

GTSAB REPORT

Recombinant DNA Advisory Committee

March 10, 2010

Protocols Submitted for March 2010

- **Eighteen submissions total**
 - **Twelve Protocols Not Selected:**
 - **OBA Protocols # 1000, 1009-1015, 1017, 1019, 1021-1022, 1025**
 - **Eight are oncology protocols**
 - **Three are infectious diseases**
 - **One for peripheral artery disease**
 - **One for elimination of GVHD**
 - **Vectors:**
 - 6 plasmid
 - 2 adenovirus
 - 1 Saccharomyces
 - 1 lentivirus
 - 2 retrovirus
 - 1 measles

MIC1 Submissions

March 2010

- **8 Protocols submitted MIC1s to OBA indicating enrollment**
- **1 Protocol (#0704-849) was reviewed by the RAC at a public meeting:**

A Phase I Study Evaluating the Use of Allodepleted T Cells Transduced with Inducible Caspase 9 Suicide Gene After Haploidentical Stem Cell Transplantation (#0704-849 reviewed June 2007)

- In subjects who develop GVHD, the RAC recommended identifying whether the reactive cells were transduced by the transgene and can be eliminated with the dimerizer drug, AP1903, or whether GVHD was caused by non-transduced cells. Blood samples will be obtained from participants who develop GVHD to monitor for the effects of the drug, AP1903, on the persistence of the transgene. Two subjects have developed mild GVHD to date and responded within 24 hours to the AP1903.
- Potential immunogenicity of the construct was a concern due to the slightly mutated FK506-binding domain. In subjects dosed to date, cells have persisted beyond 6 weeks without an apparent immune response. If transduced T cells disappear rapidly from circulation, evidence of an immune response will be sought but may be technically challenging due to the fact that subjects remain lymphopenic for a year after transplant.

Serious Adverse Events

- 18 serious adverse events reviewed by GTSAB from 12 protocols, including initial and follow-up reports.
- In follow-up to the presentation at the December RAC meeting regarding a death on a trial using a chimeric T cell receptor against Her2/neu a safety symposium, *Gene-Modified T Cells: Challenges in Clinical Trial Design*, is being planned for June 15, 2010.

Recent Publication of Note:

Stein, S., et. al., Genomic Instability and Myelodysplasia with Monosomy 7 Consequent to EVI1 Activation after Gene Therapy for Chronic Granulomatous Disease, Nature Medicine 16: 198-205, 2010.

- **Follow-up report on two subjects with chronic granulomatous disease treated in 2004 with a gamma retroviral vector (SFFV) vector expressing gp91^{phox} following busulfan preconditioning.**
- **There was initial clinical benefit, including eradication of life-threatening bacterial and fungal infections, but loss of oxidase positive granulocytes began by month 9 in one subject and month 15 in the other subject.**
- **Insertional activation of MDS1-EVI1 and genes encoding PR domain containing protein 16 (PRDM16), a homolog of MDS1-Ev11, and SET-binding protein triggered a three to five fold increase in the number of gene transduced cells in the peripheral blood and ultimately led to oligoclonal hematopoiesis, monosomy 7 and myelodysplastic syndrome (MDS) with the loss of transgene expression.**
- **One subject died of sepsis 27 months after gene transfer and post mortem data suggests subject developed MDS, probably with transition to acute myelogenous leukemia. The second subject underwent an allogeneic bone marrow transplant at month 45 after developing refractory cytopenias and multilineage dysplasia.**

Recent Publication of Note:

Kang, E.M., et. al., *Retrovirus gene therapy for X-linked granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils*, Blood 115 (4): 783-790, 2010.

- **Report on 3 subjects with treatment refractory infections enrolled in a trial using a MFGS retroviral vector expressing gp91^{phox} after preconditioning with busulfan. The third subject was also given rapamycin after the second subject had loss of marked cells that was thought to be due to a possible immune response.**
- **One subject had resolution of liver abscesses after gene transfer and 34 months after gene therapy is free of infection and remains well on standard CGD antimicrobial prophylaxis. The percentage of oxidase normal peripheral blood monocytes and neutrophils is 1.1%.**
- **The second subject, who had early loss of gene marking unfortunately succumbed to his fungal infection.**
- **The third subject demonstrated significant radiological evidence of regression of pulmonary *Aspergillus* infection followed by stabilization at 6 months post gene transfer but was also given allogeneic irradiated granulocyte infusions when neutropenic, “complicating the interpretation of the role of gene therapy in resolution of the fungal infection.” Percentage of oxidase normal peripheral blood cells is 0.03% at 13 mos.**
- **No evidence of oligoclonality or clonal dominance.**

Recent Publication of Note:

Pule, M.A., *et. al.*, Virus-Specific T cells engineered to coexpress tumor specific receptors: persistence and antitumor activity in individuals with neuroblastoma, *Nat. Med.* 14(11): 1264-1279, 2008.

- **Both Epstein-Barr virus (EBV)-specific cytotoxic T lymphocytes (CTLs) and CD3-specific antibody OKT3 activated T cells (ATCs) were transduced with a chimeric antigen receptor (CAR) directed to the GD2 antigen, present on tumor cells of individuals with neuroblastoma.**
- **Eleven individuals with relapsed or refractory neuroblastoma who had EBV-specific IgGs received a single injection of an equal number of CAR-CTLs and CAR-ATCs, for a total dose of 2×10^7 to 2×10^8 cells. No adverse events were attributed to the cells with follow-up of 24 months.**
- **After 24 weeks, the CAR-CTLs consistently expanded in response to native receptor stimulation by EBV+ target cells resulting in a 2-20 fold enrichment of PCR signal. No evidence for such expansion was found in the CAR-ATC population but the authors note that highly specific methods for selective expansion of CAR-ATC in *ex vivo* culture are lacking.**
- **Infusion of these cells was associated with regression or necrosis in four of the eight subjects with evaluable tumors and one subject achieved complete remission that was sustained for 12 months without further therapy.**

Recent Publication of Note:

Kantoff, P.W., et al: Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral-Based PSA-Targeted Immunotherapy in Metastatic Castration-Resistant Prostate Cancer, Journal of Clinical Oncology 28: 1099-1105, 2010

- The study used two recombinant viral vectors (vaccinia and fowlpox) that encoded the transgenes for PSA along with three immune costimulatory molecules (B7.1, ICAM-1 and LFA-3) (PROSTVAC-VF)
- In this double blind study 82 subjects with hormone resistant metastatic prostate cancer received the gene transfer vectors and 40 comparable subjects received control vectors (empty vaccinia vector and empty fowlpox vector)
- While at three years post study, no significant difference was noted in the primary endpoint of progression free survival ($p=0.6$), in the PROSTVAC-VF group, a 44% reduction in the death rate and a 8.5 month improvement in the median overall survival was noted when compared to the control (stratified log rank $P = .0061$).