Advancing Disease Modeling in Animal-Based Research in Support of Precision Medicine

A Workshop of the Roundtable on Science and Welfare in Laboratory Animal Use
with support from the Office of Research Infrastructure Programs,
National Institutes of Health

October 5-6, 2017

2100 C Street NW, Washington, DC
Historic National Academies of Sciences Building
Fred Kavli Auditorium

An ad hoc planning committee will plan and conduct a public workshop to explore the potential of ongoing and future research in animal models with implications for precision medicine. This workshop will bring together experts on the use of state-of-the art technologies and technological advances to explore:

- How the design, creation, and analysis of current and next-generation animal models can inform the practice of precision medicine;
- Reproducibility concepts to improve the clinical relevance of animal-based validation experiments and pre-and co-clinical trials in the context of precision medicine;
- Welfare and regulatory considerations of current and especially next-generation animal models that would inform the design of targeted, personalized therapies.

According to the National Institutes of Health, precision medicine "is an approach for disease treatment and prevention that takes into account individual differences in lifestyle, environment, and biology[1]." During the next two days state-of-the-art animal-based research and its relevance to precision medicine will be presented and discussed. The workshop's sessions will explore ways with which *in vivo* "precision modeling", next-generation animal models and phenotyping platforms can catalyze and accelerate the advent of precision medicine. Complementary *in vitro* and *in silico* approaches to advance the Three Rs and means to ensure reproducibility of methods and data will be prominent features of the sessions and discussions.

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[1] https://allofus.nih.gov/about/about-all-us-research-program

8:00 - 9:00am	**Registration**

8:45   **Opening Remarks**

9:00   **Where We Are Today in Precision Medicine**

Moderator: Kent Lloyd, University of California, Davis (Organizing Committee Co-Chair)

This session will provide the historical context and roots of Precision Medicine; present the current definitions and framework of the field; discuss the anticipated goals and outcomes of the Precision Medicine Initiative; and expand on the hurdles to achieve these goals. It will also provide an overview of the regulatory framework and the ethical and welfare challenges relating to the use of animals in precision medicine.

The evolution and foundations of precision medicine -
India Hook-Barnard, University of California, San Francisco

The vision and goals of the All of Us Research Program -
Christopher P. Austin, National Center for Advancing Translational Sciences

The regulatory landscape of precision medicine -
Robert M. Califf, Duke University School of Medicine (remotely)
(*Organizing Committee Member*)

Ethical and welfare considerations regarding precision animal modeling-
Elizabeth Heitman, University of Texas Southwestern Medical School

10:15   **Coffee Break**

10:30   **Defining "Precise": Translation and Human Relevance of Current Animal Models**

Moderator: Melissa Haendel, Oregon Health and Sciences University (Organizing Committee Member)

In their most classic use, animal models express phenotypic alignment rather than biological relevance at the molecular level. Do precise animal models currently exist? What characteristics should a precise animal model embody to be relevant in the context of precision medicine? This session will explore the translatability, alignment and relevance of current animal models to the human condition.

Elements of precision in the design, creation, use, and data analysis of current animal models -
David Valle, Johns Hopkins University

Comprehensive phenotyping of the mouse genome -
Steve Brown, Medical Research Council, United Kingdom

Functional analysis of genes essential for life -
Mary Dickinson, Baylor College of Medicine

Exploring genetic variability using precision pathology in animals -
Keith Mansfield, Novartis

12:10 **Lunch** (will not be provided. There is a cafeteria in the basement of the National Academies of Sciences, Engineering, and Medicine.)

1:00 **Applying "Precise": New Ways of Modeling Diseases in Animals**
Moderator: Rhonda Wiler, Genentech (ILAR Roundtable Member)
Improving the relevance of animal models to human diseases is at the heart of preclinical and translational research. Focusing on the application of precision, this session will explore new approaches to disease modeling, e.g., can modeling platforms improve the clinical relevance of current animal models, and what lessons have we learned from transformative uses of animals to support human clinical trials?

Precision disease modeling in animals
Genetic modeling in zebrafish and other animals -
Nicholas Katsanis, Duke University School of Medicine (remotely)

Improving diagnostics and therapeutics for Mendelian diseases using precision mouse models -
Robert Burgess, The Jackson Laboratory

Co-clinical trials of mice and human patients -
J. Sean Clohessy, Beth Israel Deaconess Medical Center

New approaches to disease modeling
Developing new "non-model" model systems -
Jennifer Maier, University of California, Los Angeles

Making connections between human and animal phenotypes -
Melissa Haendel, Oregon Health and Sciences University

The Animal Rule: A holistic approach to "precision" -
Jens Kuhn, NIH/NIAID Integrated Research Facility at Fort Detrick

3:20 **Coffee Break**

3:35 **Improving Predictivity in Precision Medicine Experimentation - Reproducibility Considerations**
Moderator: Cory Brayton, Johns Hopkins University School of Medicine (Organizing Committee Member)
This session will begin with an overview of the essential elements that uphold and strengthen the reproducibility of study design. Subsequent presentations will examine ways with which reproducibility can be sustained in the context of precision modeling.

The translational potential of animal models -
Ulrich Dirnagl, Charité, Germany

Systematic reviews, meta-analysis, and reproducibility -
Merel Ritskes Hoitinga, Radboud University Medical Center, the Netherlands

Biomedical computing, large databases, and reproducibility -
Arjun Kumar Manrai, Harvard Medical School

Reproducibility in the alignment of the individual human patient and the "precise" animal model -
Jonathan Kimmelman, McGill University, Canada

5:15   **Adjourn for the Day**

8:30   **Precision Modeling In Vitro**
Moderator: Brian Berridge, GlaxoSmithKline (Organizing Committee Co-Chair)
Rapid advances in technologies involving iPSCs and microphysiological systems offer new opportunities to improve modeling of the human condition. This session will explore how these capabilities are both a valuable adjunct to and a potential replacement for precision modeling in animals.

Disease modeling and human iPSCs -
Paul Burridge, Northwestern University

Modeling Barth syndrome-associated cardiomyopathy with human iPSCs and microphysiological systems -
Megan McCain, University of Southern California

Functional coupling of human microphysiological systems -
John Wikswo, Vanderbilt University (remotely)

Quantitative systems pharmacology and the bridge from in vitro to in vivo toxicity testing -
D. Lansing Taylor, University of Pittsburgh

10:10   **Coffee Break**

10:30   **Precision Safety and Toxicology in the Age of Precision Medicine**
Moderator: Jill Ascher, U.S. Food and Drug Administration (ILAR Roundtable Member)
Protecting the public's health and increasing the longevity of the human population presents unique challenges. This session will explore how precision medicine may change two scientific disciplines that depend on data from large population cohorts: drug safety and toxicology. At the level of the individual patient, speakers will explore modeling and monitoring of drug safety; at the level of population health, the session will focus on population outcomes looking at the example of modeling environmental exposures to potential intoxicants. How can data from animal models inform the transformation from healthcare that depends on population outcomes to one exploiting solely an individual's unique characteristics?

Defining "precise" while modeling patient susceptibilities to drug-induced toxicity
Patient susceptibilities in preclinical drug safety assessment -
Brian Berridge, GlaxoSmithKline

Co-expressed gene network analysis as a bridge for extrapolation between species -
James Stevens, Eli Lilly and Company

Defining "precise" in environmental toxicology and public health

Using diversity outbred mice to mimic human population dynamics in susceptibility to environmental chemicals -
Alison Harrill, National Institute of Environmental Health Sciences, National Toxicology Program

Approaches to integrating evidence from animal and human studies in chemical assessments -
Kristina Thayer, U.S. Environmental Protection Agency

12:10pm   **Lunch** (will not be provided. There is a cafeteria in the basement of the National Academies of Sciences, Engineering, and Medicine.)

1:00

Precision Medicine Around the World
Moderator: Brian Berridge, GlaxoSmithKline

The speakers of this session will present a number of national approaches and strategies to creating precision medicine initiatives. The session will provide a platform to highlight the rationales, expected outcomes and possible convergence of these different approaches. The speakers will also address how central animal-based research is or can be to these initiatives, and strategies to sharing the data generated at a global scale.

The UK's 100,000 Genomes Project -
Damian Smedley, Genomics England, United Kingdom

The French Plan for Genomic Medicine -
Catherine Nguyen, ITMO Génétique, Génomique & Bioinformatique (GGB), Paris, France

Japan's Initiative on Rare and Undiagnosed Diseases -
Kenjiro Kosaki, Keio University School of Medicine, Japan

The World Economic Forum's Precision Medicine Effort -
Genya Dana, World Economic Forum

2:15

Linking Animal-Based Research to Precision Medicine: The Patient's Perspective
Moderator: Donna Matthews Jarrell, Massachusetts General Hospital (ILAR Roundtable Member)

Patients are powerful supporters and advocates for sustaining research to improve care and treatment. How do patient advocacy groups understand the relevance of animal-based research in the era of precision medicine? How could researchers explain new approaches to research with and without the use of laboratory animals?

Patient advocacy in the context of precision medicine -
Daryl Pritchard, Personalized Medicine Coalition

Pets with naturally occurring tumors - A natural model for improving cancer care and treatment -
Amy K. LeBlanc, National Cancer Institute

Using precision medicine to help patients with Parkinson's Disease -
Brian Fiske, The Michael J. Fox Foundation for Parkinson's Research

Community advisory boards and research in precision medicine -
Richard Sharp, Mayo Clinic

3:30   **What Can We Expect from Integrating Precision Animal Modeling Into the Precision Medicine Paradigm?**
The speaker will discuss a possible future in which animal precision models are integral to fulfilling the promises of precision medicine for improving human health.

Kent Lloyd, University of California, Davis

4:15   **Adjourn Meeting**