

Introduction to the Pilot Centers Program for Precision Disease Modeling

Oleg Mirochnitchenko, Ph.D. Program Director, Division of Comparative Medicine/ORIP



H National Institutes of Health Office of Research Infrastructure Programs

Precision Medicine

Precision medicine is the expansion of the concept of *personalized medicine*, where therapeutic strategies are precisely tailored to each patient's requirements."









Precision Medicine

EDITORIAL

PRECISION MEDICINE

Animal-based studies will be essential for precision medicine

Lloyd KC, Robinson PN, MacRae CA. 2016. Sci Transl Med 8(352):352ed12

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



"Animal Models and Personalized Medicine"

October 28–29, 2013 Natcher Building, NIH, Bethesda, MD

Recent advances in divene areas of biomedical science and breakthroughs in technology such as affordable whole genome sequencing and molecular profiling provide a unique opportunity to study the generics and pathogenesis of a wide variety of human diseases with the eventual goal of using this information to inform clinical practice. Hereogeneity of patient populations and the absence of effective means to interpret patient genetic/omic information for clinical use are significant obstacles toward achieving this goal.

The purpose of the symposium is to provide opportunity for biologists and clinicians to exchange ideas, interact and enhance collaborations in advancing animal disease models to overcome some of the most difficult challenges in the post-genomic era, namely, to validate disease-associated genetic variations and biomarkers in humans, to reduce drug candidate attrition and develop new types of individualized therapies for both monogenic and complex human disoiders.

Session Topics

1. The Use of Comparative and Functional Genomics to Build Animal Models of Human Diseases

- 2. Technological Advances and Available Resources for Building Predictive Animal Models
- 3. Using Personalized Animals for Drug Discovery and Biomarker Development
- 4. Which Human Disease Conditions Are the Best Candidates for Use of Personalized Animal Models?
- 5. How Personalized Animal Models Can Guide Clinical Trials?

Division of Comparative Medicine ORIP/DPCPSI National Institutes of Health, OD



14 invited guests, 12-15 NIH staff

Next Generation of Precision Animal Models

- Understanding the relationship between gene and phenotype
- Stratification of diseases into subtypes according to their underlying biological mechanisms
- Testing complex genetic variations in relevant biological systems
- Improvement of the disease simulation process, with recapitulation of molecular mechanisms
- Clinical trial "like" animal model testing and clinical/model iterations
- Rigorous evaluation of predictability and validity



Pilot Centers for Precision Disease Modeling (U54) Tight association GWAS Medical records Human/animal Phenotypes/ with patient-specific Patient's genetics Genetic/omics Disease databases/ ontologies knowledge Patient's omics Animal models databases environment **Integrated Data** Rare and Common Diseases Collection/ Training/ Biospecimens (tumors, iPSCs) **Bioinformatics** Education Disease Tissue/organ engineering Section GM animals Modeling Humanized animals Unit Human disease-associated variations in "patient-specific" \overline{A} Coordination Core environment Use model system Disease mechanism to guide clinical Target identification application and validation Biomarker's development Drugs/therapeutics development High-throughput screening Translational/ **Genetics/Omics/** Toxicity, safety studies **Co-Clinical Disease Mechanism-**Identification of resistant and sensitive population Section Based Preventive care development **Clinical Trials**



Pilot Centers for Precision Disease Modeling (U54)

PAR-14-280, application due date October 1, 2014

3 Centers funded in Summer 2015

The Jackson Laboratory Center for Precision Genetics: From New Models to Novel Therapeutics Robert Burgess, Jackson Laboratory, ME

A New Disease Platform Leveraging Complex Drosophila and Mammalian Models Ross Cagan, ICAHN School of Medicine at Mount Sinai, NY

MSKCC Pilot Center for Precision Disease Modeling Scott Lowe, Sloan-Kettering Institute for Cancer Research, NY

Pilot Centers for Precision Disease Modeling PIs Introductory Meeting occurred on March 29, 2016 (Bethesda, MD)



The Jackson Center for Precision Genetics



Clinical Collaborations:

- Cedars-Sinai Medical Center, Los Angeles, CA
- Duke University, *Durham, NC*
- UCSD, La Jolla, CA
- UCSF, San Francisco, CA
- The Research Institute at Nationwide Children's Hospital, Columbus, OH
- Columbia University, *New York, NY*
- University of Massachusetts Medical School, Worcester, MA



The Jackson Center for Precision Genetics

Disease Modeling Unit	Principal Investigator(s)	Preclinical Partner(s)
Charcot Marie-Tooth Peripheral Neuropathy	Robert Burgess	Scott Harper, NCH, Steven Gray
Intractable Epilepsies	Wayne Frankel	David Goldstein, Stephen Traynelis, Daniel Lowenstein
Amyotrophic Lateral Sclerosis	Cat Lutz	Robert Baloh
Human Autoimmune Diseases	Dave Serreze, Lenny Shultz	Dale Greiner, Sally Kent
Chronic Kidney Disease	Ron Korstanje	Adrzej Krowlewski
Age-related Macular Degeneration	Patsy Nishina	Jonathan Lin, Stephen Tsang



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[®] A New Disease Platform Leveraging Complex Drosophila and Mammalian Models

Icahn School of Medicine at Mount Sinai, New York, NY

Administrative Core

Bioinformatics Core

Preclinical/Co-clinical Section

Pathology Core

External Advisory Committee

Four Projects



[°] A New Disease Platform Leveraging Complex Drosophila and Mammalian Models

Icahn School of Medicine at Mount Sinai, New York, NY



A New Disease Platform Leveraging Complex Drosophila and Mammalian Models

 Project 1: Complex colorectal cancer, RASopathy fly models **Project I** Collaborate to develop related approaches ti _ر٥ rational polypharm. Ross Cagan Patient validation Project 2: Polypharmacology drug development Project 3: Noonan iPSCs to **Project IV** Project II assess Model Hypertrophic drugs Carlos Cordon-Arvin Dar Cardiomyopathy Cardo develop, assess compounds Project 4: Patient-Derived Compare drug effic tailored to RASopathies Xenografts from Tumor Mendelianus. comple Initiating Cells (PDX-TIC): A **Project III** Novel Platform for Discovery **Bruce Gelb** and Validation of Therapeutic Targets, Colorectal Cancer



MSKCC Pilot Center for Precision Disease Modeling

Memorial Sloan Kettering Cancer Center, New York, NY

PI: Scott Lowe, Ph.D.

Chair of the Cancer Biology and Genetics Program at Memorial Sloan Kettering Cancer Center

Chairman of the Geoffrey Beene Cancer Research Center

Professor, Weill Cornell Graduate School of Medical Sciences

