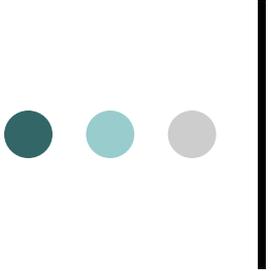


GTSAB REPORT

Recombinant DNA Advisory Committee

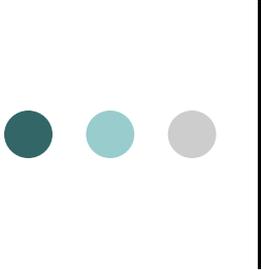
June 16, 2010





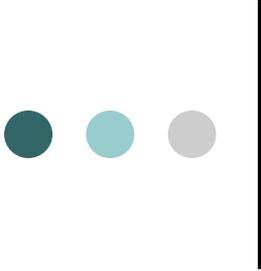
Protocols Submitted for June 2010

- **Sixteen submissions total**
 - **Ten Protocols Not Selected:**
 - **OBA Protocols # 1027, 1030-1033, 1035, and 1038-1041**
 - **Six are oncology protocols**
 - **Two are infectious diseases**
 - **One for diabetic peripheral neuropathy**
 - **One is a vaccine study; non-therapeutic**
 - **Vectors:**
 - **5 plasmid**
 - **2 adenovirus**
 - **1 herpes**
 - **1 fowlpox**
 - **1 measles**



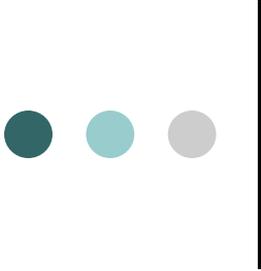
MIC1 Submissions June 2010

- **11 Protocols submitted MIC1s to OBA indicating enrollment**
- **3 Protocols (#0810-942, #907-988, #0910-1004) were reviewed by the RAC at public meetings:**



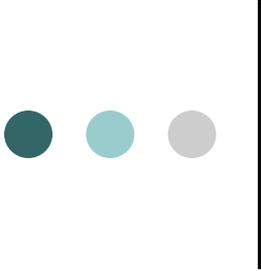
A Phase Ib, Multi-Center, Single Blinded, Placebo-Controlled, Sequential Dose Escalation Study to Assess the Safety of Topically Applied AGO13 in Subjects Receiving Induction Chemotherapy for the Treatment of Cancers of the Head and Neck (#0810-942 reviewed December 2008)

- **Concerns were raised regarding the stability of the thymidine (thy) minus *L. lactis* strain that will be used. Additional experiments conducted to show that no thyA+ revertants could be detected in at least 2×10^{10} CFU of AGX0085.**



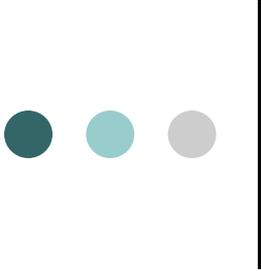
A Phase Ib, Dose Escalation Study of Topically Applied AGO13 (cont.)

- **Additional studies were performed to evaluate the risk of disease from systemic circulation of the gene modified *L. lactis* in neutropenic patients.**
 - **While delivery into the cheek pouch of neutropenic hamsters showed limited systemic circulation, it also demonstrated that the bacteria could not survive in systemic circulation.**
 - **Studies in neutropenic rodents and with pooled serum similarly demonstrated that the bacteria could not survive in systemic circulation.**



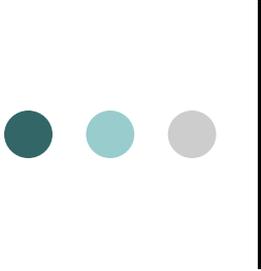
A First-in-Human Safety and Dose-Finding Study of a New Type-16 Human Rhinovirus (RG-HRV16) Inoculum in Healthy Volunteers (#0907-988 reviewed September 2009)

- In collaboration with Drs. Steve and Clare Liggett (University of Maryland), RG-HRV16 from nasal secretions of a limited number of Phase I study volunteers will be collected and sequenced after inoculation in order to detect variations in the genome during the course of infection. Sequencing of an unmodified strain of rhinovirus during natural infection will be done to compare mutation rate.**



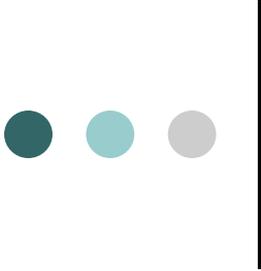
A First-in-Human Study of a New Type-16 Human Rhinovirus (RG-HRV16) (cont.)

- Since the transmission rate of this particular virus has not been investigated, the first 5 participants in each dosing group will not be living in a communal environment. In addition, household contacts, after proper consent is obtained, will be encouraged to participate to monitor the spread of this virus.**
- One-by-one inoculation (spaced by at least 7 days to obtain adverse event data) will occur whenever the dose is increased.**



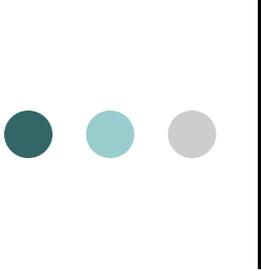
A First-in-Human Study of a New Type-16 Human Rhinovirus (RG-HRV16), (cont.)

- Stopping rules have been implemented so that for the first 5 subjects in any new dose cohort, if a household contact develops cold symptoms within 10 days, the study will be halted until the etiology can be established. If RG-HRV16 is the cause, the data on transmission and severity will be reviewed by an independent medical monitor and a NIAID Medical Officer prior to proceeding.**



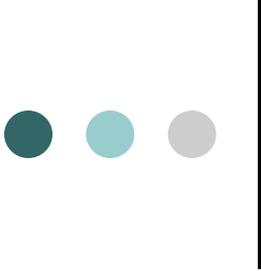
An Open Label Dose Escalation Study to Evaluate the Safety of a Single Escalating Dose of ACRX-100 Administered by Endomyocardial Injection to Cohorts of Adults with Ischemic Heart Failure (#0910-1004 reviewed December 2009)

- As a preclinical model used porcine stromal cell-derived factor (SDF-1), a question was raised regarding whether the human SDF-1 binds the porcine receptor as this could inform the starting dose. Additional data was sought on transgene expression. The study sponsor has performed efficacy, biodistribution, and toxicology studies and has submitted this information to the FDA.**



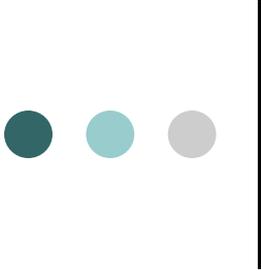
An Open Label Dose Escalation Study of ACRX-100 Administered by Endomyocardial Injection to Cohorts of Adults with Ischemic Heart Failure (cont.)

- **Given the high incidence of cardiac events, the stopping rules for the trial have been revised to include the following as events that would halt enrollment:**
 - **2 or more subjects having a severe cardiac adverse event regardless of attribution or new onset of a ventricular arrhythmia within 14 days or a myocardial infarction within 48 hours to 4 weeks.**
 - **The following ECG changes: RBBB within 7 days, LBBB within 7 days or 3rd degree AV block within 7 days of administration**



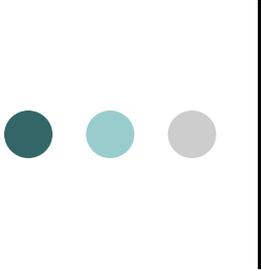
Serious Adverse Events

- **21 serious adverse events were reviewed by the GTSAB from 11 protocols, including initial and follow-up reports. No reports need additional discussion.**



RNA-Based Gene Therapy for HIV Using Lentiviral Vector– Modified CD34+ Cells in Patients Undergoing ASCT for AIDS- Related Lymphoma (David L. DiGiusto *et al.*, *Science Translational Medicine*, June 16, 2010)

- **Lentiviral vector in autologous peripheral blood progenitor cells for AIDS lymphoma**
- **Multivalent anti-HIV RNAs expressed long-term**
- **Low marking consistent with input cells**
- **Suggestion of HIV-induced selection**

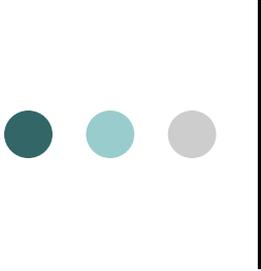


Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations

**Hyatt Regency Bethesda Hotel
June 30 - July 1, 2010**

**Chairs: Howard Federoff, M.D., Ph.D.
Anthony Lang, FRCPC, M.D**

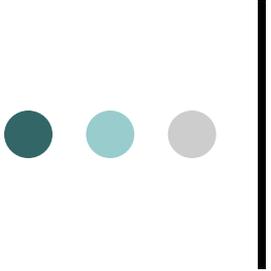
**Supported by OBA and the National Institute of
Neurological Disorders and Stroke**



***Integrating Vectors in Gene Transfer:
Update on Insertional Mutagenesis
and Vector and Study Design***

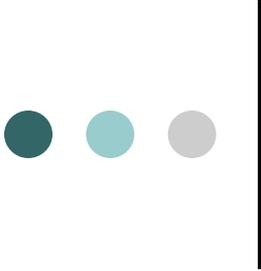
**NIH/RAC
in partnership
with CliniGene**

Dec 9-10, 2010



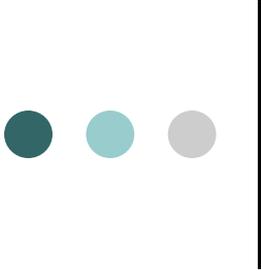
Symposium Objectives

- **Insertional oncogenesis has occurred in human gene transfer trials involving the integration of retroviral vectors near oncogenes in hematopoietic stem cells. In light of recent reports regarding myelodysplasia in a trial for chronic granulomatous disease and the development of a relative clonal dominance in a trial for thalassemia, the RAC together with CliniGene will convene a symposium to provide comprehensive updates on:**



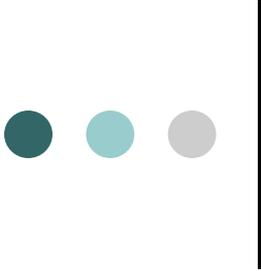
Symposium Objectives, cont.

- **Retro/lentivirus integration and insertional mutagenesis research, including non-enhancer mediated mechanisms of insertional mutagenesis**
- **Safety modifications for retro/lentiviral vectors**
- **Development of *in-vitro* and animal models to predict safety of vectors in human gene transfer**
- **Clinical and ethical considerations for review of new human gene transfer research with novel vectors**



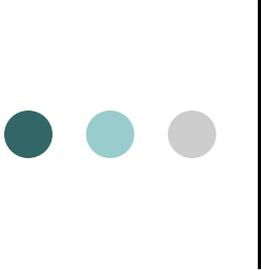
Session I. Overview of human gene transfer trials involving retroviral/lentiviral vector

- Introductory session to review the results from clinical trials that have used integrating vectors in hematopoietic stem cells for acquired immunodeficiency and for other clinical conditions with an emphasis on understanding what these studies reveal about clonality monitoring and insertion sites.**



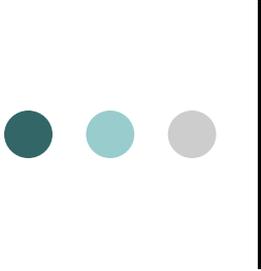
Session II. Non-enhancer mediated mechanisms of insertional oncogenesis

- **Studies of experimentally induced tumors by several retroviruses in animal model systems have identified other 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 vector design.**



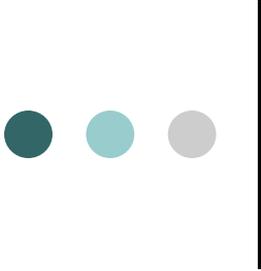
Session III : Lessons from oncogenic retroviruses

- **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. Hence, 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.**



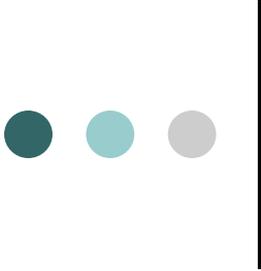
Session IV. Improving design and safety of gene transfer vectors

- Design for 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.**



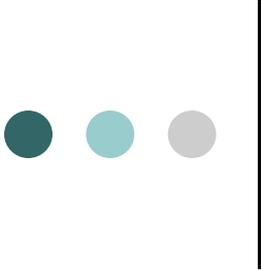
Session V. Models for assessing safety in RV/LV gene transfer experiments

- **The goal of this session is review of 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.**



Session VI. Monitoring for insertional mutagenesis and stopping rules

- **This session will focus on the data regarding insertion sites, assessment of risk associated with certain sites, monitoring for the development of clonal dominance, and the criteria that should be considered in determining stopping rules.**



Session VII. Clinical and ethical issues in the design of gene transfer trials using integrating vectors in stem cells

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