

**Retroviral and Lentiviral Vectors for Long-Term Gene Correction:
Clinical Challenges in Vector and Trial Design
Co-sponsored by the National Institutes of Health
Recombinant DNA Advisory Committee (RAC)
And CliniGene, the EC DG-research NoE for the Advancement of
Clinical Gene Transfer and Therapy**

**December 9-10, 2010
Bethesda, MD**

8:00 AM Welcome and Introductions

8:15 AM Session I. Overview of Human Gene Transfer Trials Involving Retroviral/Lentiviral Vector Transduction of Human Stem Cells
Introductory session to review the results from clinical trials that have used integrating vectors in hematopoietic stem cells for inherited and acquired immunodeficiency and for other clinical conditions with an emphasis on understanding what these studies reveal about clonality monitoring and insertion sites.

Moderator: Gösta Gahrton, M.D., Ph.D., John Zaia, M.D.

1. X- SCID and Chronic Granulomatosis Disease (CGD) Trials - Clinical Overview
 - Harry Malech M.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD
2. ADA-SCID, Wiskott-Aldrich Syndrome, and Adrenoleukodystrophy (ALD) - Clinical Overview and Genetic and Epigenetic Determinants of Integration Site Selection
 - Alessandro Auiti, M.D., Ph.D., Fondazione San Raffaele del Monte Tabor, Milano, Italy
 - Luigi Naldini, Ph.D., Fondazione San Raffaele del Monte Tabor, Milan, Italy
3. Clonal Repertoire of Insertional Vector Systems
 - Christof von Kalle, M.D., Ph.D., National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany

9:15 AM Session II. Non-enhancer Mediated Mechanisms of Insertional Oncogenesis
Studies of experimentally induced tumors by several retroviruses in animal model systems have identified other potential mechanisms of oncogenesis besides promoter/enhancer activation of proto-oncogenes.

This includes alterations of cellular protein function by truncations, inactivation of tumor suppressor genes and micro-RNAs. These alternate mechanisms will be reviewed. The aim of this session is to inform on vector design.

Moderators: Naomi Rosenberg, Ph.D., and Susan Ross, Ph.D.

1. Update on the Lentiviral- β thalassemia Trial – Gene Activation by microRNA and enhancer Based Mechanisms,
 - Philippe LeBoulch, M.D. Harvard Medical School and Brigham and Women’s Hospital, Boston, MA
2. Alternate Mechanisms of Mutagenesis
 - a. Alternate splicing
 - b. Gene inactivation (e.g. p53)
 - c. Truncations of cellular mRNAs or proteins (e.g. c-myb)
 - d. microRNA activation
 - Linda Wolff, Ph.D., National Cancer Institute, NIH Bethesda, MD
3. Mechanisms Uncovered from large-scale Screening with Retroviruses or Retroelements (e.g., sleeping beauty transposons) Designed to induce Tumors (i.e., how not to design gene transfer vectors)
 - David Largaespada Ph.D., University of Minnesota, Minneapolis, MN
4. LV Integration in Human Genes Generates Abnormal Transcripts Through the Usage of HIV Splice Sites
 - Fulvio Mavilio, Ph.D., San Raffaele Scientific Institute, Milan, Italy

10:35 AM BREAK

10:50 AM Session III. Lessons from Oncogenic Retroviruses

Studies of oncogenesis by animal and human retroviruses have demonstrated that retroviral oncogenesis is frequently a multi-step process, with years intervening between viral infection and development of tumors. Virus-driven pro-oncogenic events may require other “hits” in order for tumors to develop; similarly tumors arising in human gene transfer experiments might develop after long latency. This session will address oncogenic mechanisms with respect to viruses to inform about potentially susceptible populations and the time frames for pathology that should be considered after gene delivery using retroviral vectors.

Moderator: Hung Fan, Ph.D.

1. 2-hit Mechanisms
 - Marc Sitbon, Ph.D., Institut de Génétique Moléculaire de Montpellier, Montpellier, France
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2. HTLV-I (long latency; virus is not expressed in tumors)
 - Lee Ratner, M.D., Ph.D., Washington University, St. Louis, MO

11:30 AM LUNCH

12:30 PM Session IV. Improving the Design and Safety of Gene Transfer Vectors

Gene transfer vectors with enhanced safety (decreased oncogenicity) profiles are being developed. Approaches to new vectors will be discussed, and the likelihood that they will also reduce oncogenesis by alternate mechanisms will be considered.

Moderator: Nikunj Somia, Ph.D.

1. Integration Site Specificity
 - Frederic Bushman, Ph.D., University of Pennsylvania School of Medicine, Philadelphia, PA
2. Safety Modifications: Insulators, SIN LTRs, Newer Designs to Address Alternative Mechanisms
 - Odile Cohen-Haguener, M.D., Ph.D., MCU-PH, Ecole Normale Supérieure de Cachan, Paris, France
3. Safe Harbor Targeted Integration Vectors
 - Luigi Naldini, Ph.D., Fondazione San Raffaele del Monte Tabor, Milan, Italy
4. Transposon-derived Vectors
 - Scott McIvor, Ph.D., University of Minnesota, Minneapolis, MN
5. Recent Advances with the SB100 Transposase
 - Thierry Vandendriessche, Ph.D., Vesalius Research Center, Flanders Institute for Biotechnology, Leuven, Belgium

PANELISTS: Donald Kohn, M.D. University of California, Los Angeles, CA
Seppo Yla-Herttuala, M.D., Ph.D. A. I. Virtanen Institute for Molecular Sciences, Kuopio, Finland
Manuel Carrondo, Ph.D., Instituto de Tecnologia quimica e biologica, Universidade Nova de Lisboa

2:10 PM BREAK

2:25 PM Session V. Models for Assessing Safety in RV/LV Gene Transfer Experiments

The goal of this session is review recent innovations in animal models and in-vitro assays that can be used to predict the risks of insertional mutagenesis and to elucidate the relative strengths and weaknesses of the current models.

Moderator: Theodore Friedmann, M.D.

1. High Throughput Integration Site Detection
 - a. Christof von Kalle, M.D., Ph.D.
 - b. Frederic Bushman, Ph.D
2. *In vitro* and Secondary Transplant Mouse Models
 - Christopher Baum, M.D., Hannover Medical School, Hannover, Germany
2. Jurkat Model of LMO2 Activation for Lentiviral X-SCID Vectors
 - Brian Sorrentino, M.D., St. Jude Children's Research Hospital, Memphis, TN
3. Mouse Models
 - Eugenio Montini, Ph.D., Fondazione San Raffaele del Monte Tabor, Milan, Italy
4. Large Animal Models
 - Hans Peter Kiem, M.D., Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA
6. Stochastic models of Hematopoiesis and Implications for Predicting Insertional Mutagenesis
 - Janis Abkowitz, M.D., University of Washington, Seattle, WA

PANELISTS: Cynthia Dunbar, M.D., NIH, Bethesda MD
Klaus Cichutek, Ph.D., Paul-Ehrlich-Institut and Johann Wolfgang Goethe University, Frankfurt/Main, Germany

5:30 PM ADJOURN

Friday, December 10, 2010

8:00 AM Session V. Models for Assessing Safety in RV/LV Gene Transfer Experiments, continued

8:45 AM Session VI. Monitoring for Insertional Mutagenesis and Stopping Rules

This session will focus on the regulatory monitoring for the development of clonal dominance, and the criteria that should be considered in determining stopping rules.

Moderators: Odile Cohen-Haguener, M.D., Ph.D.

1. Current FDA guidance
 - FDA Representative
2. Current European guidance
 - Klaus Cichutek, Ph.D.,

PANELISTS: Harry Malech, M.D.
Theodore Friedmann, M.D., University of California, San Diego, CA,
Kenneth Cornetta, M.D., Indiana University, Indianapolis, IN
Christof von Kalle, M.D., Ph.D.
Christopher Baum, M.D.

10:30 AM BREAK

10:45 AM Session VII. Clinical and Ethical Issues in the Design of Retroviral/Lentiviral Vector Gene Transfer Experiments

Given the likelihood of uncertainty in defining the risks of insertional mutagenesis, how does one best design initial trials with new vectors and target diseases including selection of the disease, population and issues in informed consent

Presentation: Phase I trial for Adult and Pediatric Disease: Framing the Issues

Speaker: Nancy King, J.D., Wake Forest University Health Sciences, Winston-Salem, N.C.

- Assessing the Risks and Benefits in the Face of Uncertainty Regarding the Risk of Oncogenesis
- Selecting an Appropriate Population for First-in-human Trials
- Optimizing the Informed Consent Process

PANELISTS: Mary Ellen Conley, M.D., Children's Research Hospital, Memphis, TN
Donald Kohn, M.D.
Robyn Shapiro, J.D., Drinker Biddle, Milwaukee, WI

12:45 PM ADJOURN