



**NATIONAL INSTITUTES OF HEALTH (NIH)
RECOMBINANT DNA ADVISORY COMMITTEE (RAC)**

**June 10 - 11, 2014
Bethesda, MD
Building 35, Conference Room 620/630**

Day One: Genomic Editing: Establishing Preclinical Toxicology Standards

9:00 AM Welcome and Opening Remarks

Chair: Donald Kohn, M.D., University of California, Los Angeles

Session I: Overview of Genomic Editing Technologies

9:15 AM DNA Breakage and Repair Mechanisms
Dana Carroll, Ph.D., University of Utah School of Medicine, Salt Lake City, UT

9:30 AM Zinc Finger Nucleases, Transcription Activator-like Effector Nucleases (TALENs), Meganucleases, and RNA Guided Endonucleases: Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)
Matthew Porteus, Ph.D., Stanford University, Palo Alto, CA

Session II: Development of Preclinical Assays

9:55 AM Bioinformatics Approaches to Identify Off-Target Effects
Gang Bao, Ph.D., Georgia Institute of Technology, Atlanta, GA

10:10 AM Improving and Defining the Specificity of CRISPR/Cas Nucleases
Keith Joung, M.D., Ph.D., Massachusetts General Hospital, Charlestown, MA

10:35 AM Unbiased Capture Approaches to Identify Double Strand DNA Breaks
Christof von Kalle, M.D., Ph.D., National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany (by teleconference)

10:50 AM BREAK

11:05 AM Chromosomal Rearrangements and Genome Analysis
Frederic Bushman, Ph.D., University of Pennsylvania School of Medicine,
Philadelphia, PA

David Roth, M.D., Ph.D., University of Pennsylvania School of Medicine,
Philadelphia, PA

11:30 AM Functional Toxicity Assays
Matthew Porteus, Ph.D., Stanford University, Palo Alto, CA

Toni Cathomen, Ph.D., University Medical Center Freiberg, Freiberg, Germany

11:55 PM Role of Animal Models in Predicting Potential for Off-Target Effects
Paula Cannon, Ph.D., Keck School of Medicine, University of Southern
California, Los Angeles, CA

12:10 pm Human Genomic Safe Harbors
Michel Sadelain, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center, New
York, NY

12:30 PM LUNCH

Session III: Preclinical and Clinical Experiences

1:30 PM Preparing TALENS and Meganucleases for the Clinic
Andrew Scharenberg, M.D., Collectis

1:45 PM Zinc Finger Nuclease Preclinical Assays and Path to the Clinic
Dale Ando, M.D. and Philip Gregory, D. Phil., Sangamo BioSciences

Session IV: Discussion

2:15 PM Discussion Session

Moderators: Paula Cannon, Ph.D.
Matthew Porteus, PhD.

Questions:

- 1. How will the appropriate preclinical assays differ depending on:**
 - a. The nuclease platform used?
 - b. The gene editing mechanism
 - i. Disruption/deletion of gene
 - ii. Repair of gene
 - iii. Insertion of new gene
 - c. Target cell type to be modified, i.e. stem cell versus differentiated?
- 2. When are bioinformatic versus cell-based assay approaches more appropriate?**
 - a. What are the sensitivities and predictive powers of different assays?
 - b. For cell-based assays
 - i. How many cells would need to be evaluated?
 - ii. Should studies be conducted in cell lines or primary cells?
 - c. Is there a hierarchy of off-target sites in terms of risk?
- 3. What is the role of whole genome, whole exome sequencing or unbiased transcriptional profiling as part of pre-clinical toxicology evaluation?**
- 4. How useful are animal models expected to be in predicting clinical experience?**
- 5. How useful would safe harbor strategies be for gene insertion approaches?**
- 6. In clinical studies, how should monitoring and long-term follow-up be conducted?**
 - a. Are there assays that can be used to monitor for adverse events?
 - b. Is it possible to determine the difference between an off-target vs. spontaneous DNA break?

4:30 PM ADJOURN