Meeting Report

Department of Health and Human Services
National Institutes of Health (NIH)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
Office of Research Infrastructure Programs (ORIP)

Twelfth Comparative Medicine Resource Directors Meeting: *Strengthening Research Resources: Integration, Innovation, and Standardization*

August 7–8, 2018

Hilton Washington DC/Rockville Hotel & Executive Meeting Center
Rockville, MD

Introduction

"Strengthening Research Resources: Integration, Innovation, and Standardization," the Twelfth Comparative Medicine Resource Directors Meeting, was held August 7-8, 2018 in Rockville, MD. All Resource Directors funded by the Office of Research Infrastructure Programs (ORIP)/ Division of Comparative Medicine (DCM) were invited to attend. This biennial meeting offers a forum for the exchange of information among grantees and NIH Program Officers provide useful information to DCM-funded Resource Directors and for developing synergistic working groups, interactions, and collaborations. A primary objective was to generate broad interests in Resources, discuss "lessons learned," and to convey a sense of what's been done and what can be done in the future. Another important objective was to allow Resource Directors the opportunity to discuss optimization of administrative processes. ORIP Program Officers and others from various NIH Institutes, Centers, and Offices (ICOs) contributed to scientific discussions to further enhance national use of DCM-funded resources. There were 69 Resource Directors and personnel from 51 DCM-funded resources from 24 states and Puerto Rico as well as 42 NIH staff representing 11 ICOs at the meeting. The meeting also included 2 outside speakers from the Rockefeller University and the University of Alabama at Birmingham. The attendees included the Principal Investigators of DCM-supported centers funded by P40, U54, UM1, and U42 grant mechanisms, as well as some grantees that have resource-related research projects funded via the R24 grant mechanism, research projects funded via the R01 grant mechanism, or contracts. There were 7 sessions with 25 presentations and a separate poster session with 42 posters that covered aspects of "Xenotransplantation: From Fish to Pigs to Non-Human Primates;" "Administrative Practices at NIH-supported Resources;" "Technology, Innovation and Animal Resources;" "Promoting a Resource's Animals and Services;" "Building Bridges Among Comparative Medicine Resources;" "Translation from Animal Models to Patients;" and "Good Resource Practices."

TUESDAY, AUGUST 7, 2018

Stephanie Murphy (Director, Division of Comparative Medicine [DCM], ORIP)
Introduction and Welcome

Dr. Stephanie Murphy welcomed the participants and presented the meeting agenda. The meeting goals include (1) providing a forum to exchange innovative ideas and scientific advancements; (2) facilitating development and continuation of synergistic working groups, interactions, and collaborations among DCM resources, NIH Institutes and Centers, and the Office of the Director; and (3) offering opportunities for sharing experiences, strategies, and best practices to optimize access, use, and administration of valuable resources.

James Anderson (Director, DPCPSI)
The Use of Centralized Research Centers in NIH Common Fund Programs

Dr. James Anderson described the NIH strategy of supporting innovative and integrated research. One element of DPCPSI's overall efforts is to coordinate provision of resources and infrastructure for the biomedical community. The Common Fund, managed by NIH's Office of Strategic Coordination, benefits the entire biomedical research community and supports 25 trans-NIH innovative scientific programs that are high-risk endeavors with the potential to significantly advance research fields. Under this umbrella, the Undiagnosed Diseases Network provides last-resort, free diagnostics for patients globally. This network is a highly coordinated effort with various components (e.g., clinical evaluations, sequencing, metabolomics) working toward the common goal of diagnoses. Out of 800 patients evaluated,

25 percent received a diagnosis. Another integrated NIH initiative, the Health Care Systems Research Collaboratory, supports investigators conducting large clinical studies in the United States. The Collaboratory conducts pragmatic trials within the distributed health care system and develops best practices. The Transformative High Resolution Cryo-Electron Microscopy Program broadens nationwide access to cryo-electron microscopy (cryo-EM) through the creation of three national service centers. This program addresses the prohibitive cost of instrumentation, limited access to high-performance data collection, and small number of cryo-EM expert investigators. The goals of these centralized centers are integration, innovation, and standardization.

Leslie Vosshall (Professor and Howard Hughes Medical Institute Investigator, The Rockefeller University)
Keynote Presentation: *Olfaction: From Mosquitoes to Humans*

Dr. Leslie Vosshall explained the importance of the *Aedes aegypti* olfactory system in pathogen transmission. She described the global prevalence of mosquito-borne pathogens, which can reemerge and spread rapidly in areas of disease eradication. Despite mosquito control programs (e.g., insecticides), malaria remains a global threat, causing 445,000 deaths in 2016. Other mosquito-borne pathogens—chikungunya virus, Zika virus, dengue virus, and yellow fever virus—persist in some regions because of human reservoirs (travelers). Areas where *A. aegypti* persists are considered higher risk regions.
Dr. Vosshall's research focuses on how *A. aegypti* retrieves blood meals (biting), which is the mode of disease transmission, and how to inhibit this process. Biting is triggered by human sensory cues (body temperature, odor, and carbon dioxide) and mosquito sensory structures (stylet, heat sensor, and maxillary palps). Host-seeking suppression is defined as the time between a blood meal and egg laying. Dr. Vosshall's laboratory is interested in neuropeptide signaling pathways that regulate host-seeking behavior in *A. aegypti*. She presented findings from her laboratory quantifying and extending this suppression after feeding. Neuropeptide Y (NPY) and the NPY-like receptor signaling modulates this suppression

Dr. Vosshall described work evaluating mosquito sensory mechanisms with the use of chemorepellents. N, N-Diethyl-meta-toluamide (DEET) insect repellent is highly effective; however, the mechanism of efficacy is unknown. Mosquitoes use sensory neurons on their legs and head to detect volatile chemicals, such as DEET. Studies from Dr. Vosshall's laboratory demonstrate that mosquitoes use the odorant receptor and co-receptor *orco* for this detection. Orco mutant mosquitoes retain attraction to human skin but are repelled on contact. This result demonstrates that mosquitoes rely on smell for attraction. These insects also rely on taste; the CApillary FEeder (CAFÉ) assay was used to measure taste preference in mosquitoes. CAFÉ data from her laboratory showed that mosquitoes dislike the taste of DEET. To further address the mechanism of repellency, Dr. Vosshall showed that mosquitoes will bite skin coated with bitter tasting compounds demonstrating that repellency is not caused by taste. Mosquitoes use the tarsi and proboscis appendages to touch the skin; mosquitoes sense with their proboscis and will bite even if their legs do not touch skin. DEET acts on the sense of smell, and this chemical repels on contact. Studies are ongoing to further delineate this repellency process.

Discussion:

- Resistance to repellants and drugs is the most relevant topic to study. The *NPY* gene is indispensable across species; however, it is important for mosquito fecundity.
- Using NPY agonist compounds in combination could more effectively decrease host seeking.
- Identifying compounds with limited toxicity for human use is warranted.
- Common mosquito species that transmit pathogens (e.g., *A. aegypti*) are well-adapted to human reservoirs, although great apes can harbor the malaria parasite.

Session 1. Xenotransplantation: From Fish to Pigs to Nonhuman Primates (NHP)

Moderators: Kristy Kraemer (National Institute of Allergy and Infectious Diseases [NIAID]); Oleg Mirochnitchenko (DCM, ORIP)

Dr. Oleg Mirochnitchenko described the use of xenotransplantation across different animal model systems. Xenotransplantation is the process of grafting or transplanting organs or tissues between species. He noted that much progress has been achieved using pig and NHP models. This technique could benefit humans by supplying organs, cells, and tissue transplants, as well as bridging transplants. Dr. Kristy Kraemer mentioned that in 2015, NIAID established a consortium focusing on xenotransplantation approaches using pigs to NHP (e.g., pancreatic transplantation). Xenotransplantation—patient-derived xenografts (PDXs), pluripotent stem cells (PSCs), and xenogeneic chimeras—is widely used in the field of precision medicine. Dr. Mirochnitchenko highlighted several ORIP grants supporting xenotransplantation projects, which align with ORIP's strategic plan. He encouraged participants to submit applications to the various funding opportunities.

David Cooper (Professor, The University of Alabama at Birmingham)
Progress in Genetically Engineered Pig to NHP Models

Dr. David Cooper mentioned that the number of humans waiting for transplants far exceeds the quantity of available donations, supporting the need for xenotransplantation. He provided a historical overview of xenotransplantation. Early attempts failed to transplant kidneys and hearts from pigs to baboons. Genetic modification of the donor is a novel approach to xenotransplantation, which could potentially revolutionize transplant medicine. Within the last few years, the survival rate has increased using heterotopic heart and kidney transplantation (from pig to NHP). Dr. Cooper noted that the thrombosis observed in recipient hearts was reversed by anticoagulants. Increased survival was accomplished in large part from genetic engineering of donor pigs and costimulation blockade immunosuppressive therapy. Dr. Cooper presented data from studies using pigs with various mutations. A pig model—deficient in a galactose antigen and transgenic for one to five human protective genes—was used for kidney xenotransplantation. Recipient animals survived for months if treated with costimulatory blockage drugs. Platelet counts, fibrinogen, serum albumin, phosphate, potassium, and calcium were more reliable markers for successful kidney transplantation. These results imply that the clinical criteria for organ rejection should be modified. In separate studies, pig islet transplantation decreases blood glucose levels in diabetic monkeys. Dr. Cooper showed results using a more optimal pig model that is deficient in three carbohydrate antigens and transgenic for six human protective genes (TKO/CD46.CD55/TBM.EPCR/HO-1/CD47). Demonstrating the utility of the triple-knockout (TKO) model, *in vitro* assays showed that the binding of human IgM and IgG antibodies to TKO pig cells was no greater than to human cells. Dr. Cooper remarked that xenotransplantation will become routine in the clinical setting.

David Langenau (Professor, Massachusetts General Hospital)
Zebrafish Avatars of Human Cancer

Dr. David Langenau discussed using zebrafish as a discovery tool for cancer. This iterative modeling makes use of human cell culture and patient-derived tissues and ultimately xenografts. His laboratory uses larval fish to engraft human tumors (100–200 cells). Immunocompromised casper strain zebrafish, which lack the canonical blue and yellow stripes, were used for single-cell imaging, metastatic progression, and clonal dynamics in tumor allograft studies. Immunodeficient fish also were used for allogenic transplantations. He presented results demonstrating that zebrafish deficient in T, B, and natural killer (NK) cells were successfully engrafted with human rhabdomyosarcomas, glioblastomas, and breast cancer. These tumors histologically mirror primary human cancer growths. Dr. Langenau described various methods (e.g., antibiotics, specialized diet) to enhance the post-transplant survivability of these animals. Tumor cell proliferation and migration were measured in zebrafish. Engraftment into the

periocular muscle allows single-cell tracking of human tumorigenic cells. Rhabdomyosarcoma cells were engineered to express a histone variant fused with Dendra2 fluorescent protein. Implantation of these cells allowed for fluorescent tracking *in vivo*. Tracked cells displayed dividing, bystander, or migratory characteristics. To determine applicability of cancer therapy in this model, immunocompromised zebrafish were treated with temozolomide (TMZ) and olaparib. The number of rhabdomyosarcoma cells were significantly reduced after therapy, and phase II trials are underway to evaluate this combinatorial approach. The fluorescent protein Fucci4 was used to evaluate cell cycle kinetics of rhabdomyosarcoma cells. The anti-cancer mechanism of TMZ and olaparib is cell-cycle arrest. Engraftment of PDXs (melanoma and breast cancer tumors) into immunocompromised zebrafish was successful. The goal is to develop zebrafish "avatars" to assess therapy responses in a patient's own tumor.

Jorge Piedrahita (Professor, North Carolina State University)
Xeno-immune Pigs for Reverse Xenotransplantation: Challenges and Opportunities

Dr. Jorge Piedrahita discussed genetic modification of pigs for reverse xenotransplantation. This process involves differentiating and reprogramming of human donor stem cells and transplantation of these cells into immunodeficient pigs. Pig tissues then could be used to engineer cells with antitumor abilities. Heterozygote pigs or pigs deficient in recombination-activating gene 2 (RAG 2) and interleukin 2 receptor gamma (IL-2γ) were developed in Dr. Piedrahita's laboratory. Mutant pigs received bone marrow transplants intravenously or via the intra-bone method. Successful T cell engraftment was observed after intra-bone injection. Xenogeneic postnatal engraftment failed. To circumvent this, *in utero* intrahepatic transplantation was performed in severe combined immunodeficient (SCID) pigs. Human cord blood and hepatocytes were engrafted *in utero* at day 40 gestation. Immunodeficient pigs were engineered to express human histone H2B green fluorescent protein (GFP). Allogeneic intrauterine engraftment of hemopoietic stem cells was evaluated by visualizing H2B-GFP in spleens. T cells successfully repopulated in lymphoid organs of RAG 2/IL-2γ-deficient pigs following engraftment.

Dr. Piedrahita showed the results of xenogeneic *in utero* transplantation of human CD34-positive hematopoietic stem and progenitor cells or T cells into RAG 2/IL-2γ-deficient pigs. Human B or NK cells engraftment failed, and cells rapidly cleared from the peripheral blood and the spleen. The thymus retained human cells out to 3 weeks. These results demonstrate an elevated level of engraftment of T cell lineage in the thymus. The goal is to develop an immunocompetent animal model with enhanced engraftment, multilineage expansion and maturation, and functionality.

Michael Brehm (Associate Professor, University of Massachusetts)
Humanized Mice for Biomedical Research

Dr. Michael Brehm presented about the use of humanized mice for regenerative medicine. He explained that maintaining engrafted cell functionality is critical for the success of mouse humanization. Targeting the innate and adaptive immune systems is important for human cell survivability. Genetic improvements to the SCID and RAG-deficient mouse models—mutations in the non-obese diabetic (NOD) genetic background—allowed for humanization. NOD SCID γ (NSG) mice and NOD RAG (NRG) animals are the gold standard for mouse humanization; however, T cell engraftment is challenging. Targeting the IL-2 γ chain in NSG and NRG mice causes NK cell deficiency, longer lifespan of the animals, and further impairment of innate immunity. These mice engraft well with human cells and tissues. Data from Dr. Brehm and his collaborators demonstrate that human pancreatic beta cell transplantation cures hyperglycemia in NRG Akita mice. He showed long-term maintenance of engrafted human myogenic cells in NRG mouse muscle xenografts. Several mouse models are used for human hepatocyte engraftment; however, these mice are typically frail. Recent work shows that NSG-PiZ mice are healthy and can support human hepatocyte engraftment and maintain serum human albumin. Components of the human immune system are transplantable into mice. Human immune system engraftment is achieved by

using SCID mice injected with peripheral blood mononuclear cells or sublethally irradiated and injected with hematopoietic stem cells (HSCs). Human T cell engraftment into NSG Forkhead Box N1 knockout (nude; T cell deficient) mice was successful if the mice were injected with HSCs and thymus. To assess the immunogenicity of induced PSCs (iPSCs)-derived cell populations, human iPSCs are differentiated into different cell types and grafted into humanized mice. Blood then is collected from these humans and injected into humanized mice to assess cell-to-cell interactions. Dr. Brehm noted that recipient mice often develop xenogeneic graft-versus-host disease. This disease is not seen using NSG mice deficient in major histocompatibility complex I (MHC I) and MHC II. These models represent the future of personalized medicine; however, optimization is needed.

Session Discussion Topics:

- Immune-based injury (inflammation) is the presumed cause of increased kidney size and organ failure in Dr. Cooper's pig model. Exogenous pig growth hormone likely contributed to growth.
- Dr. Langenau indicated that zebrafish avatars grow hypoxic and normoxic tumors. Enhanced fish growth was attributable to growth factors in the feed.
- Participants discussed the relevance of transplantation of hepatocytes into the spleen and not the native liver (intraportal). Splenic injection is technically advantageous and results in more hepatocyte distribution in the liver. Intraportal liver injections is possible if performed before severe disease onset.
- Dr. Cooper acknowledged that infection contributed to death in transplanted animals. Infections in transplanted patients are easily treatable.

Session 2. Administrative Practices at NIH-supported Resources
Moderators: Sheri Hild (DCM, ORIP); Stephanie Murphy (DCM, ORIP)

Dr. Murphy remarked that the DCM supports more than 90 centers and resources through a variety of grant and cooperative agreement mechanisms. These centers and resources vary widely with respect to development, preservation and distribution of different model organism types; research support services offered; training provided; and technology developed and shared. Some examples of resources and centers include the National Primate Resource Centers (NPRCs), Specific-Pathogen Free (SPF) Macaque Colonies, the Mutant Mouse Resource and Research Centers (MMRRCs), the Rat Resource and Research Center (RRRC), the National Swine Resource and Research Center, the Zebrafish International Resource Center, and the Bloomington Drosophila Stock Center. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 (CRISPR-Cas9) and enhanced imaging modalities are examples of technologies that are supported by DCM. The need for and impact of these resources must be conveyed to the NIH for budget justification and continued support. She encouraged the participants to submit their Research Performance Progress Reports (RPPRs) on time and provide other updates regarding center and resource accomplishments to ORIP. It was recommended that participants consider the future of animal resources, synergy and shared activities, and rigor and reproducibility.

Artisha Eatmon (Grants Management Specialist, National Center for Advancing Translational Sciences, Office of Grants Management, NIH)
NIH Grants Policy: Some Things Have Changed, Others Remain the Same

Ms. Eatmon described the various changes to NIH policy and grants, as well as issues pertaining to grants management. She emphasized the need for investigator compliance and mentioned that the update to the NIH Grants Policy Statement is available online. Effective on or after January 25, 2018, the Human Subjects and Clinical Trials Information Form (FORMS-E) should be used for grant applications that include new human subjects and clinical trials information. Guide notices regarding human subjects research are available for review. The NIH issued its final rule 45 CFR Part 46 to enhance protection of

human subjects. Investigators are responsible for carefully reviewing their award documentation to maintain compliance. Effective March 22, 2018, a notarized letter is required for new entity registration in www.sam.gov, which should occur at least 6 weeks prior to application due dates. Several policy changes have occurred; the NIH updated its renewal application procedure to include a new type 2 policy grants management policy statement. Ms. Eatmon outlined RPPR types (annual, interim, and final) and a description of their implementation. Final RPPRs are required for all grants. The NIH will publish the Project Outcomes Section of all final and interim RPPRs submitted on or after October 1, 2017. The NIH is strengthening enforcement of longstanding closeout requirements, and unilateral closeout will be initiated by the NIH when recipients fail to submit timely reports. The NIH has changed the inclusion-of-children policy that applies to all competing grant applications for due dates on or after January 25, 2019. Late progress reporting could result in a prorated award. Investigators were instructed to contact their program official, grants management specialist, or authorized organization representative (AOR).

Session Discussion Topics:

- Participants discussed the importance and possible reformatting of the RPPR. The RPPRs highlight research accomplishments, which the NIH uses to advocate for investigators, programs, and initiatives. It was recommended that the RPPR incorporate a "what not to do" section.

Session 3. Technology, Innovation, and Animal Resources
Moderators: Miguel Contreras (DCM, ORIP); Natalia Kruchinin (NIAID)

Dr. Miguel Contreras introduced Session 3 and mentioned two congressionally mandated NIH mechanisms—the Small Business Technology Transfer (STTR) and the Small Business Innovation Research (SBIR) programs. Dr. Natalia Kruchinin described the STTR and SBIR programs, which support U.S. companies with less than 500 employees. The STTR supports businesses engaged in federal research and development (R&D) in collaboration with academic institutions and with potential for commercialization. The SBIR supports federal R&D with potential for commercialization. NIH's budget allocation for fiscal year 2017 included 3.2 percent for SBIR and 0.45 percent for STTR, totaling $1.02 billion. These programs support various technologies (e.g., vaccines, next-generation therapies, computational tools). Dr. Kruchinin highlighted an SBIR-supported business—Mapp BIO, Inc.—that developed the experimental therapeutic ZMapp™ for Ebola virus infection. Participants were invited to attend the 20th annual U.S. Department of Health and Human Services SBIR/STTR conference that will be held October 30 to November 1, 2018.

Anthony Santella (Senior Research Scientist, Memorial Sloan Kettering Cancer Center)
WormGUIDES: Making Neural Development Visible and Accessible at the Single Cell Level

Dr. Anthony Santella presented the tool WormGUIDES, an interactive atlas of *Caenorhabditis elegans* neural development. The neuronal simplicity (302 neurons and 7,000 synapses) of *C. elegans* permits the understanding of how complex neural structures emerge. The atlas captures and builds a highly detailed spatial and temporal model of developmental stages. The emergence of embryonic neural structure is visualized using time-lapsed fluorescent imaging; however, the volume of data captured via this process is too great to easily navigate and understand. The atlas allows for navigation of neural outgrowth dynamics in four dimensions (4D). Generation of the 4D neurodevelopmental atlas involved genetic promoter screening, cell identification, neural segmentation and 4D modeling, and online dissemination of information to the research community. The screened promoters are selected from transcriptional factors involved in neural differentiation. Lineaging software allows for tracking of promoter expression in neurons and permits for cell identification. So far, 30 percent of neurons have been mapped in the atlas. The atlas model is organized according to the hierarchy of neural structures in *C. elegans* that include the major tracks and neurites. The tracks are built using tissue guide posts (consistently positioned anatomical structures). After the hierarchal model has been built, one can systematically search outgrowth dynamics

for correlations, which are used to search for mechanisms underlying developmental processes. Dr. Hari Shroff is evaluating post body twitching developmental processes in an untwisted model of *C. elegans*. WormGUIDES 4D atlas has visualization tools for customization, data assemblage and sharing, annotation, and integration with community resources. Available resources include WormGUIDES and StarryNite software, promoter database, website (www.wormguides.org), and a phone application of the atlas.

Randall Prather (Professor, University of Missouri)
Toward Patient-Specific Gene Editing by Using CRISPR-Cas9 to Create Swine Models of Human Disease

Dr. Randall Prather described CRISPR-Cas9 editing of pigs for human disease modeling. His laboratory created several gene edited pig zygotes to study ophthalmological disorders, such as retinitis pigmentosa. Ophthalmology studies from his laboratory and others demonstrate that the phenotype, physiological size, and genomic counts are similar between edited pigs and humans. Dr. Prather's laboratory is developing three patient-specific pig models. The Adenosine Triphosphate Binding Cassette Subfamily A, Member 4 (ABCA4) model has multiple mutations resulting in various ocular phenotypes. He explained the molecular strategy for generating ABCA4 edited animals. $ABCA4^{A1038V}$ was injected into zygotes and cultured until the blastocyst stage; blastocysts were genotyped to verify the mutations. Two hundred nucleotide single-stranded (ss) donor ultramers were used to introduce the mutations. Synthetic multiple, not single, guides were effective. Despite this efficacy, there were no pregnancies after five embryo transfers. Another model, rhodopsin (RHOP23H), used five guides with 508 nucleotide ss oligodeoxynucleotides (ssODN), which represented a repair template (RT). The ssODN worked well; however, humanized ssRT or double-strandedRT did not work. Dr. Prather explained another project to create protected Cas 9. The long noncoding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was cloned to the Cas9 sequence, transcribed *in vitro*, and used as an alternative to the typical Cas9 RNA source. MALAT1 Cas9 edited blastocysts at equivalent rates to Cas9. MALAT1 Cas9 circumvents the loss of RNA observed with Cas9 RNA.

Steve Murray (Associate Professor, The Jackson Laboratory [JAX])
Frequent Insertional Mutagenesis in Transgenic Lines Revealed by Targeted Locus Amplification

Dr. Steve Murray presented the targeted locus amplification in transgenic lines project. The goal of the Cre Driver Resources Program at the JAX is to enhance the value of recombinase tools for the research community. More than 350 recombinase mouse lines are available at the JAX and are functionally characterized. Data are disseminated via the Cre Portal at Mouse Genome Informatics. The JAX has initiated a pilot study to discover transgene integration sites and their consequences. The integration site for most transgenes and the frequency of insertional mutagenesis are unknown. Targeted Locus Amplification (TLA) provides a robust and cost-effective means to discover integration loci. Dr. Murray commented that TLA is a novel approach and more efficient than genome sequencing. TLA is used for genotype transgenic lines. The JAX devised a pilot study for evaluating Cre driver strains with known problems (e.g., off-target activity) and technology limitations. The insertion sites were successfully identified in the 40 lines tested, which included Cre driver strains and Parkinson's and Alzheimer's disease models. Insertions caused complex structural changes, duplications, and deletions. Many inserted transgenes affected endogenous genes, which likely affects transcription. Several insertional mutagenesis approaches caused deletions and lethality. This insertion approach allows for mapping back to the human genome. Unexpectedly, "passengers" or *Escherichia coli* sequences co-integrated with transgenes. These passengers were derived from cloning vectors and in some cases were as large as 200 kilobases. This is relevant because prokaryotic genes can cause transgene silencing. TLA provides a robust and cost-effective tool to discover and define transgene integration sites and their consequences. Dr. Murray noted that these approaches could be applied to other model systems.

John Bischof (Professor, University of Minnesota Twin Cities)
Laser Nanowarming Enabled Cryopreservation of Zebrafish Embryos

Dr. John Bischof explained a technological approach toward cryopreservation of zebrafish embryos. Cryopreservation occurs in nature; many animals have biological antifreeze agents that allow them to survive cooling to a vitrified state (i.e. stable glassy state) and rewarming. Dr. Bischof's work looks at the vitrification process in zebrafish embryos. He cited Dr. Peter Mazur's breakthrough experiments using ultra-rapid laser warming of mouse oocytes from the outside using India ink laser absorption. Unfortunately, this approach did not work in zebrafish embryos because of their large size (1000 x larger than mouse oocytes). Dr. Bischof's laboratory discovered that this laser approach can be modified for zebrafish by injecting biocompatible gold nanoparticles (GNP) directly into the embryo (not just around it). He indicated that nanoparticle morphology determines optical properties such as laser absorption. Because of plasmon resonance, lasers are strongly absorbed by the injected GNP thereby distributing heat throughout the embryo and warming the embryos in a reproducible and quantifiable process. Embryos routinely survive 24 hours after laser rewarming; further experiments to optimize long term survival are ongoing. For instance, survival after the rewarming with single versus double injections and modified GNP and laser conditions has yielded some embryos that grew into adult fish several months after laser warming. These fish survived up to 3 months and spawned successfully several times. Dr. Bischof noted that the goal was to create a system that can reproducibly cool at a rate of 100,000° Celsius per minute and rewarm at 10 million° Celsius per minute. This depends on the amount of cryoprotectant and size of droplet within which the embryo is suspended. Further studies have now shown that increasing the nanoparticle concentration or increasing laser fluence rate can widen the temperature difference across the droplet, which negatively affects survival. The laser GNP warming system is a cryopreservation platform technology being optimized to accommodate other organisms. For instance, the approach has recently shown success in cryopreservation of other aquatic species such as coral larvae and may ultimately also be used for pancreatic islets or assisted reproductive technology in a clinical setting. Dr. Bischof's laboratory and others are also evaluating microfluidics systems and high-throughput approaches to increase the applicability and reach of this technology. He reiterated that the GNP warming is being optimized as a platform cryopreservation system.

Session Discussion Topics:

- In the GNP warming system, the particles permeate the zebrafish body, including the gut and the tail. The amount that is taken up is difficult to quantitate. Freezing timepoints longer than overnight have not been evaluated.
- Dr. Prather indicated that the Cas9 protein worked equally well as *Cas9* mRNA for the CRISPR-Cas9 experiments. Lowering temperatures has not been evaluated.

Session 4. Promoting a Resource's Animals and Services
Moderators: Bruce Fuchs (DCM, ORIP); Desiree von Kollmar (DCM, ORIP)

This session was provided to introduce newly DCM-funded resources and new attendees. The format allowed for short "elevator speeches" or videos followed by a question and answer period.

Joe Simmons (Professor, Michale E. Keeling Center for Comparative Medicine and Research [Keeling Center], The University of Texas MD Anderson Cancer Center)
SPF Baboon Research Resource

On behalf of Dr. Christian Abee, Dr. Joe Simmons outlined the process of transporting baboons from the University of Oklahoma Health Science Center to the SPF Baboon Research Resource at the M.D. Anderson Cancer Research Center in Bastrop, Texas. SPF baboons are free from many of the viral,

parasitic, and bacterial agents that are commonly found in research baboons including herpesviruses, retroviruses, polyomaviruses, arteriviruses, measles, *Bordetella spp*., and Mycobacterium tuberculosis complex bacteria. The conventional baboon colony at the Keeling Center comprises 50 NHPs and provides additional animals for nursery rearing and introduction into the SPF colony for eventual research use. These baboons are conventionally housed in Primadomes™ with dwelling areas for nesting, and they are provided with environmental and food enrichments. Animals can grow up to 40 kilograms and use the horizontal and vertical spaces of the Primadomes™. The Keeling Center has approximately 160 SPF baboons in an area that formerly housed chimpanzees, which consists of indoor and outdoor runs, as well as attached Primadomes™. Dr. Simmons commented that the Keeling Center is the first housing system for SPF baboons to allow outdoor access. To ensure that the animals would remain SPF, juvenile SPF animals were housed in the facility and were extensively tested for excluded pathogens for 6 months; these animals now are well adjusted to their environment. SPF animals are used in transplantation studies, vaccine testing (Bordetella pertussis, respiratory syncytial virus), as infectious disease models (Zika virus, schistosomiasis), and in reproduction and gynecology research. He explained the transport process, during which baboons were relocated between May 15 and December 6, 2017. By December, approximately 200 animals were transferred to the Keeling Center. To date, an additional 47 live births have occurred at the Keeling Center.

Betsy Ferguson (Associate Professor, Oregon Health & Science University)
Sequencing to Establish a Macaque Genotype and Phenotype (mGAP) Research Resource

Dr. Betsy Ferguson talked about the mGAP resource project to sequence the genomes of thousands of rhesus macaques (NHPs). The sequence data generated are analyzed to identify and annotate genetic variants present in rhesus macaques living at the Oregon NPRC. Currently more than 17 million sequence variants have been identified, including nearly 26K that are either identical to human variants associated with disease, or are strong candidates for being pathogenic based on their effects. The macaque variant data are made available through the public mGAP database (https://mgap.ohsu.edu/). Dr. Ferguson noted that investigators from more from 35 research institutions have already accessed macaque genomic data through mGAP. Investigators use mGAP to identify potential genetic links to established NHP genetic models, as well as to identify potential new natural disease models that are needed for the study and treatment of inherited human disease. Dr. Ferguson highlighted several successful uses of the mGAP resource, including the discovery of new natural disease models associated with vision loss, neurodegeneration and developmental disorders. The discovered models are already being used for gene therapy trials (e.g., gene editing) and the testing of precision medicine therapies. Expansion of the database (additional phenotypes and variants) is underway.

Jeffrey Essner (Professor, Iowa State University)
Development of Tools for Site-directed Analysis of Gene Function

Dr. Jeffrey Essner explained zebrafish resource tools for site-directed analysis of gene function. Dr. Essner described the traditional gene editing repair mechanisms as well as ss annealing and alternative end joining, which can predominate in the zebrafish embryo and cells by providing templates with some homology. This process could result in high rates of transgene integration. Dr. Essner noted that his laboratory developed predictive alleles for somatic mutagenesis of homologous regions using CRISPR-Cas9 and efficient knock-in alleles. The strategy for short-homology-directed knock-in incorporates genomic guide RNA and a guide RNA that recognizes the plasmid vector containing cargo sequences. Cargo is flanked by short homologous sequences. By targeting a vascular gene in zebrafish, the germline transmission frequencies ranged from 20 to 64 percent. These CRISPR precision gene-targeting tools for gene inactivation in zebrafish are available online. Scientists can choose from GFP, galactose 4, or plasmids for PRecise Integration with Secondary Markers (pPRISM) vectors that permit secondary

following of alleles for genotyping. The pPRISM vectors target the heart and eye and distinguish heterozygotes from homozygotes. The strategy for creating invertible and conditional alleles in animal models involves intron targeting via CRISPR. This method integrates the cassette in reverse orientation. The goal is to determine which genes are curative. These vectors are being distributed to the research community.

John Vanchiere (Assistant Professor, Louisiana State University)
Development of an NHP Model of Polyomavirus Disease

Dr. John Vanchiere described the development of an NHP model for polyomavirus disease, which is implicated in a variety of diseases (e.g., multiple sclerosis, AIDS). Identifying the risk factors for polyomavirus diseases is challenging. No prevention strategies exist for this virus. To address this, Dr. Vanchiere's laboratory developed an NHP model in collaboration with the Keeling Center. The goal of this model is to induce at least 50–60 percent rate of polyomavirus disease in immunosuppressed animals to accurately assess therapeutic and immune reconstitution approaches. To model polyomavirus disease in the context of AIDS, NHPs were temporarily immunosuppressed using monoclonal antibodies (e.g., rituximab). Suppression out to 6 months caused virus spread from the primary site of infection to the brain and kidney. A current project is to evaluate long-term suppression in 24 juvenile male Bolivian squirrel monkeys using rituximab alone or in combination with other therapeutics. Unsurprisingly, some animals experienced pneumonia and chronic diarrhea and had detectable polyomavirus in the urine and serum. Several animals had measurable regulatory region sequence anomalies in viral genes. A SBIR-funded project assessing John Cunningham virus (JCV) in polyomavirus naïve animals is challenging because of rituximab intolerance, 40 percent death rates, and fulminant hepatitis. Future studies aim to enhance immune suppression and use neurotropic JCV strains, alternative delivery routes, and additional antibodies from the Nonhuman Primate Reagent Resource (supported by ORIP).

Wesley Warren (Associate Professor, Washington University School of Medicine in St. Louis)
Development of Genome References for Aquatic Models of Human Disease

Dr. Wesley Warren highlighted the importance of developing genomic references for aquatic models of human disease. The focus of the project he presented is to build reference genomic assemblies and their corresponding protein coding gene predictions to support computational needs of the research community. This project involved initially creating *de novo* assemblies with short- and now long-read sequencing technology. The assemblies were developed to assist in linking genotypes to phenotypes relevant to human disease. The sequenced genomes and identified proteins of several aquatic species are available online (www.ncbi.nlm.nih.gov). Dr. Warren acknowledged the initial low quality of the short-read references; however, long-read sequencing in combination with new mapping technologies are producing reference genome assemblies with high contiguity. He explained the best practice for *de novo* genome assembly with few gaps. Dr. Warren outlined the importance of the various species already sequenced (e.g., platyfish, Mexican blind cavefish, sea hare) by using an example of the cavefish to discover molecular mechanisms of insulin resistant diabetes.

Keith Cheng (Professor, Penn State College of Medicine)
Video Presentation

Dr. Keith Chang showed a video illustrating quantitative histological approaches relevant to cancer research and diagnostics. Microcomputed tomography was used to image cross sections of body areas (e.g., skeletal muscle) of genetically engineered zebrafish. His laboratory developed tools to quantitatively image all brain nuclei. Sensitive detection of individual variations, such as cell morphology, is achieved via these tools. His approach is applicable to other species (e.g., *Drosophila melanogaster*). A goal is to apply these tools to mice and achieve optimal surface scanning. Ongoing

work involves creating transgene specific expression. This new volumetric approach permits for quantitative analysis of three-dimensional histology samples and data interpretation.

Session Discussion Topics:

- Participants were encouraged to peruse the mGAP website and database. Dr. Ferguson indicated that annotating the MHC region is limited by the resolution of the rhesus macaque reference genome.
- Dr. Vancherie mentioned that in previous studies, JCV viremia was detected in the spleen months after infection; these animals were not immunosuppressed.
- Participants were encouraged to use Dr. Cheng's online resource (www.viewtool.chenglab.com).

Session 5. Building Bridges Among Comparative Medicine Resources
Facilitators: Christian Abee (Director and Chair, Michale E. Keeling Center for Comparative Medicine and Research, The University of Texas MD Anderson Cancer Center); Michael Tyers (Professor, University of Montreal); Randal Voss (Professor, University of Kentucky); Harold Watson (DCM, ORIP)

Dr. Harold Watson convened a discussion on centralizing and integrating existing ORIP DCM resources. Participants explored integrative ways to strengthen the impact of these resources on human disease research.

Session Discussion Topics:

- Can the RPPR be modified to better elicit useful information for assessing current and future resources and for long-term strategic planning?
    - The participants discussed the importance of using the RPPR as a compliance mechanism to communicate scientific accomplishments and the possibility of restructuring the document. Several participants agreed that the auto-populated fields and the calendar month sections of the RPPR need to become editable.
    - Investigators should consider describing their research highlights in the first paragraph of the RPPR in a format that is understandable to lay persons. Highlights could be presented to the public.
    - Participants were encouraged to increase interaction with their AOR, who will answer questions regarding the RPPR, and who are the official link between the grantee and ORIP's grants management representatives.
    - Investigators should not only document their research but should better describe the impact of their research in the RPPR.
    - The RPPR should incorporate resource web page analytics (e.g., number of web page visits).
- How can interaction among resources to coordinate activities that will increase efficiency best be encouraged?
    - Participants were encouraged to contact Dr. Fuchs to receive weekly notifications and provide him with resource updates.
    - Ms. Desiree von Kollmar will provide to the participants resource affiliations of all meeting attendees.
- Can a web-based template be developed and shared to better advertise ORIP resources and better attract research investment?

- The Resource Identification Portal (www.scicrunch.org/resources) is an online tool that could better advertise resources. Participants can use Research Resource Identifiers (RRIDs) to help track the use of resources.
- Participants should contact their program officers to update resource descriptions and activities on ORIP's website (orip.nih.gov). Institutional public information offices could help with this process.
- Word-of-mouth is one of the most cost-effective methods of advertising resources.
- Resource web pages could incorporate weblinks to other sites (e.g., ORIP, NIH Common Fund Programs); change the verbiage of links to improve understandability.
- DCM-funded resources should be advertised to undergraduate and high school students; NIH's Bridges to the Baccalaureate and Doctorate Programs train students transitioning into the next stage of academic development.
- ORIP is seeking to better communicate success metrics for each resource; each resource website should consider posting a synopsis of these metrics to its website.
- Resource fact sheets should incorporate links to recent articles written for the public.

Day 1 Recess

Dr. Watson encouraged the participants to send news articles highlighting their resources to ORIP. The oral presentation and discussion portion of the meeting was recessed at 5:06 p.m.

Session 6. Poster Presentations

There were 42 resource- and research-related posters presented and discussed during the session.

WEDNESDAY, AUGUST 8, 2018

Franziska Grieder (Director, ORIP)
Welcome

Dr. Franziska Grieder welcomed attendees to Day 2 of the meeting and acknowledged her ORIP colleagues for their hard work to organize this meeting. She emphasized the importance of ORIP's status as an infrastructure organization, stressing that ORIP must advertise its resources well enough to reach those who would benefit from them. She also emphasized ORIP's role to facilitate connections and encouraged researchers to inform ORIP of their activities, accomplishments, and changes to their program. She added that attendees should begin to think about ideas for the next ORIP strategic plan.

Session 7. Translation from Animal Models to Patients
Moderators: Sige Zou (DCM, ORIP) and Cindy Roy (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK])

Drs. Sige Zou and Cindy Roy introduced Session 7, showcasing translational projects that demonstrate how animal models are being used to study a variety of diseases. Dr. Roy highlighted several NIDDK resources available to the community and emphasized the focus on high-impact interdisciplinary science intended to generate hypotheses and data. Participants should visit the NIDDK website (https://www.niddk.nih.gov/research-funding/process/apply/funding-mechanisms/rc2) for more details.

John Postlethwait (Professor, University of Oregon)
The Transcriptomic Disease Signature: A New Screen for Therapeutics

Dr. John Postlethwait presented a transcriptomic disease signature approach to screen for therapeutics. He explained that many failures in experimental medications occur at late stages, which increases the cost of medications. Experimental drugs may be developed from target-based screens, which do not predict important biological features, or phenotypic screens, which require a long time to produce results. Small aquarium fish could be studied to identify the transcriptional disease signature and develop a faster assay. Dr. Postlethwait provided examples of this process for Fanconi anemia and malignant melanoma. Mutations in human Fanconi anemia genes lead to poor repair of DNA double-strand breaks by homologous recombination. Mutations in the corresponding zebrafish genes disrupt the transcriptome in characteristic ways, constituting the transcriptional disease signature. In malignant melanoma, 85 genes are upregulated, and 160 are downregulated, including immune system genes. After these transcriptional disease signatures have been described, the next step is to utilize a nanostring assay. Dr. Postlethwait reiterated that examining the difference between the transcriptomes of healthy and diseased fish provides a much more rapid screen than searching for pathology-based phenotypes. Small molecules that make the transcriptional disease signature return to normal provide candidates for human therapeutics.

Larisa Poluektova (Professor, University of Nebraska Medical Center)
HIV Cure Research

Dr. Larisa Poluektova provided a history of the use of humanized mice in HIV research and examples of how this model is used in developing long-acting slow effective release antiretroviral therapy (LASER ART). She presented examples of mouse models that can be used to address complex treatment questions in people with HIV. The basic mouse model—mice with human immune systems—allows researchers to control viral replication while observing the suppression of replication and viral rebound. This model also can be used to study LASER ART using nanoparticle-formulated dolutegravir, which protects most mice against viral replication for longer periods. Dr. Poluektova also described an experiment in which the integrated HIV genome was excised with CRISPR-Cas9 technology. She presented two new models in which human immune systems and microglia were integrated into mice; these models can be used to test therapeutic regimens for HIV and other infectious diseases and cancers. Dr. Poluektova emphasized that although humanized mice remain the basic platform for testing long-acting therapeutics and new eradication strategies, they are insufficient to cover all human adaptive immune responses, and development of better models must continue.

Randall Peterson (Professor, University of Utah)
In Vivo Drug Discovery in Zebrafish

Dr. Randall Peterson explained how zebrafish can be used in drug discovery, noting that zebrafish allow researchers to perform *in vivo* experiments at a scale and throughput usually only possible *in vitro*. He explained how zebrafish can be housed compactly and manipulated with new microfluidics tools. Zebrafish display a rich repertoire of behaviors even at early life stages, which enables researchers to study many complex biological conditions. He reiterated that attrition rates in drug discovery are high, leading to high costs, and pointed out that most attrition occurs between the *in vitro* and *in vivo* stages, so zebrafish models can help address this chasm. Dr. Peterson provided examples of how his laboratory has applied this approach, such as identification of a cause of dorsoventral development problems, leading to generation and characterization of many dorsoventral analogues shown to be efficacious in rodent models and soon to enter human studies. He provided other examples of successful zebrafish studies but noted that there are limits to the genetic and physiological conservation and thus the translatability of results. Rodent models are not perfect predictors of efficacy and safety in humans, and zebrafish are even further removed from humans. Dr. Peterson also noted that although researchers have become skilled at delivering drugs to rodents, drug delivery in fish is limited in its precision. He added that drug metabolism differences and difficulty screening zebrafish in later life stages are additional complications. Dr. Peterson noted some frontier areas of research, including genetic suppressor screens, complex

physiologic readouts, and behavioral and social investigations on adult fish.

Ross Cagan (Senior Associate Dean and Professor, Icahn School of Medicine at Mount Sinai)
Fly to Bedside

Dr. Cagan explained that therapeutics are beginning to have a noticeable effect on cancer rates. The two major approaches beyond chemotherapy, Molecular Analysis for Therapy Choice-like trials and immunotherapy, have the potential to be successful on approximately 50 percent of tumors. For the other 50 percent, one path to explore is model organisms. Fruit fly models allow researchers to address disease in a whole-animal setting. Animal screening can help researchers identify the many points of the body that drugs can affect, although fruit fly models are not always accurate at the complexity of humans. Dr. Cagan presented the example of Ret tumors, which can be driven by point mutation or the fusion of an intracellular domain to a motor domain. The signaling problems caused by this fusion may contribute to the highly metastatic nature of these tumors by pulling signaling complexes to other sites within the cell. Because of this, Ret inhibitors alone are not sufficient to control the cancer. Dr. Cagan stressed the need to analyze the biology of a cancer to understand what is happening when targeted therapies are unsuccessful. He also emphasized that the genetic complexity of tumors conveys resistance, so models for patients must be sufficiently complex to be effective. Dr. Cagan's team operates a Center for Personalized Cancer Therapeutics at which a patient's tumor can be sequenced and used to create a personalized fly avatar. These avatars then can be used to test the library of 1,500 U.S. Food and Drug Administration-approved drugs and identify those appropriate for a cocktail to treat the patient. Dr. Cagan stressed that this approach is not always successful, but in the early stages it shows promise. He reiterated the importance of considering the appropriate level of complexity needed for models that can effectively reveal human treatments.

Session Discussion Topics:

- When asked the rationale for including passenger mutations, Dr. Cagan explained that drugs that work in a base gene model rarely work in a full model with the passenger mutations included, so although the role of passenger mutations is unknown, they are clearly changing drug response.
- Dr. Cagan described the imperfect algorithms used to predict which mutations are studied in his models. He stressed that neomorphic mutations are poorly understood and thus not integrated in the algorithm, which reduces the accuracy of the model.
- The presenters discussed the difficulty in screening for phenotyping at higher resolutions and different developmental stages. Many drugs that work well during screening cause toxicities in humans, and these may not manifest early in development. Some drug toxicity effects can be mapped in zebrafish and paralleled in humans.
- When asked about the methods for self-dosing fish, Dr. Peterson explained that soluble drugs at a known concentration are provided in a flow-through arena where the water is changed often, giving fish a localized higher dose when they swim through that area. He commented on the potential of microfluidics technologies being developed in other laboratories.
- Attendees discussed the difficulty of screening for the effects of therapeutic antibodies in animal models. These antibodies can be injected into the yolk and show results, but intravenous injection requires additional delicacy, and automated systems have not yet been developed for zebrafish.
- Attendees discussed the sources of chemical matter used in screening. Many publicly available libraries are not applicable to the pharmaceutical industry—private companies require more sophisticated chemical libraries, and the choice of library significantly affects the ability to further drug development. Additionally, collection of both positive and negative data is important, because researchers can combine negative data from multiple sources to repurpose drugs or further understand complex processes. Presenters discussed the complexities posed by

patent clocks and emphasized the importance of teaching basic researchers to understand the liabilities associated with drug development.
- When asked about the percentage of patients who benefit from a combined treatment approach, Dr. Cagan explained that two of six patients currently under treatment have strong responses, but he emphasized that the response rate for standard therapy is much lower. Although the final results of this study cannot be predicted, his team is cautiously optimistic.
- In response to a question about funding for patient trials, Dr. Cagan elaborated on the ethical discussions that occurred and the ultimate decision not to accept money from patients, and he noted that his team continues to seek creative funding solutions.

Session 8. Good Resource Practices
Moderators: Ronald Adkins (DCM, ORIP); Stephanie Murphy (DCM, ORIP)

This session introduced new issues concerning rigor, reproducibility, and transparency of animal resources. Presenters discussed examples in their own facilities and how issues were identified and addressed.

Betsy Ferguson (Associate Professor, Oregon Health & Science University)
Information/Data Sharing and Promoting Resource Transparency: Experiences from the NPRCs

On behalf of Dr. John Nylander, Dr. Ferguson explained that there are seven NPRCs across the nation; in the last 12 years, many short- and long-term working groups composed of members of these centers have addressed a variety of common issues. Working groups allow researchers to discuss various approaches transparently and determine uniform, efficient, consistent solutions. Dr. Ferguson encouraged the attendees to consider whether any of the forums used by the NPRC working groups could be a way to address common problems among other DCM-funded resources. Web conferences are the most common meeting method for the working groups; face-to-face meetings are rarer but can be very productive and involve multiple working groups. The groups also host training forums, which may be web-based or face-to-face. Most of these forums are clinical- or pathology-based and are developed in the working groups before they are deployed to a wider audience. The NPRC also has a consortium website (www.nprcresearch.org), where common information can be stored and shared. The biological research community has used this shared information to help develop many useful tools, such as a genetic variant database, a national DNA bank, an animal locator, a pathology image database, a biomaterials query system, and a reporting system. This model has improved efficiency across the National Primate Research Centers, reduced redundancies, and allowed users to identify common solutions. Dr. Ferguson asked attendees for suggestions on how these types of approaches could be used to make resources more available and useful to the broader research community.

Anita Bandrowski (University of California, San Diego [UCSD])
What Value Does the RRID Bring to Stock Centers?

Dr. Anita Bandrowski explained that many key biological resources, such as mice, are not cited in journals in a way that allows other researchers to find them. However, when an author includes an RRID—a unique identifier created jointly by the NIH, journal editors, UCSD, and other researchers—90 percent of research resources are findable. RRIDs cover key biological resources as defined by the NIH, including antibodies, cell lines, transgenic organisms, and software projects. Utilization of RRIDs helps track the use of resources, increases reproducibility, encourages the reuse of resources, and unifies the message to journals and publishers. Dr. Bandrowski encouraged attendees to follow best practices when publishing the records for animals on stock center webpages, which includes an RRID. This allows authors to see a uniform message as they prepare their manuscripts. The number of journals utilizing RRIDs has increased dramatically, and many common laboratory animals have been labeled by authors

and are currently linked from journals to stock center web pages, via the RRID. Important future directions include improving data-use tools and text-mining programs. Dr. Bandrowski presented example scenarios to study the findability of resources from various resource centers. Repositories that use RRIDs on their web pages lead to an increase in RRID use in papers. Dr. Bandrowski asked attendees to help present a unified front in this effort by using RRIDs, asking for RRIDs when reviewing peers' papers, confirming that administrative staff can answer questions about RRIDs, and ensuring that RRIDs represented the resource to the level of individual animals/strains.

Malgorzata Klosek (Director, Division of Construction and Instruments, ORIP)
Reproducibility, External Factors, and Animal Research

Dr. Malgorzata Klosek commented that ORIP's mission involves supporting modernization and improvement of animal research facilities, expanding access to animal models, and improving rigor and reproducibility. She illustrated several examples (dietary and facility variation) of experimental irreproducibility. The NIH addresses this issue by offering researchers an online resource (www.nih.gov/research-training/rigor-reproducibility). Since 2016, the NIH updated grant application instructions to include consideration of sex and other relevant biological variables, rigorous experimental design, and scientific premise of proposed research. The results from ORIP's request for information—*Effects of Extrinsic Environmental Factors on Animal Research: Rigor and Reproducibility*—show that extrinsic environmental factors (e.g., housing, husbandry, welfare interventions) must be monitored and documented in experimental protocols and publications, which promotes rigor and reproducibility. Although it is not ORIP's responsibility to establish and enforce regulations or call for extrinsic factors to be universally used as experimental variables, ORIP has sponsored activities aimed at improving rigor and reproducibility. The September 2017 workshop sponsored by ORIP—*Zebrafish and other Aquatic Models: Description of Extrinsic Environmental Conditions for Rigorous Experiments and Reproducible Results*—resulted in several zebrafish researchers changing their laboratory practices and manufacturers updating their data-sharing methods. Another ORIP-sponsored meeting—*Defined Reference Diets for Zebrafish and Other Aquatic Biomedical Research Models: Need and Challenge*—addressed the need for reference diets and the role of nutrition in zebrafish models. Dr. Klosek invited the participants to the October 2018 American Association for Laboratory Animal Science panel discussion, *From the Tank/Cage Side for Better Research, Reporting, and Reproducibility*. She encouraged attendees to consider reproducibility of published results and extrinsic environmental factors relevant to their research.

Craig Franklin (Professor, University of Missouri College of Veterinary Medicine)
Microbiota Considerations in Model Rigor and Reproducibility

Dr. Craig Franklin described the importance of analyzing the gut microbiota for optimizing rodent models distributed through the MMRRCs and the RRRC. Important questions to ask are: Does complex gut microbiota vary in contemporary rodent colonies? What factors influence gut microbiota variation? Does variation influence model phenotypes? How can complex gut microbiota variability be exploited in animal modeling? Dr. Franklin presented studies demonstrating that the microbiota composition varies in contemporary rodent colonies and is dependent on age and mouse source. An unlimited number of factors could influence this variation; however, rodents can be maintained with stable microbiota. Experiments using isogenic pups with different microbiota demonstrate varied phenotypes; therefore, microbiota could modulate disease outcome. Similar results were observed in a model for autism spectrum disorder. To leverage this variability, outbred mice were colonized with standardized complex microbiota. Mice from these colonies can be used as surrogates for embryo transfer of any model for which the role of complex microbiota in phenotype is unknown. These complex microbiota mice also can be used for cross-fostering surrogates and as donors post-antibiotic treatment. Dr. Franklin outlined the possible strategy for assessing microbiota, which could be coupled with mechanistic studies (e.g., gnotobiotics). He noted that the phenotypes observed in a complex microbiota community may not be seen in defined communities

and mentioned the decrease in microbial diversity in laboratory mice. Studies show that pet store mice have a more robust immune response compared to laboratory animals, which implies that the microbiota found in the wild should be adapted for laboratory mice. Laboratory mouse microbiota may lack certain antigens and therefore may not be translatable for some models. One must consider defining microbiota for projects and fecal banking when changes are anticipated.

Session Discussion Topics:

- Participants discussed the possibility of the NIH better defining examples of relevant biological variables for grant applications. Devising a list of specific examples is unfeasible because of the vast differences between laboratory models, disciplines, and institutions.
- Participants conversed about NHP resources bridging information with other animal resources. Dr. Ferguson indicated that there is an opportunity to bridge models through ORIP or by other means.

Randal Voss (Professor, University of Kentucky)
Planning for the 2020 Meeting

Dr. Voss thanked the presenters and meeting organizers for their efforts and encouraged participants to continue discussing the meeting topics. He announced that he will host the 13th Comparative Medicine Resource Directors meeting in 2020, and he solicited participants' help in organizing the meeting.

Stephanie Murphy (Director, DCM, ORIP)
Closing Remarks

Dr. Murphy encouraged the attendees to donate their posters so that their work could be displayed within ORIP. She noted the diversity of DCM resources and encouraged collaborations among resources and the optimization of research methods. She summarized the themes of the meeting as follows:
(1) centralization and integration of research resources; (2) precision and personalized medicine;
(3) application of newer technologies to research and impact of such technologies on resources; (4) use of multiple or alternate model systems to address questions; (5) single versus multigene manipulations in animal models such as *Drosophila*, mice, and pigs; (6) resource promotion; and (7) rigor, reproducibility, and transparency. Dr. Murphy thanked Dr. Voss for his efforts and adjourned the meeting at 12:03 p.m.

Appendix 1 – Meeting Roster

Twelfth Comparative Medicine Resource Directors (CMRD) Meeting
Strengthening Research Resources: Integration, Innovation, and Standardization

List of CMRD Invitees

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Appendix 2- Agenda

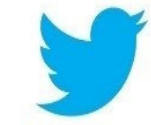
Twelfth Comparative Medicine Resource Directors (CMRD) Meeting
Enabling Biomedical Research: Strengthening Research Resources Through Integration, Innovation, and Standardization

August 7 and 8, 2018
Hilton Washington DC/Rockville Hotel & Executive Meeting Center,
Rockville, MD

Purpose of these Biennial Meetings: The 2018 meeting is designed to provide useful information to Division of Comparative Medicine (DCM)-funded Resource Directors and to provide an opportunity for developing synergistic working groups, interactions, and collaborations. A primary objective is to generate broad interest in Resources, discuss "lessons learned," and convey a sense of what's been done and what can be done in the future. Another important objective is to allow Resource Directors to discuss optimization of administrative processes. NIH program officers and other staff from various NIH Institutes and Centers will contribute to these conversations to further enhance national use of DCM-funded resources.

Overview of the Meeting: There are 8 major Sessions: Xenotransplantation: From Fish to Pigs to Non-Human Primates; Administrative Practices at NIH-supported Resources; Technology, Innovation and Animal Resources; Promoting a Resource's Animals and Services, Building Bridges Among Comparative Medicine Resources; Poster Session; Translation from Animal Models to Patients; and Good Resource Practices

Dr. Leslie Vosshall will present the Keynote address at the beginning of the meeting and a Poster Session will be held at the end of the first day. All DCM funded resources are invited to present at the Poster Session both a resource-related poster as well as a research-related poster. Exhibits on the ORIP/NIH SBIR/STTR Program will be available during the entire meeting.



ORIP Tweets! ORIP has a Twitter account @ORIP_NIH that is used to announce information about ORIP resources, funding opportunities, conferences, workshops and more. ORIP will be live tweeting throughout CMRD. Follow along, and participate, using the hashtag: #CMRD2018.

- **Scientific Advisory Board for the R13 Conference Grant to the University of Kentucky**: Chris Abee (MD Anderson Cancer Center), Ross Cagan (Icahn School of Medicine at Mount Sinai), David Langenau (Massachusetts General Hospital), Oleg Mirochnitchenko (DCM/ORIP/DPCPSI/OD/NIH), Stephanie Murphy (DCM/ORIP/DPCPSI/OD/NIH), Larisa Poluektova (University of Nebraska Medical Center), Mike Tyers (Université de Montréal), S. Randal Voss (University of Kentucky), and Harold Watson (DCM/ORIP/DPCPSI/OD/NIH).

Day 1 – Tuesday, August 7, 2018

7:30–8:30 Registration[1]

8:30-8:40 Introduction and Welcome
Stephanie Murphy (Director, DCM)

8:40–9:00 Presentation
James Anderson (Director, DPCPSI), *The Use of Centralized Research Centers in NIH Common Fund Programs*

- **9:00-9:45 Keynote Presentation**

Leslie Vosshall (Rockefeller University), *Olfaction: From Mosquitoes to Humans*

9:45-10:00 Questions/Discussion

10:00 –10:15 Break[2]

- **10:15–11:15 Session 1. Xenotransplantation: From Fish to Pigs to Non-Human Primates**
  - Moderators: Oleg Mirochnitchenko (ORIP/DCM) and Kristy Kraemer (NIAID)

This session will address challenges and opportunities in xenotransplantation, highlighting the unifying theme it provides across linking animal models and resources.

- David Cooper (University of Alabama at Birmingham), *Progress in Genetically-Engineered Pig-to-Nonhuman Primate Models*
- David Langenau (Massachusetts General Hospital), *Single cell imaging of human xenografts grown in immune deficient zebrafish*
- Jorge Piedrahita (North Carolina State University), *Humanized Pigs: Challenges and Opportunities*
- Michael Brehm (University of Massachusetts), *Development of Humanized Mice for Biomedical Research*

11:15-11:30 Questions/Discussion

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- **11:30-12:00 Session 2. Administrative Practices at NIH-supported Resources**
  - Moderators: Stephanie Murphy (Director, DCM) and Sheri Hild (DCM)
  - **Artisha Eatmon**: *NIH Grants Policy: Some Things Have Changed, Others Remain the Same*

12:00-12:15 Questions/Discussion

12:15-1:15 Lunch[2]

1:15-2:15 Session 3. Technology, Innovation and Animal Resources

Moderator: Miguel Contreras (ORIP/DCM) and Natalia Kruchinin (NIAID)

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

Anthony Santella (Memorial Sloan Kettering Cancer Center), *WormGUIDES: Making Neural Development Visible and Accessible at the Single Cell Level*

- Randall Prather (University of Missouri), *Patient-Specific Gene Editing by using CRISPR/Cas9 to Create Swine Models of Human Disease*
- Steve Murray (The Jackson Laboratory), *Frequent Insertional Mutagenesis in Transgenic Lines Revealed by Targeted Locus Amplification*
- John Bischof (University of Minnesota at Twin Cities), *Laser Nanowarming Enabled Cryopreservation of Zebrafish Embryos*

2:15–2:30 Questions/Discussion

2:30–3:00 Session 4. Promoting a Resource's Animals and Services

- Moderators: Desiree VonKollmar (ORIP/DCM) and Bruce Fuchs (ORIP/DCM)

Elevator speeches/videos from newly DCM-funded Resources and new attendees.

- Chris Abee (MD Anderson Cancer Center), *New Baboon Resource*
- Betsy Ferguson (Oregon Health and Science University), *Genomic Sequencing to Establish a Macaque Genotype and Phenotype Research Resource*
- Jeffrey Essner (Iowa State University), *Development of Tools for Site Directed Analysis of Gene Function*
- John Vanchiere (Louisiana State University Health Sciences Center), *Development of a Nonhuman Primate Model of Polyomavirus Disease*

- Wes Warren (Washington University School of Medicine), *High Quality Genome Assemblies for Aquatic Models of Human Disease*

3:00-3:15 **Break**[2]

3:15-4:30 **Session 5. Building Bridges Among Comparative Medicine Resources**

Facilitators: Harold Watson, Randal Voss, Chris Abee, and Mike Tyers

This session will engage participants in exploring integrative ways to strengthen the impact of ORIP-CM resources on human disease research.

5:00-7:00 **Session 6. 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 of A-L will present from 5:00 - 6:00. PIs with last names from M-Z will present from 6:00 – 7:00.

7:00 **Dinner**[3]

Day 2 – Wednesday, August 8, 2018

7:30–8:30 **Registration**[1]

8:30-8:40 **Welcome**

Franziska Grieder (Director, ORIP)

8:40–10:00 **Session 7: Translation from Animal Models to Patients**

Moderators: Sige Zou (ORIP/DCM) and Cindy Roy, (NIDDK)

This session will address challenges, approaches and opportunities for translating information about diseases between animal models and patients.

- John Postlethwait (University of Oregon), *The Transcriptomic Disease Signature: A New Screen for Therapeutics*
- Larisa Poluektova (University of Nebraska Medical Center), *HIV Cure Research*
- Randall Peterson (University of Utah), *In Vivo Drug Discovery in Zebrafish*
- Ross Cagan (Icahn School of Medicine), *Fly to Bedside*

10:00-10:15 **Questions/Discussion**

10:15-10:30 Break[2]

- **10:30-11:30 Session 8: Good Resource Practices**
  - Moderators: Ronald Adkins (ORIP/DCM), Stephanie Murphy (ORIP/DCM)

  This session will address new issues concerning rigor, reproducibility, and transparency of animal resources.
  - Anita Bandrowski (University of California, San Diego), *RRIDs and Citation Practices for Animal Resources*
  - Malgorzata Klosek (NIH Office of Research Infrastructure Programs), *Reproducibility, External Factors, and Animal Research*
  - John Nylander (NyTech Strategic Planning), *Information/Data Sharing and Promoting Resource Transparency: Experiences from the NPRC*
  - Craig Franklin (University of Missouri), *Microbiota Considerations in Model Rigor and Reproducibility*

11:30–11:45 Questions/Discussions

11:45-11:50 Planning for 2020 Meeting
Randal Voss (University of Kentucky)

- **11:50-12:00 Closing Remarks**
  Stephanie Murphy (Director, DCM)

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[1] Please arrive before the start of the meeting to say hello, obtain meeting materials, and complete paperwork for reimbursement.

[2] The Hilton Washington DC/Rockville Hotel & Executive Meeting Center has a restaurant (Olives) and café (Pike).

[3] You are on your own for dinner, there are many good restaurants to choose among in Bethesda.

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