Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS

# Next Generation Animal Models Targeting Personalized Disease Phenotypes

## Bethesda, MD; September 6, 2012

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# MEETING SUMMARY

## Next Generation Animal Models Targeting Personalized Disease Phenotypes

### Division of Comparative Medicine, Office of Research Infrastructure Programs/DPCPSI/OD, NIH

### Bethesda, MD; September 6, 2012

In the "pre-genomic" era, efforts to functionally annotate human and animal genomes provided information regarding the structure and biological activity of individual genes, leading to a better understanding of the genetic basis of a variety of human monogenic diseases. In the "post genomic" era, sequencing of entire genomes and development of complex bioinformatic tools such as the human HapMap have revealed specific alleles associated with monogenic as well as complex diseases in humans. One of the most frequently used approaches to verify that particular genetic changes lead to human disease is to recapitulate and test these changes in genetically-modified animal models. Although large scale knockout and transgenic efforts are essential to reveal and catalog the biological functions for all genes in the genome, in most cases these approaches will not precisely model the diversity of disease genotypes and phenotypes in humans. In contrast, precision animal modeling of human disease genotypes have the potential to accelerate scientific and medical advances and catalyze the development of personalized diagnostics, therapeutics, and disease prevention strategies.

To begin to formulate a vision for precision animal modeling, the Division of Comparative Medicine/ ORIP/DPCPSI/OD assembled scientific and clinical experts in animal disease modeling and bioinformatics at a brainstorming workshop entitled "Next generation animal models targeting personalized disease phenotypes." The purpose of the workshop was to discuss the derivation, validation, characterization, application, and dissemination of animal models and associated data and information for personalized pre-clinical, co-clinical, and post-clinical studies. The workshop was in support of a trans-NIH initiative to assist and guide coordinated efforts for the development of a general pipeline allowing precision modeling of human disease conditions. This modeling should be focused on the animal species most appropriate for a particular application, with the eventual goal of applying animal data to advances in clinical practice.

In general, the workshop participants concluded the following: Personalized animal models should be used to investigate mechanisms of disease, for target identification and validation, development of diagnostics, biomarkers and new drugs, and for testing and optimizing therapies. The workshop recommended holding a larger meeting at the NIH with wide national and international participation by biomedical scientists, biotech/pharma researchers, medical professionals, bioinformatics specialists, and representatives from FDA and other government agencies, as well as NIH staff. The meeting should be held in 2013 to further develop the concept of personalized animal models and include at least some of the following specific topics:

- Improving methods to rapidly model disease-specific genomic alterations, including robust phenotyping to assess if specific genetic changes recapitulate human phenotypes.

Developing new and optimizing extant methods and technologies to improve humanized animal models for personalized medicine.

- Disease targets should be considered broadly, including both rare (Mendelian) and complex diseases.
- Although an agnostic approach to the development of next generation technologies and models will be useful to a wide audience and across the broadest spectrum of diseases, usage models should be developed in specific disease areas (e.g., cancer, neurodegenerative disease, metabolic disorders) to demonstrate proof-of-concept.
- The wealth of data from whole genome deep sequencing of clinical patients should be used to inform development of animal models. Consolidation of patient and model animal information onto pathways as well as functional annotation will be required.
- Precision animal models developed using data on human disease-specific alleles will be informative for mapping phenotypes. This approach will also extend to and facilitate other scientific associations, such as linking animal models with iPS cell technologies. This effort will require an intense and dedicated bioinformatics “superstructure” to fully capitalize on genome sequencing data to identify critical linkages between genes, phenotypes and networks.
- New and improved phenotype ontologies to better assist translation of information across species and to facilitate systems biology approaches will be required.
- Improved methods to track experiments, document workflows and link this information to databases will facilitate standardization of metadata and data capture tools. This will also enable the creation of a human / animal database exchange that will drive the dissemination of both electronic (data) and physical (animal models) information and facilitate outreach to the research community.
- The resources developed under this program can also be leveraged by multiple users, for example, to access results of toxicological screens.
- The NIH should consider funding precision animal model Centers that should focus on development and applications of personalized animal models and will have the following features:

    - Accessible to both basic and translational scientists.
    - Contain Integrated imaging centers, biomarker development and pathology facilities.
    - Have the capacity to test the impact of a variety of environmental factors.
    - Some of the Centers should have small molecule screening facilities providing services, reagent collections and high throughput screening methodology and platforms applicable to a variety of animal model species.
    - To maximize utilization and impact, Centers should also serve as training sites for graduate students and post-doctoral scholars, including veterinary and medical scientists.

**Near-term actions based on the brain storming session:**

1. DCM staff will assemble an organizing committee, including representatives from other ICs, participants from the brain storming meeting and other leaders in the field to plan a larger workshop at the NIH in 2013. With collaboration from other NIH staff, DCM staff will help lead analysis of the NIH portfolio for current support of the use of personalized animal models in biomedical research to identify possible overlaps as well as directions that will require future coordinated efforts.
2. NIH staff should organize and conduct conversations with other groups with related interest, such as regulatory agencies (FDA, USDA), the biotech/pharmaceutical industry and, international societies to plan joint efforts to support community needs in development and use of personalized animal models.

## Attachment

**Meeting Agenda**

***Brain Storming Meeting Agenda***

# "Next generation animal models targeting personalized disease phenotypes"

DCM/ORIP/DPCPSI/OD,
September 6, 2012
6701 Democracy Blvd.
Room 989
Bethesda, MD 20892

14 invited guests, 12-15 NIH staff

**Purpose of the meeting:** Recent achievements in the ability to genetically modify the whole organism or transplant/regenerate certain cells and tissues in a number of laboratory animal species, as well as whole genome and exome sequencing analysis, are providing unique opportunities to create reliable animal phenotypes analogous to that of particular human patients. Such approaches will help solve one of the most difficult challenges in the post-genomic era: validating disease-associated genetic variations and biomarkers in humans and developing new individualized therapeutics. The **purpose** of the workshop is to discuss the current status of and requirements for the development and use of animal models for personalized pre-clinical studies, with the eventual goal of wide application of this practice in clinics. Meeting participants will provide insight to the Division of Comparative Medicine and other NIH units for the development of potential initiatives in this new area of research and translational medicine.

## September 6, 2012

**8:00 – 8:30 AM** **Introduction and welcome**

**Oleg Mirochnitchenko/Harold Watson/Franziska Grieder/James Anderson** (OD/NIH)

**8:30 – 9:10 AM** **Keynote Presentation**

**Pier Paolo Pandolfi** (Beth Israel Deaconess Cancer Center/Harvard Medical School, Boston, MA)

**Scientist Presentations**

**9:10 – 9:50 AM**

**Kevan Herold** (Columbia University, New York, NY)
**Gregory Poland** (Mayo Clinic and Foundation, Rochester, NY)
**Leonard Shultz** (The Jackson Laboratory, Bar Harbor, ME)
**Jeff Gordon** (Washington University, St. Louis, MO)

**9:50 – 10:00 AM** **BREAK**

**10:00 – 11:00 AM** **Megan Sykes** (Columbia University, New York, NY)
**Leonard Zon** (HHMI/Children's Hospital/ Harvard Medical School, Cambridge, MA)
**Jerome Zak** (UCLA, Los Angeles, CA)
**Calum MacRae** (Brigham and Women's Hospital/ Harvard Medical School, Boston, MA)
**Daniel Geschwind** (UCLA, Los Angeles, CA)
**Mark Ellisman** (UCSD, La Jolla, CA)

**11:00 – 11:10 AM** **BREAK**

**11:10 – 11:40 AM** **Kent Lloyd** (UC Davis, Davis, CA)
**Monte Westerfield** (University of Oregon, Eugene, OR)
**Andrew Lackner** (Tulane University, New Orleans, LA)

**11:40 – 12:30 PM** **WORKING LUNCH**

**12:30 – 2:30 PM** **Open Discussion**

**Moderators and Sessions:**

1. **Gregory Poland -** *Current status of personalized animal model applications*
2. **Mark Ellisman -** *Personal Genomics/omics/databases/human and animal disease database*
3. **Leonard Shultz -** *Technologies/resources/animal genetic modifications/building the animal model*
4. **Megan Sykes -** *Disease targets/Rare versus complex diseases, broad applications*
5. **Kevan Herold-** *Research hypothesis/preclinical testing/clinical trials pipeline/Pharma*
6. **Leonard Zon -** *High throughput screening, target search/validation/drug discovery*

7. **Calum MacRae –** *Immediate needs*
8. **Jerome Zack/ Pier Paolo Pandolfi –** *Future Directions*

**2:30 – 2:40 PM** **BREAK**

**2:40 – 3:40 PM** **Conclusion and recommendations**

## Participants:

**Cheryl Marks** (NCI/NIH)
**Robert W. Karp** (NIDDK/NIH)
**Kristin Abraham** (NIDDK/NIH)
**Mary Ellen Perry** (OD/NIH)
**Trish Labosky** (OD/NIH)
**James Anderson** (OD/NIH)
**Betsy Wilder** (OD/NIH)

**Oleg Mirochnitchenko** (OD/NIH)
**Harold Watson** (OD/NIH)
**John Harding** (OD/NIH)
**Franziska Grieder** (OD/NIH)
**Manuel Moro** (OD/NIH)
**Raymond O'Neal** (OD/NIH)
**Michael Chang** (OD/NIH)
**Miguel Contreras** (OD/NIH)
**Desiree VonKollmar** (OD/NIH)

**Pier Paolo Pandolfi** (Beth Israel Deaconess Cancer Center/Harvard Medical School, Boston, MA)
**Kevan Herold** (Columbia University, New York, NY)
**Gregory Poland** (Mayo Clinic and Foundation, Rochester, NY)
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