping, and distributing mouse models, and the team builds on a combined expertise in metabolism, imaging, genomics, and lipidomics. MPRR also actively seeks collaborative opportunities that advance scientific knowledge and address complex research challenges relevant to peroxisome biology in health and disease.

Community Resource for Germline and Somatic Genetic Disease Modeling in Zebrafish
Calum MacRae, M.D., Ph.D., Harvard Medical School

The Community Resource for Germline and Somatic Genetic Disease Modeling in Zebrafish has many technologies to characterize complex human disease phenotypes in zebrafish at the cellular and molecular levels, as well as model primary germline variations, gene–gene and gene–environment variations, and somatic variations using a range of both phenotypic and genetic modifying technologies. Important features include very high-throughput CRISPR-based droplet technology, allowing researchers to tag individual CRISPR guides in lipid droplets and then recover genes associated with a particular phenotype. Another technology is tissue editing with inducible stem-cell tagging via recombination, allowing the establishment of mosaic mutagenesis and, therefore, model clonal hematopoiesis of indeterminant potential, which is seen as a major contributor to many chronic diseases.

Precision Medicine Nonhuman Primate Resource
Larry Sherman, Ph.D., Oregon National Primate Research Center (ONPRC)

The Precision Medicine Nonhuman Primate (NHP) Resource at the ONPRC aims to provide opportunities for investigators who want to use NHP models for human genetic diseases and who wish to identify novel models for disease in ONPRC's colony of Japanese macaques and rhesus macaques. This center has had numerous spontaneous models for disease that have to be preserved for researchers to evaluate and use for preclinical studies. The resource aims to facilitate NHP precision medicine and genomic research by providing accessible, high-quality data and analysis tools, including central management of the ONPRC genomic data, harmonization of data and analyses, and web-accessible data and tools. The goal is to support everything from colony management to individual studies, including using the Macaque Genotype and Phenotype (mGAP) Database, which is already widely used to identify animals for research at the ONPRC. The second aim is to identify novel genetic models and genetically valuable animals in the colonies, which will involve using phenotype-to-genotype and genotype-to-phenotype strategies to identify models for human genetic disorders and leveraging that through a resource to develop a macaque embryo bank to allow storage and later use. Data will be entered into mGAP and will go through the embryo bank or into harem breeding for animals to expand in numbers and be used by investigators in the study.

JAX Center for Precision Genetics
Catherine Lutz, Ph.D., M.B.A., JAX

The JAX Center for Precision Genetics creates precision animal models for incurable and genetically complex diseases. It serves as a foundational grant for the JAX Rare Disease Translational Center and the rare diseases community and academic groups. The program has generated more than 90 complex alleles

across 40 rare diseases, advancing therapeutics for Investigational New Drug–enabling studies. Each project begins with the end goal of therapy, using state-of-the-art genetic engineering to develop a mouse model to match the patient's genetic mutation that is then validated as a disease model for preclinical testing and distributed globally via the MMRRC. The goal is to provide resources and research through an accessible, scalable platform integrating a vast array of preclinical capabilities and services for the rare disease community.

Comprehensive Resource for the* Drosophila *4th Chromosome
Stuart Newfeld, Ph.D., Arizona State University

The fourth chromosome is small and often neglected, and it has a reputation as a tough place to work, but it has 79 protein-coding genes, so it is important to understand this chromosome to understand *Drosophila* holistically. This resource was created to mainstream the fourth chromosome. The resource assists others in understanding the protein-coding genes on this chromosome, 95% of which are conserved in humans. The resource provides five types of stocks for gain- and loss-of-function studies of each protein-coding gene and the opportunity to create humanized stocks. The resource has generated and deposited more than 500 stocks at U.S. and Japanese stock centers, with 443 shipped to NIH-funded researchers as of March 2024. The project is ongoing, and RNAi stocks are planned for addition.

New World Monkey Immunoreagent Resource
Luis Giavedoni, Ph.D., Trinity University

The New World Monkey Immunoreagent Resource aims to improve the translational value of New World monkey biomedical models by developing monoclonal antibodies that can be used in immunological assays for the identification and quantification of biomarkers of inflammation and metabolism in marmosets, owl monkeys, and squirrel monkeys. Marmosets are particularly important for the development of new disease models using genetic engineering. One shortcoming is that many monoclonal antibodies specific to human biomarkers are unable to recognize the equivalent target in New World monkeys. The resource has partnered with several institutions to study 10 targets that include important biomarkers of inflammation, metabolic hormones, and lymphocyte activation. The approach involves the expression of the marmoset biomarkers in mammalian cells, immunization of mice, hybridoma production and monoclonal antibody screening, identification of optimal antibody pairs for immunoassays, and validation of the selected antibodies with New World monkey samples, as well as the release of reagents to investigators. The resource facilities include cryogenic storage and immunoassay testing. The resource has an active website with information on each of the targets and protocols.

Xenopus *Cell Atlas*
Leon Peshkin, Ph.D., Harvard Medical School

Xenopus has been used as an excellent model for human disease. The *Xenopus* Cell Atlas at Harvard Medical School and the Marine Biological Laboratory in Woods Hole, Massachusetts, is working to characterize exactly when *X. laevis* and *X. tropicalis* are appropriate models. Tools developed for those species could be used to model human disease. The resource aims to characterize embryonic stages and adult tissues and to assist others in doing so by chaperoning researchers' participation in the project, offering appropriate equipment for single-cell transcriptomics, and ensuring the experiments run well. The *Xenopus* Cell Atlas also developed protocols for effective and rapid blood perfusion and organ dissection and is working to create a bulk proteomic characterization of frog proteins across tissues, which would be very similar to a human protein atlas. The resource also makes the resulting data easily available and browsable and will support researchers in using the data.

Xiphophorus *Genetic Stock Center (XGSC)*
Yuan Lu, Ph.D., Texas State University

XGSC supports education and research for investigators who use fish models to discover solutions to human diseases. *Xiphophorus* species were collected in many habitats throughout Central and South America, and the center now maintains 23 of the 26 documented species of *Xiphophorus*, including 60 distinct genetic lines and at least eight species confined to extremely small geographic areas and threatened by habitat destruction by humans. The center also hosts several *Xiphophorus* genomes and genetic resources, as well as bioinformatic pipelines and a high-performance computer cluster. *Xiphophorus* are small, live-bearing fish that serve as animal models for a wide range of research topics. *Xiphophorus* can produce hybrid offspring, but these hybrids have incompatible genetic interactions, which leads to disease or disease-associated genetic dysregulation, similar to humans. The number of species and fully annotated gene map provide endless potential research questions. The stock center also includes other model species to allow for transgenic studies with species that lay eggs. The center provides scientists in many countries with fish from many strains.

Session V: Administrative Practices at NIH-Supported Resources

Moderators: Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP, and Ki-Cha Flash, M.S., National Heart, Lung, and Blood Institute (NHLBI)

Ms. Ki-Cha Flash, NHLBI, provided a high-level overview of administrative practices for NIH-supported resources. The most recent policy update is a common form for biosketches across a number of federal agencies, which will be implemented at NIH by May 25, 2025. Ms. Flash emphasized the importance of Authorized Organization Representatives (AORs) and encouraged attendees to check in with them regularly with any questions on policy or guidance. AORs are heavily involved in such processes as prior approval requests and can advise awardees on whether a proposed change requires prior approval. Grants management officers or specialists may respond to prior approval requests via email or revised awards, but only these responses are considered official. Subrecipients must submit prior approval requests to the primary recipient organization. Typical prior approval requests include changes in personnel, effort, or budget; Ms. Flash noted a law requiring that the AOR notify NIH within 30 days of any program director, principal investigator, or key personnel receiving disciplinary actions or being removed as a result of harassment.

Ms. Flash outlined the rules for no-cost extensions, which can be executed by the AOR through the eRA Commons. No-cost extensions cannot include requests for additional funds or changes in project scope and must include confirmation that additional work remains on the project and resources are available to continue the work. Prior approval is required for changes in scope. A change in recipient organization is known as a transfer, which shifts legal and administrative responsibility from the initial recipient to a new organization. The AOR will relinquish the award to the applicant and then coordinate the transfer with the AOR from the new institution. Ms. Flash noted that this action is often significantly delayed, so awardees who plan to change institutions should contact their AORs as soon as possible. NIH expects both relinquishing and applicant organizations to disclose whether the transfer is occurring as a result of misconduct.

Requests for carryover of unobligated funds must be submitted by the AOR to NIH staff, the grants management specialist, and the program official. Such requests must meet an immediate need, and funds must be spent within the current budget period. A federal financial report (FFR) must be submitted and accepted before the carryover request is honored. Program income must be reported on the FFR. Changes in other support should be submitted as soon as possible—Ms. Flash emphasized the need for researchers to maintain integrity in this area. She reiterated that any researchers experiencing challenges should contact their AOR as soon as possible.

Discussion

- An attendee asked why the biosketch form was not made electronically. Ms. Flash explained that agency harmonization is the first area of focus but that an electronic form is likely in the future.
- Ms. Flash advised attendees to submit an FFR several days before a carryover request.
- Ms. Flash confirmed that the AOR must submit a just-in-time request.
- Attendees encouraged NIH to revisit the requirement for P40 awardees to spend their entire yearly budget.

DAY 2: WEDNESDAY, AUGUST 7, 2024

Welcome

Tara Schwetz, Ph.D., Deputy Director, NIH; Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

Dr. Tara Schwetz emphasized the importance of meetings such as this to NIH's mission of seeking and applying knowledge about the fundamental behavior of systems. She noted that the ACD working group's report on enhancing rigor, translatability, and transparency in animal research, published in 2021, emphasized the significance of animal models and made recommendations for improvements, which NIH has begun addressing. Dr. Schwetz also commented on Complement-ARIE, which addresses recommendations from an ACD working group on NAMs, which complement but will not replace animal studies.

Discussion

- A session participant asked about collaborative mechanisms across agencies to address severe problems in society worldwide. Dr. Schwetz emphasized the importance of collaboration to DPCPSI's work within NIH and noted that the same skills can be used to reach other federal partners.
- Another attendee asked about updates on the shortage of NHPs. Dr. Schwetz responded that a new report from ORIP on this topic will be available soon.

Session VII: Summary of Breakout Sessions

Moderators: Miguel Contreras, Ph.D., DCM, ORIP, and Kent Lloyd, D.V.M., Ph.D., University of California, Davis

Breakout 1 Summary—Animal Models

Oleg Mirochnitchenko, Ph.D., DCM, ORIP, and Bradley Yoder, M.D., The University of Alabama at Birmingham

Dr. Yoder summarized the breakout group's discussion on animal models, which began by considering new areas of animal model application and research. Humanized models, which involve replacing sections of the genome to make the models more relevant, were emphasized, as was a need for models for specific impact areas, like aging and rare diseases. The group also noted the need to balance *in vitro* and *in vivo* resources, iPSCs that parallel existing models, and tissues on a chip. Group members discussed the difference between validated, standardized, and consistent models and the need for validation steps for models that may not mimic exact diseases but will provide consistent results. The impact of the microbiome, its variability at different institutions, and how that affects the phenotype of models were discussed. Group members also discussed the need to remain open to new model systems—especially those that would provide benefits for studying an aspect of human disease—and noted the need to address patient diversity, genotype-phenotype correlations, and the use of inbred and outbred models to mimic the human population. Members also noted the possibility of genetic drift in model organisms.

The second question focused on services and how the research community can support new research; most of this discussion focused on data analytics and data analytics pipelines. Centers must be able to help analyze variation, and there is a need to look across model systems and non-animal model systems used in this realm. White papers that describe the benefits of model systems are needed, and structural or epigenetic changes that differ between models must be defined. Other needs include expanded toxicology studies, increased knowledge of the reproductive biology of model systems, and single-cell technology resources across the community.

The third question focused on challenges and opportunities. Group members emphasized the need for support from ORIP to revitalize infrastructure and facilities. Data science resources are needed, and training must be developed to integrate data scientists into biology programs. Ensuring people are using the same terminology across disciplines is critical. Group members also noted the challenge of budgets and retaining personnel, especially in informatics. The diversity of extrinsic factors must be addressed, and interspecies comparisons and correlations with organoid systems are needed to determine how to mimic phenotypes in non-animal model systems. The group emphasized the critical need for better and much earlier integration of biology and data science components and suggested training programs that could teach biologists data science or teach data scientists biology.

Although time was limited for discussing the fourth question, which centered on how to address issues that may affect emergency situations, group members noted that resources are restricted in their ability to adjust funds for backup contingencies, and they discussed how to back up colonies at other institutions to enable quick recovery from emergencies.

Breakout 2 Summary—Physical Infrastructure
Yong Chen, Ph.D., DCI, ORIP, and Diogo Magnani, Ph.D., University of Massachusetts Chan Medical School

Dr. Diogo Magnani, University of Massachusetts Chan Medical School, explained that many working group members were unaware of the existing award mechanisms from DCI, so the group discussed the programs available to the resources and how to apply for instruments, equipment, and construction. They reviewed the current strategic plan's emphasis on supporting the acquisition of modern scientific instrumentation and modernizing the infrastructure of laboratories and research facilities. Many attendees already had access to instruments funded by these mechanisms, usually available at their core facilities or animal facilities. Group members discussed how to keep instruments well maintained during the current budget leveling. Institutions may be able to contribute funding to complement the grant, but this may be a disadvantage for lower-resourced institutions. Service contract costs are skyrocketing, and no mechanisms offer support for service contracts, so maintaining instruments often is not financially feasible. The group noted that the language of many funding announcements is focused on core facilities and eligibility for different funding mechanisms should be clarified. The discussion also touched on how to measure and report a successful equipment acquisition. Group members expressed interest in centralized cage washing as a future need. Dr. Magnani emphasized that the mechanisms are easily identifiable on ORIP's website and social media, but those avenues have not been sufficient for spreading awareness. The group also recommended that ORIP consider how to address current equipment that is functional but underfunded.

Breakout 3 Summary—Training
Ritesh Tandon, Ph.D., DCM, ORIP, and Craig Franklin, D.V.M., Ph.D., University of Missouri

Dr. Craig Franklin, University of Missouri, explained that the group's discussions focused on the need for broad training that would allow researchers to move between fields and develop interdisciplinary skills, especially with a constant translational component. ORIP's existing programs focus on training veterinarians but could be expanded, and animal model training could be provided at core facilities with

many trainees in different specialties, facilitating collaboration. Formal training is also needed in computational and transferrable skills, such as collaboration, negotiations, operations management, and business. Partnerships with institutes and centers (ICs) could be explored to support such programs. Current training programs push researchers into silos, and trainees often move into industry, making them difficult to track. Candidates have become nimbler and want faster results, which could be addressed by certificate or apprenticeship programs—Dr. Franklin emphasized the need to consider what trainees want when developing training programs. The group also discussed the R50 mechanism and ORIP's summer research programs for veterinary students, for which tracking is challenging. Training opportunities are also needed for existing scientists who want to change careers. Resource centers may be able to offer sabbaticals, workshops, or collaborative model-specific training. Transition planning is needed for resource directors, and academic culture must shift away from R funding; such a shift will require institutional support, dedicated time, and support for broad-based scientists who may not apply for individual R awards. The group also discussed the importance of starting diversity initiatives early and developing long-term diversity support.

Breakout 4 Summary—Outreach
Bettina Buhring, Ph.D., DCM, ORIP, and Marko Horb, Ph.D., Marine Biological Laboratory

Dr. Buhring explained that outreach to the public is important for justifying taxpayer funds, educating the next generation, helping inform the public's voting priorities, and supporting medical professionals' decision-making. Public outreach can be conducted through social media, patient advocacy days, outreach events that include both scientists and artists, and creative evaluation criteria—such as judging posters on how well the topic is explained to a lay audience—as well as by using the animal model as a demonstration if feasible, providing summer programs for schoolchildren or tours for staff and families, and supporting Take Your Child to Work Day events. Outreach to other investigators can involve a wide range of actions, from holiday cards (a cost-effective method) to conference booths, which are expensive and time-limited but can increase the enthusiasm of newer researchers and build relationships in person. Other mechanisms include Google ads, listservs, email signatures, and social media. The group also noted that NIH supports a Slack channel for zebrafish researchers.

Outreach metrics may include tracking how many inquiries a resource receives, performing Google analytics, or conducting annual surveys of publications that mention the resource. Although stock centers may have metrics, the product is often generated at an academic institution. Showcasing the science via a website and formalizing the acknowledgement of resources with an MOU can help increase awareness. Staff should receive training to write and speak about animal research, screen people for access, and work with nonprofits who have experience explaining biomedical research involving animals. Success stories with a human element, such as curing a disease, are good to showcase, and researchers should review the stories before release to ensure that information is not taken out of context. Researchers should also make efforts to explain the value of biomedical research to legislators.

Discussion

- Although humanized mice were discussed, other humanized models also should be considered.
- One session participant encouraged attendees to consider acknowledging statistical variation and characterizing the degree of variation. A mechanism is needed to compare the histopathology of human diseases to animal models when the tissue phenotype is seen as the gold standard.
- Another individual suggested that outreach efforts should include the promotion of good research practices, such as clear citation of resources.
- A question focused on what centers can do to help early-career researchers access NHPs. Dr. Magnani noted that some special programs for early-career investigators are available, but specific grants may be necessary. A participant pointed out that the shortage of NHPs makes using

primate centers difficult for all researchers, especially early-career investigators. Centers are optimizing the use of animals as much as possible through such methods as precision medicine, preservation techniques, and tissue-sharing networks, but research is sometimes too specialized for these methods.

- In addition to the seven primate centers, several P40 grants support NHP research, and some prioritize ESIs. An attendee pointed out that primate centers often have pilot grant programs and visiting scientist programs that could be used by early-career investigators. Although these efforts are known, they often are insufficient to deliver the resources investigators need.
- One session attendee encouraged researchers to discuss the need for additional funding with their program officers to identify whether supplements are available. He asked about suggestions for IC partnerships with training programs. The panelists explained that the suggestion focused on broad-based, interdisciplinary training with the option to partner with an IC to develop skills in a specific focus area.
- Another individual encouraged early-stage scientists to use less common animal models to generate robust preliminary data if NHPs are unavailable.
- One participant pointed to the loss of many trainees due to lack of funding, which has been occurring across veterinary medicine subspecialties. He encouraged collaboration between human pathologists and comparative medicine pathologists and suggested using case-based learning in many training areas.
- An attendee pointed out that improving training requires addressing pipeline issues by finding ways to engage nontraditional students and increasing the number of people interested in science. Career paths are needed that allow people to afford to live in the areas where institutions are located. Another participant pointed out that current training paradigms unintentionally push researchers into niche areas, so intentional efforts to expand training—such as providing information about alternative careers and creating relationships with instructors and mentors to engage students regularly—are needed.
- A session attendee asked about opportunities to discuss outreach with the leadership of granting agencies and was advised that individual researchers should pursue these efforts within their agencies.
- Another participant recommended working with local PBS stations to increase outreach.

Attendees were asked to repeat the exercise in which they selected one word that characterizes the essential role of DCM in NIH-sponsored biomedical research using Slido word clouds; “support” was the most popular selection, followed by “resources,” “funding,” “collaboration,” and “training” in the respective order of times mentioned.

Videos Highlighting ORIP Research Resources #3
Moderator: Desirée von Kollmar, ORIP

National* Xenopus *Resource (NXR)
Marko Horb, Ph.D., Marine Biological Laboratory

NXR is home to more than 10,000 frogs comprising hundreds of mutant lines. The facility features picoinjectors, micromanipulators, stereoscopes, and equipment necessary for research. A fluorescent microscope enables researchers to visualize the numerous transgenic lines currently available at the NXR. The *Xenopus* mutant resource allows collaborators to increase experimental capabilities, engage with other researchers, and train in the latest genome-editing technologies, aided by experienced research staff. Experienced husbandry staff can accommodate multiple generations of lines, and projects infeasible for independent researchers can be accomplished at pace for collaborators, assisted by full-time staff. Cryopreservation has been ramped up to increase the availability of genetically modified *Xenopus* lines, and the NXR resources help researchers expedite and achieve their experimental goals.

Session VIII: Key Considerations When Adding a Curation and Informatics Component to a Comparative Medicine Resource

Moderator: Oleg Mirochnitchenko, Ph.D., DCM, ORIP

New Curation and Informatics Component of ORIP's P40

Oleg Mirochnitchenko, Ph.D., DCM, ORIP

ORIP has developed a new component of the P40 mechanism that requires recipients to develop DMS plans, improve access to resource databases, and track usage and impact metrics. ORIP's request for applications (RFA-OD-23-001) for the Animal and Biological Material Resource Centers (P40) (Clinical Trials Not Allowed) will be active until 2026. Competitive supplements to add a Curation and Informatics component to existing P40 Centers (Notice of Special Interest [NOSI] NOT-OD-23-068) were developed and announced in 2023. Upcoming due dates for supplement applications include September 26, 2024; January 28, 2025; and May 28, 2025. The goal of the new component is to support development and maintenance of in-house data management systems according to findable, accessible, interoperable, and reusable (FAIR) principles; curate stocks of animals and biomaterials and generate associations with related genotypic and phenotypic information; maintain a web portal that allows resource catalogs to be searched (according to model phenotype and reagent properties) and enables client-friendly ordering and outreach; report on the downstream effects of distribution activities and services provided to the biomedical community; and train in-house curators in informatics management and webpage development skills. The study section review of the Curation and Informatics component will consider both supplemental activities and the overall efforts of the parent center. Reviewers will evaluate several aspects of the proposal, including existing infrastructure, proposed additions and innovations, the potential value of the proposed changes, the inclusion of clear goals and metrics for measuring outcomes, updates to automated or real-time tracking systems, interactivity with other databases, website improvements, and plans for future growth. Those interested in applying for P40 supplements are encouraged to contact Dr. Oleg Mirochnitchenko and the ORIP program officer for the parent award to confirm that the supplement falls within the scope of the parent award and discuss the Curation and Informatics component in further detail. To facilitate efficient processing of the request, the ORIP NOSI scientific contact should be notified that a request has been submitted in response to this NOFO.

Backstage at the MMRRC Informatics, Coordination and Service Center

Ian Korf, Ph.D., University of California, Davis

The MMRRC consortium is a repository that breeds, cryopreserves, and distributes genetically engineered mouse strains and mouse embryonic stem cell lines with potential value for the biomedical research community. Founded in 1999, the MMRRC offers more than 64,000 resources and supports approximately 1,800 orders and 400 scientific publications annually. The MMRRC consists of four Centers (University of California, Davis; University of Missouri; The University of North Carolina at Chapel Hill; and JAX) and one Informatics, Coordination and Service Center (ICSC). The ICSC supports the MMRRC and external users, providing social media outreach, customer service, legal and logistical coordination, data analysis, database management, programmatic access, computer infrastructure, and applied research. More than half of the ICSC's budget supports informatics (36%) and service (19%) activities. Other budget categories comprise curation (17%), outreach (14%), coordination (13%), and research (1%). The ICSC employs four full-time equivalent employees and six part-time staff.

The ICSC maintains the MMRRC website, which includes a catalog of available mouse strains, a portal for strain submission, a selection of scientific methods and best practices, and applications for internal administration and curation accessible only to internal users. A Strain Detail Sheet (SDS) is maintained for each mouse strain or resource in the repository; it describes each product's genotype, phenotype, history, husbandry, and availability and includes links to relevant databases and resources. SDS

information is manually curated to ensure that each strain is described accurately. Ordering mice is complicated: Shipping costs vary, mouse strains often require time to recover from cryopreservation, and material transfer agreements must be negotiated and tailored to academic or private research organizations as needed. Strain submissions are complex, as well. Investigators can initiate a submission, which then undergoes review by the MRRCC Coordinating Committee to ensure that the strain is unique, valuable, and generated using sound scientific methods. A limited number of strains are submitted directly by NIH.

ICSC informatics activities center on databases (e.g., data storage models, file storage, programmatic access), infrastructure (e.g., space, power, HVAC, servers, networks, workstations, backup/archives, security, support), and website support (e.g., content management, external applications, internal applications). Data curation is a scientific activity that cannot be outsourced to an external builder. Only scientists understand the data relationships, and because software must adapt to data and policy advancements, the software development cycle is unending. Cooperation between biologists and informatics professionals can be costly and challenging but is critical for organizations like the MMRRC.

Building Data Bridges in Research: Curation, Informatics, and Impact on the Nonhuman Primate Reagent Resource
Diogo Magnani, Ph.D., University of Massachusetts Chan Medical School

The Nonhuman Primate Reagent Resource (NHPRR) provides specialized therapeutic biologics to advance research involving NHPs, with data related to these biologics being just as crucial as the products themselves for ensuring effective, reproducible, and safe research. Species-specific reactivity data, for example, help researchers select the appropriate reagent for their NHP models, while additional metadata informs biologic behavior *in vivo*, including half-life and mechanisms of action. The NHPRR informatics component—a new addition introduced in the 2024 P40 renewal—aims to streamline the development, cataloging, curation, dissemination, and reporting of data tied to NHP research resources. NHPRR's data workflow integrates product design, development, and production with its catalog, ordering system, and metadata, and links this information to customer orders, usage, and outcomes. To develop this informatics resource, data science experts were consulted to improve the searchable catalog of NHP reagents by incorporating validated metadata. Previously shared in a proprietary PDF format, product metadata was transitioned to a more accessible table format, aligning with FAIR and TRUST (transparency, responsibility, user focused, sustainability, and technology) principles. Proposed updates to the data and metadata models, including revisions to vocabulary and relationships, aim to ensure rigorous data management. New reporting tools are also being created to reduce the effort of curating the NHPRR database. Persistent identifiers (e.g., RRIDs) facilitate the collection of reporting metrics and publication aggregation, supporting validation activities and enhancing reproducibility. For example, implementing RRIDs in 2020 led to an increase in NHPRR citations in subsequent publications. Through these initiatives, the new NHPRR informatics component supports the development of new data associations that improve research rigor and reproducibility, resource efficiency, and create novel opportunities for the aggregated analyses of outcomes of NHP research using our reagents.

Open Discussion with Panelists
Elizabeth Bryda, Ph.D., University of Missouri; Mike Schmale, Ph.D., University of Miami; and S. Randal Voss, Ph.D., University of Kentucky

Dr. S. Randal Voss, University of Kentucky, emphasized that Curation and Informatics components should be tailored to the needs of each resource. He noted that the AGSC had applied for a supplement in May 2023 to address immediate recordkeeping needs. The resource initially recorded information on cards before transferring it to a structured query language (SQL) database; it is currently hiring two full-time employees to help shift to an entirely wireless recordkeeping approach.

Dr. Elizabeth Bryda, University of Missouri, noted that the Rat Resource and Research Center received funding in July 2024 and will submit a renewal application in spring 2025. She pointed out the benefits of coordinating with the Rat Genome Database and highlighted the challenge of finding and hiring data scientists when one lacks expertise in that field. Coordination within the scientific community is necessary to address crosscutting data needs.

Dr. Mike Schmale, University of Miami, remarked that the National Resource for *Aplysia* also applied for a supplement in the past year. He highlighted the importance of implementing informatics solutions that have worked for other organizations (rather than using precious resources to invent novel data solutions) and noted efforts to develop training videos for the resource website.

Discussion

- In response to a question about software costs, Dr. Schmale noted that software licenses can cost up to hundreds of thousands of dollars. Smaller resources with minimal budgets can benefit from communicating with other organizations about cost-effective data system solutions.
- One session attendee emphasized that early coordination between biologists and data scientists guarantees their efforts to develop curation workflows will be cheaper and more efficient.
- Another individual described their experience with the *Caenorhabditis* Genetics Center's transition to a cloud-based website with custom software. The biggest challenge was communication between the biologists and the programmers, who each had their jargon, viewpoints, and expectations. Another participant agreed and noted that communication gaps could be addressed through training.
- A participant noted positive experiences with FileMaker Pro software, which is practical, inexpensive, easy to learn, and suitable for smaller resources.
- Several participants pointed out that smaller resources would benefit from interacting with and receiving guidance from larger, more established resources with more developed data curation and integration systems.

Session IX: Planning for the Expected and the Unexpected

Moderators: Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP, and Elda E. Sánchez, Ph.D., Texas A&M University–Kingsville

Cryopreservation of *Drosophila* Embryos: Importance of Repeatability and Reproducibility in Protocol Dissemination

John Bischof, Ph.D., University of Minnesota

Protocols that are not robust and repeatable are not adopted within the scientific community. In 2020, the National Science Foundation jointly awarded funding to the University of Minnesota and Massachusetts General Hospital Center for Engineering in Medicine to establish an Engineering Research Center for Advanced Technologies for the Preservation of Biological Systems (ATP-Bio) to address the main barriers to successful cryopreservation. Cryoprotective agents (CPAs) must be engineered, and nontoxic means to deliver them must be developed. Multiscale thermodynamics of water must be studied to address excessive ice formation and associated thermal and mechanical stress. Techniques for rewarming to a physiological temperature must also be established. Techniques for freezing *Drosophila* embryos had been developed at the University of Minnesota (Hays/Bischof groups) for a number of common lines and were published in 2021, but embryo staging issues and other barriers to reproducibility remained, especially for new lines. With NIH R24 support, the University of Minnesota group developed a method for addressing these challenges and improving survival during cryopreservation (e.g., collecting eggs at a specific time and temperature, permeabilizing with gentler reagents, ensuring that embryos are rehydrated properly after dehydration and before CPA loading, reducing the Leidenfrost effect during freezing, warming frozen embryos in a sucrose solution, feeding newly thawed embryos an optimal diet to support

their reanimation). Recent improvements to the method will be published shortly and posted on a Canvas website that disseminates the NIH supported protocol. This work will also be amplified on the ATP-Bio website. In-person training activities related to the method are being planned.

A Nonhuman Primate Precision Medicine Resource: Discovery, Characterization, and Preservation of Novel Models of Human Diseases
Larry Sherman, Ph.D., ONPRC

Naturally occurring mutations in animal models can inform the understanding of human disease. The ONPRC recently experienced several cases of monkey infants being born healthy but developing serious neurological symptoms at 3 or 4 weeks of age. The sick animals were euthanized and found to lack myelin in their central nervous systems. Further studies showed that these animals carried proteolipid protein 1 mutations, identical to those associated with Pelizaeus-Merzbacher disease. RNA-sequencing has been performed on tissues from these animals to identify early biomarkers that can be used to screen for Pelizaeus-Merzbacher disease in infants, who often appear healthy immediately after birth. Researchers at the ONPRC are assessing several other naturally occurring mutations in NHPs that mimic such conditions as Batten disease and multiple sclerosis. ONPRC's NHP Precision Medicine Resource is focused on improving methods for identifying and preserving these valuable models and developing ways to manage and harmonize relevant genomic data, including integrating ONPRC data with mGAP. An NHP embryo bank is also being developed using an iPSC strategy.

A Cautionary Tale About Federal Export Controls
Kevin Cook, Ph.D., Indiana University Bloomington (IUB)

Research in *Drosophila* often involves using transgenes to activate gene expression artificially in specific cell types. In general, a GAL4 transcription activator protein is expressed under the control of a tissue-specific enhancer; when present in a cell, GAL4 drives the expression of a target gene via an upstream activating sequence (UAS). FlyLight, based out of Janelia Research Campus, is a major effort to catalog the spatiotemporal expression patterns of different GAL4 activator transgenes in the fly nervous system. Similar efforts are being made to identify intestinal cell–specific activators at IUB.

UAS–Ricin A transgenes are useful for studies of *Drosophila* development because intracellular expression of the A protein subunit of the Ricin toxin ablates cells. Combined expression of tissue- or cell-specific GAL4 transcription activator and a UAS–Ricin A construct rapidly and efficiently eliminates cells expressing GAL4. The A subunit of Ricin requires the presence of the Ricin B subunit to enter a cell; in the absence of the B subunit, the A subunit is harmless unless directly expressed within a cell. The Ricin holotoxin (i.e., combined A and B subunits) is highly toxic and classified as a Select Agent and Toxin by the U.S. Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC). Transgenes expressing the A subunit exclusively are considered innocuous and are not classified as regulated products. After conferring with an IUB institutional biosafety committee, an internal research compliance officer, an external biosafety consultant, and a CDC representative, standard distribution practices were used to disseminate strains containing the Ricin A subunit. International shipments began in 2016. In 2021, guidance from a newly established IUB export control office indicated that more stringent U.S. Department of Commerce (DOC) regulations required a license to export Ricin A–containing products. A total of 42 shipments had infringed upon these regulations, and the violation was disclosed to the DOC that year. IUB was subjected to DOC penalties (e.g., mandatory institutional education efforts around the incident and additional training to prevent future violations) and the focus of negative press. Federal regulations surrounding exports involving unusual reagents—especially any toxins or pathogens—should be reviewed carefully with institutional support, and licenses must be obtained when necessary. IUB has halted exports of Ricin A–containing *Drosophila* strains, and stocks for the most effective cell-ablation method in flies are no longer available from a public repository to any researcher outside the United States.

Surviving Challenges at the Caribbean Primate Research Center (CPRC)
Melween Martinez, Ph.D., University of Puerto Rico (UPR)

The CPRC, located in San Juan, Puerto Rico, experiences unique weather-related challenges. The resource has developed a hurricane season checklist to prepare for incoming storms, which includes preparations to complete 48 and 12 hours before a storm is scheduled to land on the island. CPRC staff, like most residents of Puerto Rico, have similar checklists for their homes. In 2017, Hurricane Maria—a deadly Category 5 storm—passed directly over Puerto Rico. The widespread flooding and subsequent devastation resulted in the loss of major utilities (including water, electricity, and internet and telephone connections) for weeks and months after the storm. Ecosystems at CPRC's Cayo Santiago Field Station, which is home to approximately 1,000 free-ranging rhesus macaques, were disrupted. The Sabana Seca Field Station lost power for 10 months. Despite the disastrous events, preparations before the storm minimized animal losses. A recovery grant was awarded to assist the recovery process, and animal allocations to the NIH-funded CPRC program continued. A new law established Cayo Santiago as a protected area from outsiders. Lessons learned included the importance of previous risk assessments, communication (e.g., among key personnel and with regulatory and funding agencies), emergency infrastructure and supplies, support for employees, and documentation of damage. Institutional and outside support, as well as small daily victory celebrations, were key to weathering the disaster.

In 2022, the CPRC faced another challenge. Access to the CPRC was denied during a UPR union strike. After negotiations with the union, two veterinarians and a research assistant were the only staff members permitted to enter the facility and provide care for the entire colony, which consisted of 2,400 rhesus macaques. The situation (which lasted for 2 days) was immediately reported to the Association for Assessment and Accreditation of Laboratory Animal Care, the NIH Office of Laboratory Animal Welfare, and the USDA through the UPR Institutional Animal Care and Use Committee. In 2022, the CPRC received critical remarks from a USDA inspector and was the subject of a complaint filed by People for the Ethical Treatment of Animals about lack of adequate care during the strike. During a second union strike in 2023, a list of permitted entrants to the facility was respected. After an investigation that ended in 2024, UPR is proposing a settlement with USDA's Animal and Plant Health Inspection Service. No further compliance issues were identified during subsequent inspections.

Discussion

- A session participant asked how animal care staff should be rewarded. Dr. Melween Martinez, UPR, suggested immediate help could be found after an emergency to show that the institutions care for the staff. Certificates of recognition also can be arranged. Dr. Sherman added that primate centers encourage researchers to engage with the animal care staff as part of the team, including presentations and events.
- Another attendee asked about ONPRC's multiple spontaneously occurring models for rare diseases; Dr. Sherman clarified that large populations of NHPs are more likely to experience genetic drift. ONPRC's Japanese macaque colony is unique because new animals have not been introduced; it supports three rare disease models. mGAP suggests that other such models may arise.
- One individual asked about public education to support more reasonable regulatory processes. He also asked whether mutations could be anticipated if genomes are known. Dr. Sherman explained that they already see examples of alleles from a variety of conditions. A naturally occurring virus arose that triggered multiple sclerosis–type disease, creating a useful model. He invited researchers interested in particular diseases to contact him. It was pointed out that solutions may seem reasonable, but that cost is limiting in some contexts, and the effort required to overcome these limitations is often not worth pursuing. Although this respondent's team tries to educate regulators, regulations written with large animals in mind are often irrelevant to other species.

Feedback, Recommendations, and Planning for 2026

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

Dr. Sánchez asked participants to complete the online meeting survey, which will help the planning team arrange the next meeting.

Closing Remarks

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

Dr. Murphy reflected on the opportunity to explore the various topics presented during the meeting and synthesize the crosscutting themes that emerged. A key theme was precision medicine models and technologies, which tied together discussions on base and prime editing, tissue chips, the work of several resources highlighted in the videos, and novel NHP genetic models. Many new approaches and complementary methodologies—including tissue chips, new cancer and therapeutic methodologies in zebrafish, multispecies genotype-phenotype data for diagnostic and discovery applications, MAGIC tools, and AI-enabled genetic discovery—were discussed. Dr. Schwetz's update highlighted NIH's efforts to apply recommendations from advisory groups and develop NAMs through Complement-ARIE. Data management and sharing were discussed in the presentation on NIH's policy, as well as the presentations on ORIP's efforts to expand curation and informatic capabilities, perspectives from both data scientists and biologists on data curation, behind-the-scenes information about the MMRRC, and challenges and opportunities for informatic capabilities. Reproducibility and transparency were discussed in the talks about extrinsic factors, RRIDs, and SciScore. Dr. Murphy noted that policy and regulations were a theme unique to this meeting, which was discussed in the presentations about the NIH DMS plan requirements, regulations for animal research, the NIH grants policy statement, and rules and regulations around federal exports. The final theme centered on preserving and protecting resources and people, which includes such topics as somatic cell nuclear transfers for germplasm conservation, the many preservation techniques highlighted in the resource videos, and overcoming unexpected challenges. Dr. Murphy concluded by thanking attendees for participating in the breakout groups and remarked on the value of feedback in developing ORIP's next strategic plan.

Meeting Agenda

Day 1 Tuesday, August 6, 2024

7:30–8:30 Registration

8:30–8:40 Introduction and Welcome
Stephanie Murphy (Division Director, ORIP/DCM)

8:40–9:25 Zoom Keynote Presentation: David Liu (Harvard University) Continuous Directed Evolution of Next-Generation Genome Editing Agents

9:25–9:40 Questions and Discussion

9:40–10:55 Session I: Emerging Complementary Models, Technologies and Methodologies
Moderators: Sige Zou (ORIP/DCM); Randal Voss (University of Kentucky)
Investigators will discuss emerging complementary models, technologies and methodologies to provide the best possible services to researchers using animal models.

- Danilo Tagle (NIH/NCATS) Microphysiological Systems: In Vitro Tools For Safety, Efficacy And Precision Medicine Studies
- David Langenau (Harvard Medical School) Defining New Cancer Biology And Therapeutic Opportunities Using Zebrafish
- Melissa Haendel (University of North Carolina, Chapel Hill), The Monarch Initiative: Using Multi-Species Genotype-Phenotype Data For Diagnostics And Discovery
- Jose Cibelli (Michigan State University) Use Of Somatic Cell Nuclear Transfer For Germplasm Conservation
- Chun Han (Cornell University) Upgraded MAGIC Tools For More Reliable And Versatile Mosaic Analysis In Drosophila

10:55–11:10 Questions and Discussion

11:10–11:25 Break

11:25–11:45 Video Presentations of New Resources (2 min per resource for preloaded videos)

11:45–12:20 Session II: Creating an Effective Data Management and Sharing Plan
Moderator: Biao Tian (ORIP/DCM)
This session will provide valuable insights into data sharing practices, standards and protocols, data governance, reproducibility and transparency, and data reuse and secondary analysis.

- Cindy Danielson (NIH/OD/OER/ORRA) and Julia Slutsman (NIH/OD/OER/ORRA) Review of NIH Policy And Expectations

12:20–12:30 Questions and Discussion

12:30–1:30 Lunch on your own

1:30–2:25 **Session III: Impact Factors for Animal Models and Related Resources**
Moderators: Bettina Buhring (ORIP/DCM); Matthew Jorgensen (Wake Forest University School of Medicine)
This session will provide information and discussions on key aspects related to ensuring the reliability and reproducibility of research in order to establish high standards for research practices, data quality, and transparency.

- Claire Hankenson (University of Pennsylvania) Lost in Translation: Extrinsic Factors in Animal Research
- Anita Bandrowski (SciCrunch), Do Mice Need an Impact Factor? A Look Across the Scientific Literature to Find How Authors Describe and Validate Key Biological Resources
- Gary Peltz (Stanford University) AI-Enabled Mouse Genetic Discovery for Improving Human Health

2:25–2:40 **Questions and Discussion**

2:40–3:40 **Session IV: Strategic Planning for Comparative Medicine Resources**
Moderators: Miguel Contreras (ORIP/DCM); Kent Lloyd (University of California, Davis)
This breakout session will provide a platform for participants to share experiences, insights, and best practices in strategic planning for resource centers, fostering collaboration and mutual learning as it relates to the themes from ORIP's Strategic Plan for 2021–2025. The topics to be discussed are:

- Animal Models: Oleg Mirochnitchenko (ORIP/DCM) and Bradley Yoder (University of Alabama, Birmingham)
- Instrumentation: Yong Chen (ORIP/DCI) and Diogo Magnani (University of Massachusetts Medical School)
- Training: Ritesh Tandon (ORIP/DCM) and Craig Franklin (University of Missouri)
- Outreach: Bettina Buhring (ORIP/DCM) and Marko Horb (Marine Biological Laboratory)

3:40–3:55 **Break**

3:55–4:15 **Video Presentations of New Resources (2 min per resource for preloaded videos)**

4:15–4:35 **Session V: Administrative Practices at NIH-supported Resources**
Moderators: Stephanie Murphy (ORIP/DCM); Ki-Cha Flash (NIH/NHLBI)

4:35–4:45 **Questions and Discussion**

4:45–7:00 **Session VI: Poster Presentations**

Posters will be up all day in an adjoining meeting room. Poster assignments will be posted in the room. PIs with last names A-L will present from 5:00-6:00 pm. PIs with last names from M-Z will present from 6:00-7:00 pm.

7:00 **Dinner on your own**

Day 2 Wednesday, August 7, 2024

7:30–8:00 Registration

8:00–8:15 Welcome
Tara Schwetz (NIH Deputy Director, DPCPSI Director) (Zoom Presentation)

8:15–9:15 Session VII: Summary of Breakout Sessions of Session IV on Strategic Planning for Comparative Medicine Resources
Moderators: Miguel Contreras (ORIP/DCM); Kent Lloyd (University of California, Davis)
This session will provide summaries from the breakout sessions held August 6, 2024, for participants to share experiences, insights, and best practices in strategic planning for resource centers, fostering collaboration and mutual learning as it relates to the themes from ORIP's Strategic Plan for 2021–2025.

- Animal Models: Oleg Mirochnitchenko (ORIP/DCM) and Bradley Yoder (The University of Alabama, Birmingham)
- Instrumentation: Yong Chen (ORIP/DCI) and Diogo Magnani (University of Massachusetts Medical School)
- Training: Ritesh Tandon (ORIP/DCM) and Craig Franklin (University of Missouri)
- Outreach: Bettina Buhring (ORIP/DCM) and Marko Horb (Marine Biological Laboratory)

9:15–9:30 Questions and Discussion

9:30–9:45 Video Presentations of New Resources (2 min per resource for preloaded videos)

9:45–10:30 Session VIII: Key Considerations When Adding a Curation and Informatics Component to a Comparative Medicine Resource
Moderator: Oleg Mirochnitchenko (ORIP/DCM)
This session will provide information to consider that will help ensure that the data and information you manage are of the highest quality and can be effectively utilized by researchers.

- Oleg Mirochnitchenko (ORIP/DCM) New Curation and Informatics Component of ORIP's P40
- Ian Korf (UC Davis), Backstage at The MMRRC ICSC
- Diogo Magnani (University of Massachusetts Chan Medical School) Building Data Bridges in Research: Curation, Informatics, And Impact on The Nonhuman Primate Reagent Resource

Open Discussion with Panelists - Randal Voss (University of Kentucky), Mike Schmale, (University of Miami), Elizabeth Bryda (University of Missouri)

10:30–10:45 Questions and Discussion

10:45–11:00 Break

11:00–12:00 Session IX: Planning for the Expected and the Unexpected
Moderators: Elda E. Sanchez (Texas A&M University–Kingsville); Stephanie Murphy (ORIP/DCM)
This session will provide information and strategies for effective planning, preparedness, and adaptability within resource centers.

- John Bischof (University of Minnesota) Cryopreservation of Drosophila Embryos: Importance of Repeatability and Reproducibility in Protocol Dissemination
- Larry Sherman (Oregon Health and Science University) A Non-Human Primate Precision Medicine Resource: Discovery, Characterization, and Preservation of Novel Models of Human Diseases
- Kevin Cook (Indiana University Bloomington) A Cautionary Tale About Federal Export Controls
- Melween Martinez (Medical Sciences Campus–University of Puerto Rico) Surviving Challenges at the CPRC

12:00–12:15 Questions and Discussion

12:15–12:30 Feedback, Recommendations, and Planning for 2026
Elda E. Sánchez (Texas A&M University–Kingsville)

12:30–12:45 Closing Remarks
Stephanie Murphy (Division Director, ORIP/DCM

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