



GTSAB REPORT

Recombinant DNA Advisory Committee

March 12, 2014



National Institutes
of Health



Protocols Submitted for First Quarter 2014

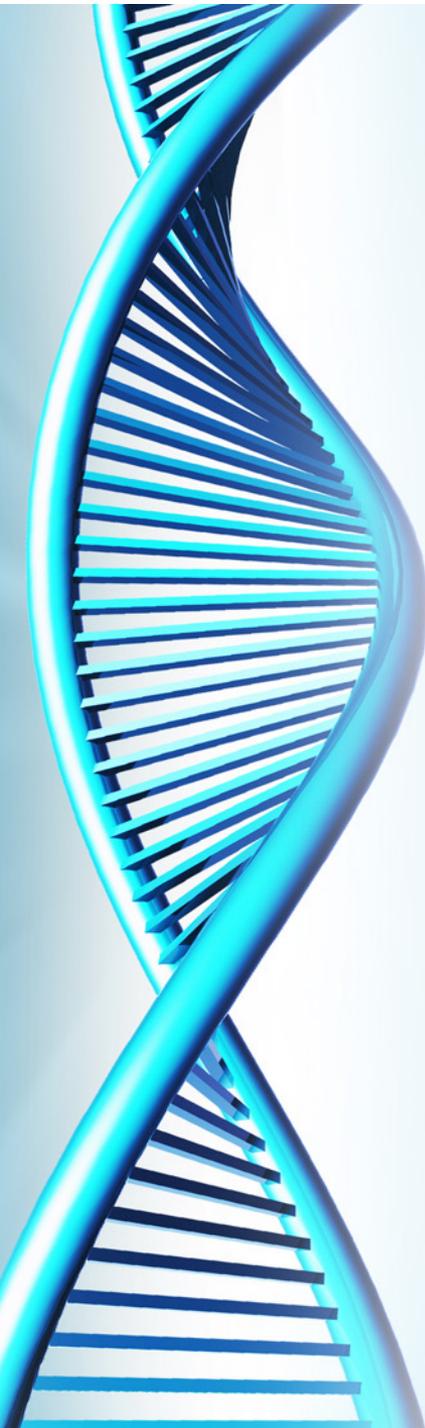
- **15 Total submissions**
Disease indications for the protocols not selected:
 - 11 for cancer**
 - 1 for aromatic L-amino acid deficiency**

Vectors	
6 Retroviruses	2 Plasmids
2 Lentiviruses	1 Pox virus
1 AAV	



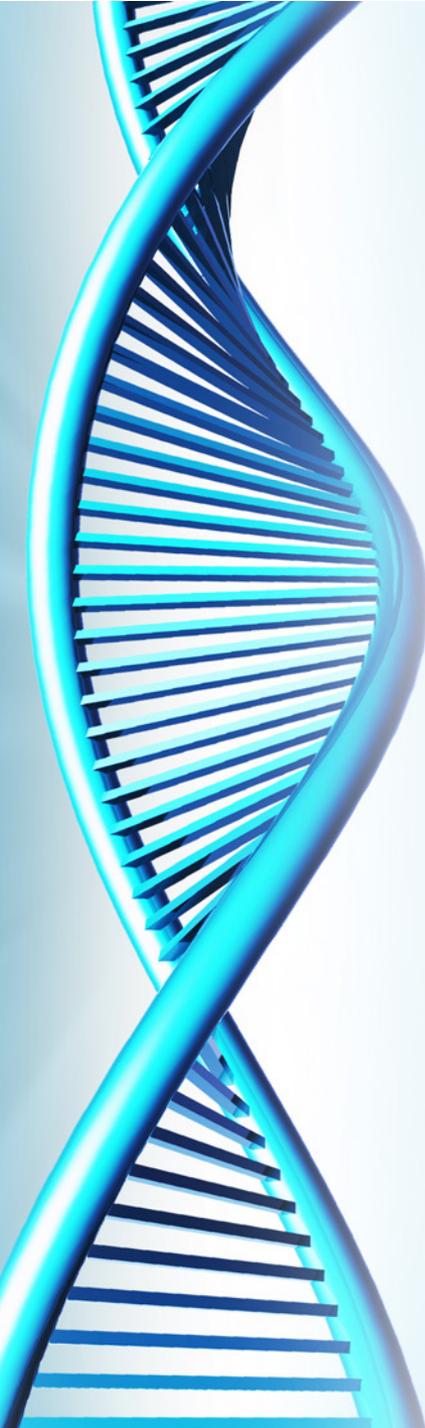
Serious Adverse Events

14 serious adverse events were reviewed by the GTSAB from 8 protocols, including initial and follow-up reports. No events will be discussed today.



Opening of New Protocols First Quarter 2014

- **12 protocols notified OBA of enrollment (MIC1 submission), five were publicly reviewed (one of the five previously submitted responses to the issues raised).**



Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa (RDEB)

(OBA Protocol #827 Reviewed March 2007)

- Due to concern that overproduction of collagen by the transduced keratinocytes could produce a T cell response, an assay for cytotoxic T cell response has been added to the clinical protocol. In addition, subjects will be closely monitored for potential autoimmune reactions.
- Trial will now enroll five adults prior to enrolling children.
- The consent procedure will include participation by a bioethicist, who will serve as a patient advocate.



An Open Label, Non-Randomized, Single Dose, Multi-Center Phase 2/3 Study of the Safety and Efficacy of Lenti-D Modified Autologous Stem Cells for the Treatment of Subjects with Childhood Cerebral Adrenoleukodystrophy

(OBA Protocol #1073 Reviewed December 2010)

- Because of the benefit of allogeneic stem cell transplant, potential subjects with a 10/10 HLA-matched sibling donor are excluded from participating in the trial.
- In addition, the consent process requires an independent physician (i.e., a physician that is not part of the site's study team) to be present during the informed consent process to answer questions about the study.
- The informed consent has been revised to make it clear that there may be no benefit from the gene transfer.



An Adaptive Phase I/II Study Of The Safety Of CD4+ T Lymphocytes And CD34+ Hematopoietic Stem/Progenitor Cells Transduced With CAL-1, a Dual Anti-HIV Gene Transfer Construct, in Busulfan Conditioned HIV-Infected Adults Previously Exposed To ART

(OBA Protocol 1130 Reviewed December 2011)

The vector encodes an shRNA against CCR5 and C46, a membrane-anchored C-peptide derived from the HIV-1 envelope to act as a fusion inhibitor

- Stored specimens will be used for analysis of C46 antibody and immunogenicity studies (CD4+ and CD8+ cellular responses).
- The section in the informed consent document regarding who will bear the costs of care for adverse events was amended to make it clear that tests and treatment costs will be covered for long-term toxicities and that subjects will be monitored for genotoxicity.



A Phase 1/2, Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects with β -Thalassemia Major by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral β A-T87Q-Globin Vector

(OBA Protocol #1164 Reviewed June 2012)

- The protocol was updated to include detection of clonality as a potential cause of enrollment suspension. If clonal analysis of peripheral blood showing gene marking in a single clone persistently representing >10% of total peripheral blood mononuclear cells (PBMCs) and concurrent presence of leukocytosis (white blood cell [WBC] count >30,000 cells/ μ L/mm³) enrollment may be suspended, pending discussions with and a recommendation from the Data Monitoring Committee.

Recent Publication from Protocol # 843



The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 6, 2014

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Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

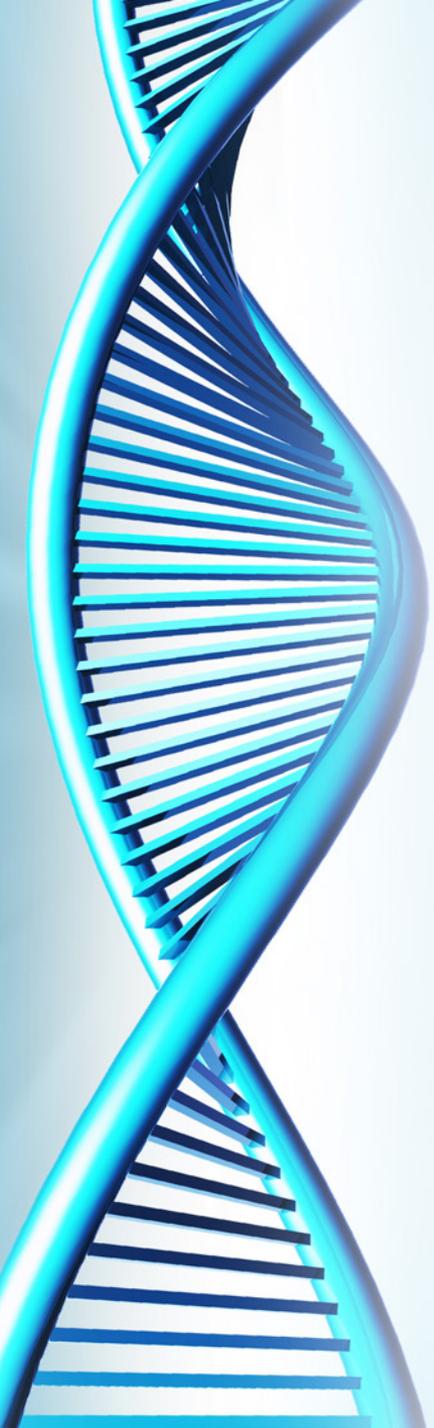
Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

- 12 patients received ZFN-modified autologous T cells; 6 patients initiated 12 week treatment interruption, 4 completed
- 1 patient suffered a transfusion related serious adverse event (fevers, chills, joint pain and back pain) and recovered
- Modified T cells had estimated mean half-life of 48 weeks
- During treatment interruption and the resultant viremia, the decline in the median number of circulating CCR5-modified T cells was significantly less than the decline in unmodified cells
- CCR5-modified autologous CD4 T cell infusions are safe within the limits of this study



**Genomic Editing:
Establishing Preclinical Toxicology Standards
RAC Workshop
June 10, 2014, Bethesda, MD**

- Genomic Editing Technologies
 - Zinc finger nucleases
 - Transcription Activator-like Effector Nucleases (TALENs) Meganucleases
 - Clustered Regulatory Interspaced Short Palindromic Repeats (CRISPR)



Questions?



PROTOCOLS INITIATED THIS QUARTER

0907-985 A Phase I Trial of Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19

1007-1058 A Phase I, Open Label, Dual Cohort, Single Center Study to Evaluate the Safety, Tolerability and Immunogenicity of Autologous CD4 T Cells Modified with a Retroviral Vector Expressing the MazF Endoribonuclease Gene in Patients with HIV

1204-1159 A Phase 1/2 Trial Evaluating Treatment of Emergent Graft versus Host Disease (GvHD) with AP1903 after Planned Donor Infusions (DLIs) of T-cells Genetically Modified with the iCasp9 Suicide Gene in Subjects with Hematologic Malignancies

1209-1182 Autologous Activated T-Cells Transduced with a 3rd Generation GD-2 Chimeric Antigen Receptor and iCaspase9 Safety Switch Administered to Patients with Relapsed or Refractory Neuroblastoma (GRAIN)

1209-1183 Phase I Study of Cellular Immunotherapy Using Central Memory Enriched T Cells Lentivirally Transduced to Express a CD19-Specific, CD28-Costimulatory Chimeric Receptor and a Truncated EGFR Following Peripheral Blood Stem Cell Transplantation for Patients with High-Risk Intermediate Grade B-Lineage Non-Hodgkin Lymphoma



PROTOCOLS INITIATED THIS QUARTER

1302-1210 A Pilot Safety Study of Vaccination with Autologous, Lethally Irradiated Colorectal Cancer cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Stimulating Factor

1304-1235 A Phase IIb Pilot study to confirm the feasibility and tolerability of a modified dosage regimen of AMG0001 in subjects with critical limb ischemia.

1307-1247 A Phase 2, Multicenter Study of FOLFIRINOX Followed by Ipilimumab in Combination with Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine in the Treatment of Metastatic Pancreatic Cancer

1308-1249 A Phase 2, Multicenter Study of FOLFIRINOX Followed by Ipilimumab in Combination with Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine in the Treatment of Metastatic Pancreatic Cancer