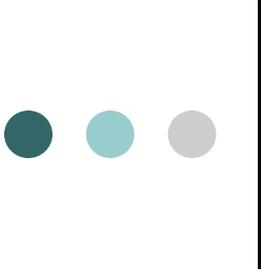


GTSAB REPORT

Recombinant DNA Advisory Committee

March 8, 2011





Protocols Submitted for 1st Quarter 2011

- 10 submissions total
 - 9 Protocols Not Selected:
 - 7 are oncology protocols
 - 1 is for monogenic diseases
 - 1 is for an infectious disease

Vectors:

○2 plasmid

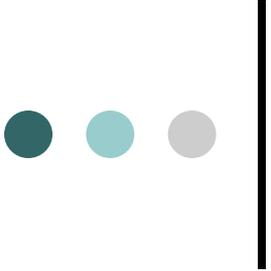
○1 *Listeria monocytogenes*

○2 adenovirus

○1 vaccinia virus

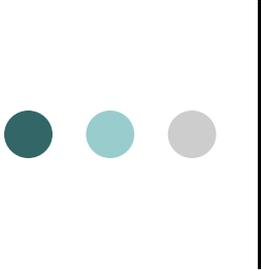
○2 lentivirus

○1 retrovirus



MIC1 Submissions 1st Quarter 2011

- 18 Protocols submitted MIC1s to OBA indicating enrollment**
- 9 Protocols were reviewed by the RAC at public meetings**



MIC1 Submissions, *continued*

For these protocols that were publicly reviewed,

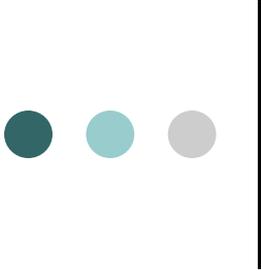
0707-864 (reviewed 12/2007);

0908-995 (reviewed 12/2006);

1004-1036 (reviewed 6/2010); and

1004-1037 (reviewed 6/2010).

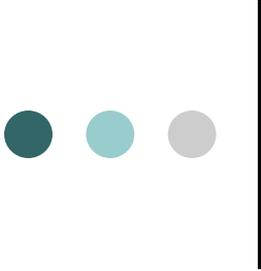
Please refer to the meeting materials for details of the response.



Pilot Study of Haploidentical Natural Killer Cell Infusions for B- Lineage Lymphoblastic Leukemia

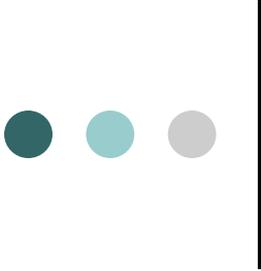
(OBA Protocol #813 reviewed December 2006)

- Protocol amended to increase the release criteria for the cells so that at least 30% of cells expressing anti-CD19 chimeric antigen receptor (CAR).**
- PI also submitted protocol amendment that will replace the retroviral vector with electroporation of mRNA for the anti-CD-19 CAR.**
- Found that electroporation can result in high expression of the CAR that then declines over 48 hours and is almost undetectable after 96 hours.**
- As the modified natural killer cells are not expected to persist long-term this transient expression is not expected to significantly affect the anti-tumor effect.**



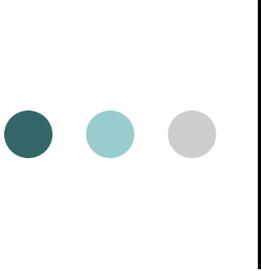
A Phase I Trial of Intratumoral Administration of Secondary Lymphoid Chemokine Gene-Modified Autologous Dendritic Cells in Advanced Non-Small Cell Lung Cancer (#807 reviewed December 2006)

- **In response to RAC concern that the balance between immunosuppression and immunostimulation may shift towards immunosuppression as CCL-21 levels increase, detailed immunological characterization of T cell populations, including flow cytometry and ELISPOT assays, will be performed.**
- **In response to concern that stimulation of the cells with KLH could result in KLH being the primary antigen presented by the dendritic cells, KLH stimulation of the final product eliminated.**



Phase 1 Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Intratumoral Infusions of an Allogeneic CD8+ Cytolytic T Cell Line Genetically Modified To Express the IL13-Zetakine and HyTK and to be Resistant to Glucocorticoids, in Combination with Interleukin-2 (#848 reviewed June 2007)

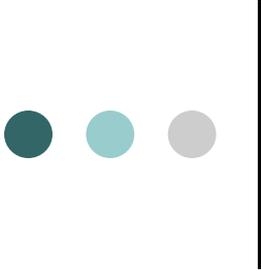
- **Data submitted to show that expression of a truncated glucocorticoid receptor (GR) protein, that results from the disruption of the GR by the zinc finger nuclease (ZFN), does not have an effect on genome wide gene expression profiles.**
- **Data also submitted to support the safety of the ZFN by examining product master cell bank for off-target activity of the ZFN, acquired clonal cytogenetic changes in the karyotypes of transduced cells, and an apoptosis assay of transduced T cells.**



Gene Therapy for SCID-X1 Using a Self-inactivating (SIN) Gammaretroviral Vector

(#950 reviewed December 2008)

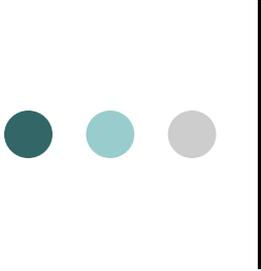
- In response to the request for additional animal studies comparing the potential genotoxicity of the new SIN vector with the MFG retroviral vectors similar to those used in the French and British X-SCID trials, data were provided from secondary transplant studies in mice along with updated *in-vitro* immortalization assays, and integration site analysis.**



A Phase I Dose Escalation Safety Study of Subretinally Injected RetinoStat®, a Lentiviral Vector Expressing Endostatin and Angiostatin, in Patients with Advanced Neovascular Age-Related Macular Degeneration

(#1061 reviewed September 2010)

- Sponsor clarified that the DSMB has the final decision as to the continuation of the study.**
- Protocol incorporates immunological studies that will analyze whether an immune response is directed against the vector or transgene products.**
- ICD clarified the potential use of samples obtained from participants.**

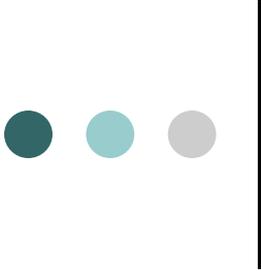


Serious Adverse Events

- **16 serious adverse events were reviewed by the GTSAB from 14 protocols, including initial and follow-up reports. No reports need additional discussion.**



Recent New Results



A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nuclease SB-728 in HIV-Infected Patients (Protocol #843)

- **Dr. Carl June, U. Penn., study sponsor, presented at the 18th Conference of Retroviruses and Opportunistic Infections (CROI), Boston, MA, March 2, 2011.**
 - **Dr. Pablo Tebas, University of Pennsylvania is study PI**
- **SB728, a engineered zinc finger nuclease creates double stranded DNA breaks.**
- **SB-728 is designed to bind to and disrupt the endogenous CCR5 locus, a locus involved in HIV entry into T cells.**
- **Autologous T cells are transduced with SB-728 and then reinfused into subjects.**

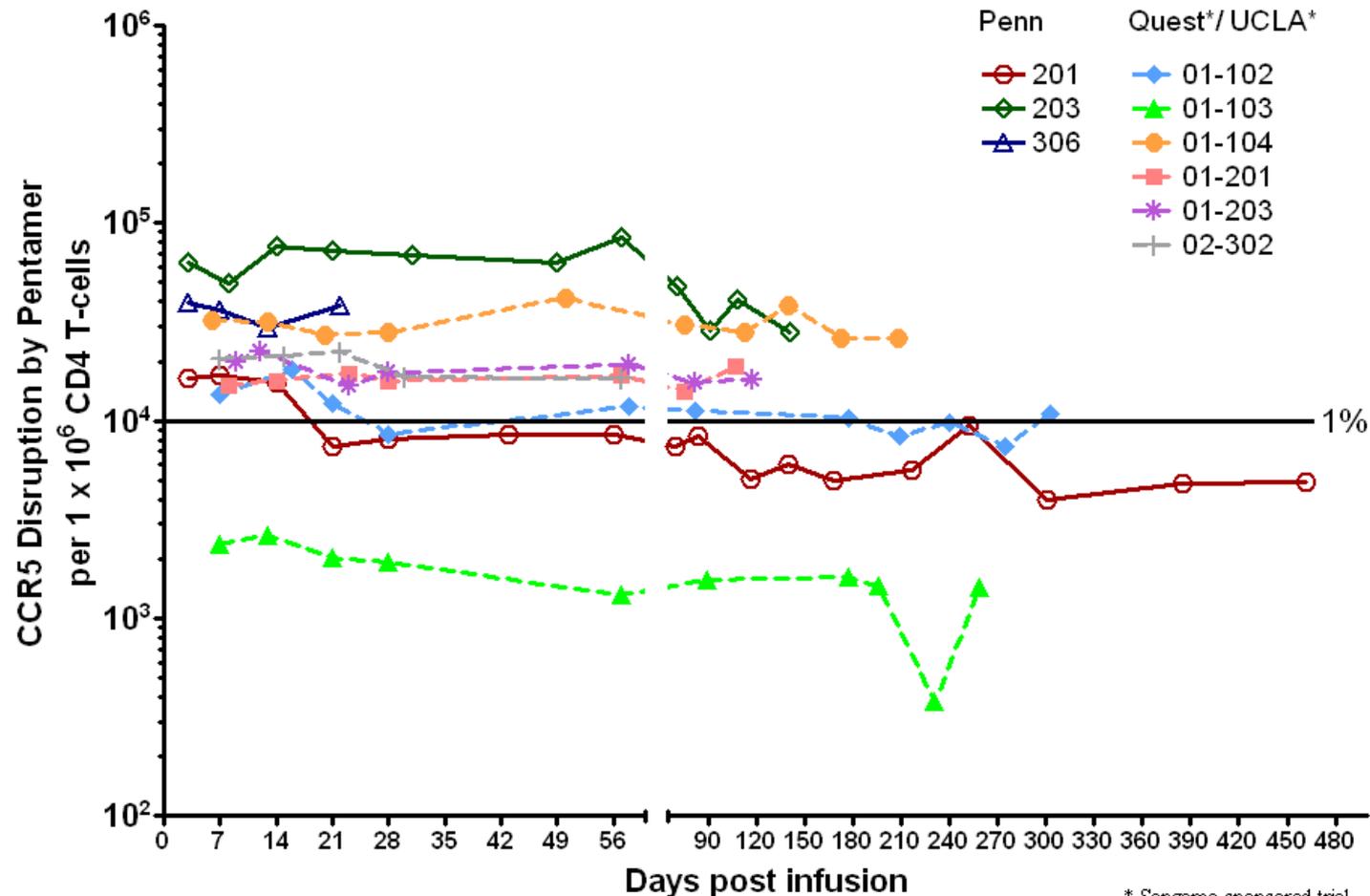


A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene, *continued*

- Infusion of up to 10×10^9 cells in 9 evaluable subjects was well tolerated and the ZFN-CCR5 modified cells persisted in the peripheral blood for over a year.**
- There was up to a 45-fold selective expansion of ZFN-CCR5 modified T cells, which is greater than seen in other studies of adoptive T cells.**
- Clinically, subjects showed improvement in CD4+ T cell counts and CD4:CD8+ ratio improved in a number of subjects.**

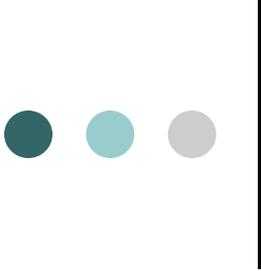
Persistence of CCR5 Modified CD4 Cells in the Peripheral Blood in all Subjects

The Pentamer assay captures ~25% of all CCR5 disruptions:
=> total CCR5 gene disruption frequency is ~ 4 fold higher



Courtesy
Of Carl
June

* Sangamo sponsored trial



A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene, *continued*

- **Webcasts of the presentation by Dr. Carl June, at CROI 2011 can be accessed via the following link**
http://www.retroconference.org/2011/data/files/webcast_2011.htm