

GTSAB REPORT

Recombinant DNA Advisory Committee

December 13, 2011



Protocols Submitted for 4th Quarter 2011

- ▶ 15 submissions total

Protocols Not Selected:

- 7 for cancer
- 1 for hemophilia
- 1 for peripheral artery disease
- 1 for wound healing
- 1 for HIV-uninfected volunteers

Vectors:

- 5 plasmid
- 1 adenovirus
- 1 plasmid and adenovirus
- 1 AAV
- 1 vaccinia virus
- 1 retrovirus
- 1 VEE replicon

Serious Adverse Events

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



Opening of New Protocols 4th Quarter 2011

- ▶ 15 Protocols notified OBA of enrollment (MIC1 submission).
 - ▶ Eight of the 15 were reviewed at a public meeting.
- 

Dose-finding and Safety Study of an Oncolytic Polio/Rhinovirus Recombinant Against Malignant Glioma

(OBA Protocol #707 reviewed June 2005)

- ▶ Preclinical biodistribution, toxicity, shedding, and neutralizing antibody studies were conducted, as requested, in *Cynomolgus* macaques. A manuscript is in preparation to publish these results.
- ▶ In response to a concern that pre-existing antibodies against poliovirus might inhibit the ability of this virus to replicate in glial tumor cells, additional preclinical studies were done in rodents and these studies demonstrate that pre-existing poliovirus immunity enhanced rather than decreased poliovirus-mediated oncolysis.

Phase II Studies of Repeat Intranodal Injections of Adenovirus-CD154 (Ad-ISF35) in Patients with Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma and in Patients with Non-Hodgkin's Lymphoma (OBA Protocols #1028 and 1029 reviewed June 2010)

- ▶ In response to RAC recommendations, concurrent preclinical studies will be done to identify the cells that are transduced by this adenoviral vector and to determine whether this viral vector has the ability to replicate in leukemic or other cell types present in a lymph node.

Phase II Studies of Repeat Intranodal Injections of Adenovirus-CD154 (Ad-ISF35), continued

- ▶ **Since the number of cells modified by the vector may be as few as 1:10,000, the RAC noted that cell-to-cell interactions are unlikely to lead to changes in the expression of cell signals on the surface of unmodified chronic lymphocytic leukemia (CLL) cells. To help elucidate the mechanism underlying the change in expression of cell signals on the surface of unmodified CLL cells, cytokine profiles and anti- and pro- apoptotic gene expression profiles will be measured.**
- 

Phase I Study of the Administration of EBV CTLs Expressing CD30 Chimeric Receptors for Relapsed CD30+ Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma

(OBA Protocol #1034 reviewed June 2010)

- ▶ In response to a concern that the spacer domain could potentially bind to IgG Fc receptors on innate immune cells, the PI acknowledged the preclinical data that led to this recommendation but noted that they have employed this endodomain in other CARs that express CD19 and have administered them to a total of eight individuals. Toxicity was not observed either immediately following administration or upon a 2-10 fold expansion *in vivo*.
- ▶ The protocol will now only enroll subjects with active disease who have failed standard therapy.

A Phase I Dose Escalation Trial Using *In Vitro* Expanded Allogeneic Epstein-Barr Virus Specific Cytotoxic T-Lymphocytes (EBV-CTLs) Genetically Targeted to the B-Cell Specific Antigen CD19 for Treatment Of Residual Or Relapsed Acute Lymphoblastic Leukemia After Transplantation (OBA Protocol #1091 reviewed June 2011)

- ▶ **This is one of the few trials that will enroll both EBV+ and EBV- patients in a trial that uses EBV specific T-cells expressing a CAR. Therefore, EBV seropositivity will be documented and correlated with T-cell activity.**
- ▶ **Changes made to the informed consent in response to RAC recommendations.**

RECENT NOTABLE PUBLICATIONS AND AWARDS



ORIGINAL ARTICLE

Inducible Apoptosis as a Safety Switch for Adoptive Cell Therapy

Antonio Di Stasi, M.D., Siok-Keen Tey, M.D., Gianpietro Dotti, M.D., Yuriko Fujita, M.D., Alana Kennedy-Nasser, M.D., Caridad Martinez, M.D., Karin Straathof, M.D., Enli Liu, M.D., April G. Durett, M.Sc., Bambi Grilley, R.Ph., Hao Liu, Ph.D., Conrad R. Cruz, M.D., Barbara Savoldo, M.D., Adrian P. Gee, Ph.D., John Schindler, Ph.D., Robert A. Krance, M.D., Helen E. Heslop, M.D., David M. Spencer, Ph.D., Cliona M. Rooney, Ph.D., and Malcolm K. Brenner, M.D.

ABSTRACT

BACKGROUND

Cellular therapies could play a role in cancer treatment and regenerative medicine if it were possible to quickly eliminate the infused cells in case of adverse events. We devised an inducible T-cell safety switch that is based on the fusion of human caspase 9 to a modified human FK-binding protein, allowing conditional dimerization. When exposed to a synthetic dimerizing drug, the inducible caspase 9 (iCasp9) becomes activated and leads to the rapid death of cells expressing this construct.

Annals of Neurology Prize for Gene Transfer for Muscular Dystrophy

Jerry Mendell, M.D., Director of the Center for Gene Therapy in the Research Institute at Nationwide Children's Hospital and his fellow researchers received the *Annals of Neurology* prize for outstanding contribution to clinical neuroscience for their publication:

Sustained Alpha-Sarcoglycan Gene Expression after Gene Transfer in Limb-Girdle Muscular Dystrophy, Type 2D

Jerry R. Mendell, MD,^{1,2,3} Louise R. Rodino-Klapac, MD,^{1,3} Xiomara Q. Rosales, MD,³
Brian D. Coley, MD,⁴ Gloria Galloway, MD,^{1,2,3} Sarah Lewis, MD,³ Vinod Malik, MD,³
Chris Shilling, MD,³ Barry J. Byrne, MD,^{5,6} Thomas Conlon, MD,^{5,6}
Katherine J. Campbell, MD,⁷ William G. Bremer, MD,⁷ Laura E. Taylor, MD,³
Kevin M. Flanigan, MD,^{1,3} Julie M. Gastier-Foster, PhD,⁸ Caroline Astbury, PhD,⁸
Janaiah Kota, MD,³ Zarife Sahenk, MD,^{1,2,3} Christopher M. Walker, MD,^{1,7}
and K. Reed Clark, MD^{1,3}

Ann. Neurol. 2010,
68(5): 629-38

Annals of Neurology Prize for Gene Transfer for Muscular Dystrophy

- ▶ **The vector used in this protocol, OBA Protocol #815, was an adeno-associated virus with a muscle specific promoter and was administered into the extensor digitorum brevis muscle.**
 - ▶ **Dr. Mendell has received an NIH grant to test regional vascular delivery to the lower limbs.**
- 