

# **GTSAB REPORT**

## **Recombinant DNA Advisory Committee**

**March 7, 2012**



# Protocols Submitted for 1st Quarter 2012

▶ 12 Total submissions

Disease indications for the nine protocols not selected:

- Cancer (7)
- Hemophilia
- Heart failure

Vectors:

- Plasmid (3)
- Adenovirus (2)
- AAV
- Transposon
- Retrovirus (2)

# **Serious Adverse Events**

**15 serious adverse events were reviewed by the GTSAB from 9 protocols, including initial and follow-up reports. No events reviewed this quarter will be discussed today.**



# **Opening of New Protocols 1st Quarter 2012**

- ▶ **17 Protocols notified OBA of enrollment (MIC1 submission).**
  - ▶ **Five of the 17 were reviewed at a public meeting.**
  - ▶ **The following are highlights of the responses on those five protocols.**
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# **A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-Modified Neural Stem Cells Expressing E. Coli Cytosine Deaminase for Treatment of Recurrent High-Grade Gliomas (OBA Protocol #878 reviewed December 2007)**

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- ▶ **Preclinical studies were done in a model with prior radiation to assess whether radiation could alter the tumor environment and make the neural stem cells, which had been transformed with the c-myc oncogene, prone to produce tumors. The effect of radiation on the ability of the cells to migrate to the tumor was also evaluated. Radiation did not change the safety profile of the cells in these models.**
- ▶ **Animal and cell migration studies also demonstrated that dexamethasone did not alter either the tumorigenicity or the tropism of the stem cells. Dexamethasone is a commonly prescribed drug in patients with gliomas.**

**A Phase 1 Open-Label, Escalating-Dose Study, Of The Safety And Tolerability Of Single Daily Doses Of CEQ 508 An RNAi-Based Therapy For Familial Adenomatous Polyposis (OBA Protocol #989 reviewed September 2009)**

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- ▶ **The response notes that immune responses to listerolysin O, one of the bacterial components of the study agent (CEQ 508), has not been seen in pre-clinical studies or in a previous phase 1 trial.**
- ▶ **The mutation seen in this disease leads to increased  $\beta$ -catenin which leads to up regulation of genes involved in cell proliferation, including the c-myc oncogene. Additional analysis of correlations between oncogenes,  $\beta$ -catenin and clinical outcomes is being considered.**
- ▶ **Only subjects with a documented mutation in the adenomatous polyposis coli (APC) gene or a clinical diagnosis and family history of this autosomal dominant disease will be enrolled.**

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**Lymphodepletion Plus Adoptive Cell Transfer with CXCR2 and NGFR Transduced T-Cells Followed by High Dose Interleukin-2 in Patients with Metastatic Melanoma**  
(OBA Protocol #1024 reviewed March 2010)

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- ▶ **This study will employ a Bayesian approach to the phase I dose escalation so that dosing cohorts will be informed by the ability of a prior cohort to tolerate the transduced tumor infiltrating lymphocytes (TIL), which may expand significantly in-vivo or be rapidly eliminated.**
- ▶ **Given recent data that indicate that CD4+ T-cells may be critical to antitumor activity, in addition to examining the tumor site for the presence CXCR2 transduced TIL, they will examine whether CD4+ T-cells are present.**
- ▶ **The age limit for pediatric subjects has been clarified to age 7 and older rather than relying on “intellectual age.”**

**Phase 1/2 Open-Label, Single-Center, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Tolerability of SNSO1-T Administered by Intravenous Infusion in Patients with Relapsed or Refractory Multiple Myeloma (OBA Protocol #1049 reviewed September 2010)**

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- ▶ **SNSO1-T is a nanoparticle-plasmid complex containing a gene for a translation initiation factor 5A (eIF5A) protein and a siRNA against the same native eIF5A. In myeloma cells the eIF5A is hypusinated and this promotes cell growth. This is the target of the siRNA. Unhypusinated eIF5A that will be made by the plasmid should then promote apoptosis.**
- ▶ **Preclinical models reviewed at the RAC meeting employed subcutaneous injection. However, results of toxicology studies demonstrate that intravenous administration leads to plasmid DNA in the bone marrow and the clinical trial will examine bone marrow samples to determine if apoptosis is occurring in myeloma cells.**

**Phase 1/2 Open-Label, Single-Center, Multiple-Dose, Dose-Escalation Study to Evaluate the Safety and Tolerability of SNSO1-T Administered by Intravenous Infusion in Patients with Relapsed or Refractory Multiple Myeloma (OBA Protocol #1049 reviewed September 2010)**

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- ▶ **A concern was raised regarding whether the study agent could alter the expression of the eukaryotic translation initiation factor 5A-like 1 (eiFAL1), which may be a pseudogene. Data presented that eiFAL1 appears to be a pseudogene and is not expressed in a myeloma cell line. Moreover, given the sequence homology between eIF5AL1 and eIF5A, any expression would likely be silenced by the siRNA.**

# **A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer (OBA Protocol #1101 reviewed June 2011)**

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- ▶ **Additional information was added to the protocol that articulated the rationale for the use of an empty fowlpox vector, rather than a vaccinia virus vector (the backbone of the study agent), as the placebo control.**
  - ▶ **Detailed instructions and precautions will be provided to those individuals who will prepare the study agent for injection or interact with subjects in order to ensure that the vector is handled in a safe manner and that healthcare workers are informed of the potential risks.**
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