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

Bethesda Marriott
Pooks Hill Road
Bethesda, MD
December 9-10, 2010

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.

Moderators: Gösta Gahrton, M.D., Ph.D., and John Zaia, M.D.
Presenter: John Zaia, M.D., Beckman Research Institute, City of Hope National Medical Center, CA

- X- SCID and Chronic Granulomatosis Disease (CGD) Trials - Clinical Overview

  Presenter: Harry Malech, M.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD

- Adenosine deaminase deficiency (ADA)-SCID, Wiskott-Aldrich Syndrome, and Metachromatic leukodystropy (MLD) - Clinical Overview and Genetic and Epigenetic Determinants of Integration Site Selection

  Presenters: Alessandro Aiuti, M.D., Ph.D., HSR-TIGET, Milan, Italy
  Luigi Naldini, Ph.D., HSR-TIGET, Milan, Italy

- Clonal Repertoire of Insertional Vector Systems
  Presenter: 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.

- Alternate Mechanisms of Retroviral Mutagenesis
  - Alternate splicing
  - Gene inactivation (e.g. p53)
  - Truncations of cellular mRNAs or proteins (e.g. c-myb)
  - microRNA activation

  Presenter: Linda Wolff, Ph.D., National Cancer Institute, NIH, Bethesda, MD

- Update on the Lentiviral-ß thalassemia Trial – Gene Activation by microRNA and Enhancer Based Mechanisms

  Presenter: Philippe LeBoulch, M.D., Harvard Medical School and Brigham and Women's Hospital, Boston, MA

- Post-transcriptional Deregulation of Gene Expression Caused by Retroviral Integration in the Human Genome

  Presenter: Fulvio Mavilio, Ph.D., Fondazione San Raffaele del Monte Tabor, Milan, Italy

- Mechanisms of Oncogenesis via Insertional Mutagenesis: Lessons from Cancer Screens in Mice Using the "Cut-and-Paste" Transposon *Sleeping Beauty*

  Presenter: David Largaespada, Ph.D., University of Minnesota, Minneapolis, MN

10:45 AM **BREAK**

11:00 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.

- 2-hit Mechanisms for Oncogenesis

  Presenter: Marc Sitbon, Ph.D., Institut de Génétique Moléculaire de Montpellier, Montpellier, France

- HTLV-I

  Presenter: Lee Ratner, M.D., Ph.D., Washington University, St. Louis, MO

11:40 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.

- Integration Site Specificity

  Presenter: Frederic Bushman, Ph.D., University of Pennsylvania School of Medicine, Philadelphia, PA

- Safety Modifications: Insulators, SIN LTRs, Newer Designs to Address Alternative Mechanisms

  Presenter: Odile Cohen-Haguenauer, M.D., Ph.D., MCU-PH, Ecole Normale Supérieure de Cachan, Paris, France

- Safe Harbor Targeted Integration Vectors

  Presenter: Luigi Naldini, Ph.D.

- Sleeping Beauty Mediated Transposition in Hematopoietic Stem Cells

  Presenter: Scott McIvor, Ph.D., University of Minnesota, Minneapolis, MN

- Recent Advances with the Sleeping Beauty and PiggyBac Transposons for Gene Therapy

  Presenter: Thierry VandenDriessche, Ph.D., University of Brussels, Belgium

PANELISTS: Donald Kohn, M.D., University of California, Los Angeles, CA
Seppo Ylä-Herttuala, M.D., Ph.D., University of Kuopio, Finland
Manuel Carrondo, Ph.D., Universidade Nova de Lisboa, Oeiras, Portugal

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.

Moderators: Theodore Friedmann, M.D. and Cynthia Dunbar, M.D.

- High Throughput Integration Site Detection

  Presenters: Christof von Kalle, M.D., Ph.D.
  Frederic Bushman, Ph.D.

- *In vitro* and Secondary Transplant Mouse Models

  Presenter: Christopher Baum, M.D., Hannover Medical School, Hannover, Germany

- Jurkat Model of LMO2 Activation for Lentiviral X-SCID Vectors

  Presenter: Brian Sorrentino, M.D., St. Jude Children's Research Hospital, Memphis, TN

- Mouse Models

  Presenter: Eugenio Montini, Ph.D., Fondazione San Raffaele del Monte Tabor, Milan, Italy

- Large Animal Models

  Presenter: Hans Peter Kiem, M.D., Fred Hutchinson Cancer Research Center and University of Washington School of Medicine, Seattle, WA

- Stochastic models of Hematopoiesis and Implications for Predicting Insertional Mutagenesis

  Presenter: Janis Abkowitz, M.D., University of Washington, Seattle, WA

5:30 PM ADJOURN

Friday, December 10, 2010

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

9:00 AM Session VI. Monitoring for Insertional Mutagenesis: Regulatory Recommendations
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.

Moderator: Odile Cohen-Haguenauer, M.D., Ph.D.

- Current FDA Guidance on Monitoring for Insertional Mutagenesis

  Presenters: Daniel Takefman, Ph.D., Center for Biologics Evaluation and Research (CBER), FDA
  Wilson Bryan, M.D., CBER, FDA

- Current European Guidance on Monitoring for Insertional Mutagenesis

  Presenter: Matthias Schweizer, Ph.D.
  Paul-Ehrlich-Institut, Langen, Germany

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.

11:00 AM BREAK

11:15 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?

Moderator: Robyn Shapiro, J.D., Drinker, Biddle and Reath, LLP, Milwaukee, WI

- Phase I trials for Adult and Pediatric Disease: Ethics, Design, and Decisions

  Presenter**:** 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., St. Jude Children's Research Hospital, Memphis, TN
Donald Kohn, M.D.

1:00 PM **ADJOURN**