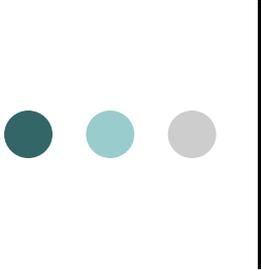


# **GTSAB REPORT**

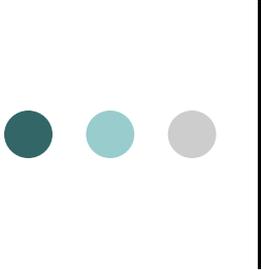
## **Recombinant DNA Advisory Committee**

**September 16, 2010**



# Protocols Submitted for 3<sup>rd</sup> Quarter

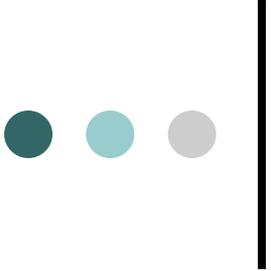
- **Twenty submissions total**
  - **Eleven Protocols Not Selected:**
    - **Nine are oncology protocols**
    - **One for a monogenic disease—Leber Congenital Amaurosis**
    - **One for an autoimmune disease—diabetes**
    - **Vectors:**
      - 4 plasmid
      - 3 retrovirus
      - 2 adenovirus
      - 1 vaccinia
      - 1 adeno-associated



# MIC1 Submissions

## 3<sup>rd</sup> Quarter 2010

- **14 Protocols submitted MIC1s to OBA indicating enrollment**
- **4 Protocols were reviewed by the RAC at public meetings:**



# Clinical Translation of a Mammaglobin-A DNA Vaccine for Breast Cancer Prevention and Therapy (#0509-727 reviewed December 2005)

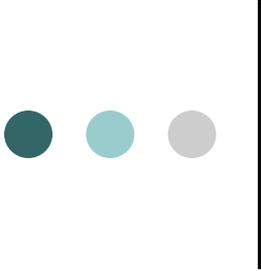
- **Data submitted to support that mammaglobin-A not associated with tumor development in response to RAC concern regarding ectopic expression**
- **Trial design changed to a fixed dose rather than dose escalation study citing RAC member comment and article<sup>1</sup> that noted "the initial clinical trial of many new vaccines will not be a toxicity or dose-ranging trial but rather will involve administration of a fixed dose of vaccine."**

<sup>1</sup>Simon *et al.*, Clinical trial designs for early clinical development of therapeutic cancer vaccines. 2001 *J Clin. Oncol.* 19:1848-54



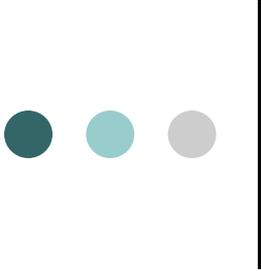
**Phase Ib Study of Autologous Ad-ISF35-Transduced CLL B Cells and Fludarabine, Cyclophosphamide, and Rituximab (FCR) in Subjects with Fludarabine-Refractory and/or del(17p) Chronic Lymphocytic Leukemia (CLL) (#0801-952 reviewed June 2010)**

- **Will be conducting studies recommended by RAC, to explore**
  - **If Ad-ISF35 vector can replicate in CLL cells.**
  - **The mechanisms underlying the phenotypic changes on unmodified, bystander CLL cells.**
- **Informed Consent to be amended to clarify**
  - **Institutional conflict of interest (due to patent rights).**
  - **Use of future patient samples.**



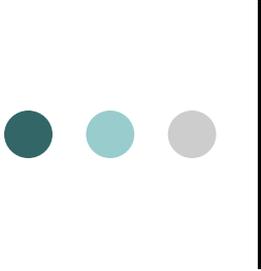
# **A Phase I Ascending Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme (#0904-976 reviewed June 2009)**

- To facilitate studies of the role of the immune response in efficacy and any unexpected adverse events, PBMCs will be collected before and after vaccine administration.**
- Tumor samples will be analyzed for the vector.**
- In the initial trial, XMRV positive subjects will be excluded to avoid inadvertent recombination.**



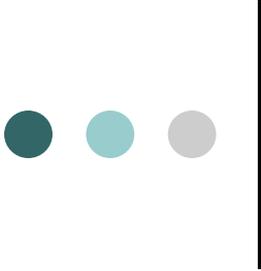
# **A Multiple-Site, Phase 2, Safety and Efficacy Trial of a Recombinant Adeno associated Virus Vector Expressing Alpha 1 Antitrypsin (rAAV1-CB-hAAT) in Patients with Alpha 1 Antitrypsin Deficiency (#0910-1002 reviewed December 2009)**

- Since the AAV vector is produced with an HSV helper, the investigators will re-examine serum samples saved from preclinical animal studies for anti-HSV antibodies.**
- Potential T cell responses to AAV capsid will be evaluated by ELISPOT assays and, as appropriate, intracellular cytokine staining assays.**



# Serious Adverse Events

- **14 serious adverse events were reviewed by the GTSAB from 11 protocols, including initial and follow-up reports. No reports need additional discussion.**



# **JX-594 (Thymidine Kinase Inactivated Vaccinia plus GM- CSF)**

- **JX-594 is an oncolytic therapeutic vaccinia virus (Wyeth strain) modified as follows:**
  - **Thymidine kinase gene deactivation,**
  - **GM-CSF insertion**
  - **Lac-Z gene insertion**
- **At least four clinical trials have been completed and two additional clinical trials have been initiated and are ongoing**
  - **4 intratumoral - metastatic melanoma (2), liver tumors, Hepatocellular carcinoma (HCC)**
  - **2 IV – refractory solid tumor, HCC**

# JX-594 (Thymidine Kinase

## Inactivated Vaccinia plus GM-CSF)

- 4 subjects enrolled in JX-594 clinical trials have developed small (< 1cm) skin pustules after IV administration ( $10^9$  pfu). In each case the overlying pustule was intact and shedding was not documented but aspiration of the fluid through the skin or removal of a scab detected JX-594.
- Pustules were covered in accordance with CDC recommendations for routine vaccinia vaccination pustules.
- Only 1-2 pustules developed in the 3 subjects who had CD4+ counts above 200, but 10-15 pustules developed in the 4<sup>th</sup> patient with a CD4+ count <50.

# JX-594 (Thymidine Kinase

## Inactivated Vaccinia plus GM-CSF)

- Quantitative PCR in the serum for JX-594 genome was negative in all 4 subjects.
- All pustules resolved within 2-3 weeks without any adverse effect and there was no evidence of toxicity or replication in other organs.
- There was no evidence of transmission to caregivers and family members.

# JX-594 (Thymidine Kinase

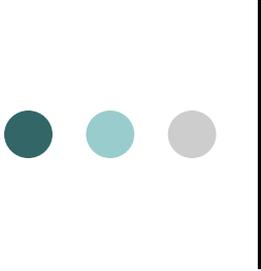
## Inactivated Vaccinia plus GM-CSF)

- It is noted by the sponsor that pustules are known to occur after vaccination with the Dryvax vaccine (backbone virus for JX-594) that was used in the eradication campaign against smallpox.
- Per the CDC, a 1968 state survey calculated the risk of transmission of the vaccinia virus from a vaccinated person to a susceptible contact as 27 infections/million total vaccinations with almost half of those contact infections being found in children aged  $\leq 5$  years (MMWR June 22, 2001).
- JX-594 is more attenuated than Dryvax (TK deactivated) and therefore may be less likely to transmit live vaccinia virus than the Dryvax vaccine

# JX-594 (Thymidine Kinase

## Inactivated Vaccinia plus GM-CSF)

- All subjects receive information that is consistent with the CDC recommendations for Preventing Contact Transmission of Vaccinia Virus after Vaccination (MMWR June 22, 2001).
- A picture of a typical vaccinia pox lesion is included in the subject training information.

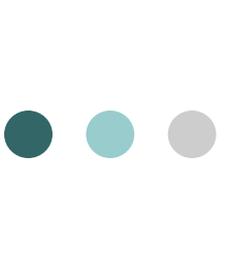


***Integrating Vectors in Gene Transfer:  
Update on Insertional Mutagenesis  
and Vector and Study Design***

**NIH/RAC  
in partnership  
with CliniGene**

**December 9-10, 2010**

**Hilton Rockville, M.D.**



# **A Phase I Trial of the Immunostimulant JVRS-100 for the Treatment of Patients with Relapses and Refractory Leukemia (#0808-936 rev'd Dec. 3, 2008) - Update**

- Dr. David Claxton, Investigator-Sponsor,  
Penn State Milton S. Hershey Medical  
Center**
- Dr. Jeff Fairman, Vice President of  
Research, Juvaris BioTherapeutics, Inc.**
- Hildegund Ertl, M.D., Director, Vaccine  
Center, The Wistar Institute, University of  
Pennsylvania**