

GTSAB REPORT

Recombinant DNA Advisory Committee

March 12, 2013



**National Institutes
of Health**

Protocols Submitted for 1st Quarter 2013

▶ 13 Total submissions

• Disease indications for the protocols not selected:

- 9 Cancer
- 1 Eye disorder (choroideremia)
- 1 Control of graft versus host disease after stem cell transplant

▶ Vectors:

- 5 Retroviruses
- 2 Vaccinia
- 1 Lentivirus
- 1 AAV
- 1 *S. cerevisiae*
- 1 Transposon

Serious Adverse Events

12 serious adverse events were reviewed by the GTSAB from 10 protocols, including initial and follow-up reports. No events will be discussed today.

Opening of New Protocols 1st Quarter 2013

- ▶ **14 Protocols notified OBA of enrollment (MIC1 submission).**
- ▶ **3 of the 14 were reviewed at a public meeting.**
- ▶ **Information on trials not selected will be available with these slides on OBA's Website after the meeting.**

Lentiviral Gene Transfer for Treatment of Children Older Than One Year of Age with X-Linked Severe Combined Immunodeficiency

(OBA Protocol #964 Reviewed March 2009)

- ▶ **Preclinical data submitted comparing the risk of insertional oncogenesis between the lentiviral vector being used in this protocol and the retroviral vector used in the clinical studies for X-SCID in which five subjects developed leukemia.**

**A safety and efficacy study in subjects with Leber
Congenital Amaurosis (LCA) using Adeno-
associated Virus vector to deliver the gene for
human RPE65 to the retinal pigment epithelium
(RPE) [AAV2-hRPE65v2-301]
(OBA Protocol #1005 Reviewed December 2009)**

- ▶ **The primary endpoint has been changed from pupillary light reflex to mobility testing.**
- ▶ **The Phase 3 eligibility criteria are restricted with respect to the primary endpoint such that those with more moderate retinal degeneration, or those with impairment so severe the improvements cannot be detected, are excluded.**

A Phase I/II Safety, Pharmacokinetic, and Pharmacodynamic Study of APS001F with Flucytosine and Maltose for the Treatment of Advanced and/or Metastatic Solid Tumors (OBA Protocol #1117 Reviewed September 2011)

- ▶ **APS001F is a recombinant *Bifidobacterium longum* strain expressing cytosine deaminase.**
 - ▶ **Additional preclinical data submitted regarding biodistribution of vector over time.**
 - ▶ **Cytokine levels for IL-6, INF- γ IL-1 β and TNF- α will be measured, as elevations in TNF- α were seen in animal studies at the higher doses and in some of the animals who died in these studies.**
 - ▶ **As necrotic tumor may serve as a nidus for abscess formation, the protocol includes a guideline on management of abscesses.**



Recent Publications of Interest

NIH/OBA Protocol 0001-381 Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer

Long-Term Follow-Up After Gene Therapy for Canavan Disease

Paola Leone *et al.*; *Sci Transl Med* 4, 165ra163 (2012)

Early detection and treatment with gene therapy-mediated enzyme replacement in the neonatal period may offer the best opportunity for a reduction in symptoms and long-term stabilization in patients with Canavan disease.

** Dr. Leone has been invited to present her results at the June 2013 RAC meeting.

NIH/OBA Protocol 9711-221

Long-Term Follow-Up Assessment of a Phase 1 Trial of Angiogenic Gene Therapy Using Direct Intramyocardial Administration of an Adenoviral Vector Expressing the VEGF121 cDNA for the Treatment of Diffuse Coronary Artery Disease

- **Todd K. Rosengart *et al.*, *Human Gene Therapy* 24: 203, February 2013**
- **From 1997 to 1999, AdVEGF121 was administered by direct myocardial injection to an area of reversible ischemia in 31 patients with severe coronary disease, either as an adjunct to conventional coronary artery bypass grafting (group A) or as minimally invasive sole (MIS) therapy, using a minithoracotomy (group B).**
- **This study provides long-term (median, 11.8 years) follow-up on these patients**

NIH/OBA Protocol 9711-221

Long-Term Follow-Up Assessment of a Phase 1 Trial of Angiogenic Gene Therapy, Cont. . . .

- **No increase in malignancy seen in these patients compared to general population (13% in the study population versus 17% in the general population).**
- **About 52% of the study subjects had diabetes, but there was a low incidence (<5%) of diabetic retinopathy, which is below that predicted.**
- **The 5- and 10-year survival was 10 of 15 (67%) and 6 of 15 (40%) for the group A patients, and 11 of 16 (69%) and 5 of 16 (31%) for group B sole therapy patients, respectively. In comparison, maximal medical therapy in comparable groups in the literature have a 3- to 5-year survival rate of 52 to 59%.**



PROTOCOLS INITIATED BUT NOT REVIEWED AT A PUBLIC MEETING.

0901-962 A Phase I Open-Label Dose Escalation Safety Study of Convection-enhanced Delivery (CED) of Adeno-Associated Virus Encoding Glial Cell Line-Derived Neurotrophic Factor (AAV2-GDNF) in Subjects with Advanced Parkinson's Disease

1001-1022 Adoptive Immunotherapy for CD19+ B-cell Malignancies using Sleeping Beauty Transposition to Express a CD19-specific Chimeric Antigen Receptor in Allogeneic Neonatal Ex Vivo expanded T cells

1006-1044 Phase II Trial of Intratumoral IL12 Plasmid Electroporation in Cutaneous Lymphoma

1008-1063 Phase I Study of Donor Derived, Multi-Virus-Specific, Cytotoxic T-Lymphocytes Redirected to the Tumor Marker GD2 in Patients with Relapsed/Refractory Neuroblastoma Post-Allogeneic Hematopoietic Stem Cell Transplantation with a Sub-Myeloablative Conditioning Regimen

1105-1109 Pilot Study Evaluating An Allogeneic GM-CSF-Transduced Pancreatic Tumor Cell Vaccine (CGVAX) and Low Dose Cyclophosphamide Integrated with Fractionated Stereotactic Body Radiation Therapy (SBRT) and FOLFIRINOX chemotherapy in Patients with Resected Adenocarcinoma of the Pancreas.

PROTOCOLS INITIATED BUT NOT REVIEWED AT A PUBLIC MEETING

1110-1128 A Phase I Clinical Trial Assessing the Safety and Feasibility of Administration of pNGVL4a-CRT/E7(detox) DNA Vaccine using the Intramuscular TriGrid™ Delivery System in Combination with Cyclophosphamide in HPV-16 Associated Head and Neck Cancer Patients

1201-1141 A Phase 1 Safety Study in Subjects with Severe Hemophilia B (Factor IX Deficiency) Using a Single-Stranded, Adeno-Associated Pseudotype 8 Viral Vector to Deliver the Gene for Human Factor IX [AAV8-hFIX19-101]

1204-1163 A Phase II, Randomized, Open Label, Parallel Arm Study to Evaluate the Safety and Efficacy of rAd-IFN/Syn3 Following Intravesical Administration in Subjects with High Grade, BCG Refractory, Relapsed or Resistant Non-Muscle Invasive Bladder Cancer (NMIBC)

1205-1168 A Phase I Study of Intraperitoneal EGEN-001 (IL-12 Plasmid Formulated with PEG-PEI-Cholesterol Lipopolymer) (IND #12,484) Administered in Combination with Peglyated Liposomal Doxorubicin (PLD), Dosxil and Lipodox (NSC# 712227) in Patients with Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

1207-1172 A Phase I/II Evaluation of ADXS11-001, Mitomycin, 5-fluorouracil (5-FU) and IMRT for Anal Cancer