

GTSAB REPORT

Recombinant DNA Advisory Committee

September 9, 2009

Protocols Submitted for September 2009

- **Eleven Submissions total**
 - **Three to be reviewed today**
 - **Protocols Not Selected:**
 - **OBA Protocols # 960, 982-987, 990**
 - **All Oncology Protocols**
 - **Vectors:**
 - **3 adenovirus**
 - **2 plasmid**
 - **1 retrovirus**
 - **1 RNA transfer**
 - **1 vaccinia virus**

Serious Adverse Events

- **16 serious adverse events reviewed by GTSAB from 10 protocols, including initial and follow-up reports.**
- **The analysis of the events were complete and no events raise issues that need to be discussed.**

MIC1 Submissions

September 2009

- **MIC1 Filings: Trials that have initiated enrollment**
 - **11 Protocols submitted MIC1s to OBA**
 - **4 Protocols were reviewed by the RAC at a Public meeting**
 - **Highlights of responses to RAC recommendations**

A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nuclease SB-728 in HIV-Infected Patients (OBA #0704-843 reviewed June 2007)

- **Karyotyping was carried out in SB-728 treated CD4+ T cells to evaluate for potential genotoxicity due to high level of expression of zinc finger nuclease in normal cells leading to double-stranded DNA breaks at the wrong sites.**
- **Immunogenicity monitoring of the Fok1 domain by Western Blot was added in response to concern that the Fok1 domain of the zinc finger nuclease may be immunogenic due to its bacterial origin.**
- **Risks associated with an interruption in HAART added to the clinical protocol and informed consent. In addition, only subjects with T cell counts above 450 cells/mm³ are eligible (instead of 350 cells/mm) and duration STI has been shortened to a maximum of 12 weeks.**

A Phase 1 Safety Study of Heat/Phenol-Killed, E. coli-Encapsulated, Recombinant Modified Peanut Proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) in Normal Volunteers Followed by Subjects Allergic to Peanuts
(OBA # 0707-868 Rev'd September 2007)

- **Inclusion/ Exclusion criteria revised in response to recommendations:**
 - *Individuals with any history of asthma will be excluded rather than basing exclusion on FEV1 or clinical features of moderate to severe asthma,*
 - *Exclusion of those with peanut-specific IgE response or prick skin test to peanut > 3mm wheal diameter,*
 - *Must document regular consumption of meal size portion of peanuts at least 2x month in previous 6 months.*

Phase 1b, Open Label Trial to Define the Safety, Tolerance, Transgene Function and Immunological Effects of Intratumoral Injection(s) of Adenoviral Transduced Autologous Dendritic Cells Engineered to Express hIL-12 Under Control of The RheoSwitch® Therapeutic System in Subjects With Stage III and IV Melanoma (OBA # 0710-881 Rv'd Dec. 2007)

- **Further data provided on safety of Activator Drug.**
- **Further preclinical data to demonstrate the relative superiority of control of IL-12 by Activator Drug compared to constitutive expression of IL-12 deemed not warranted prior to initiating this Phase I.**
- **With respect to the potential for IL-12 to promote T regulatory response, biopsies of tumors and associated draining lymph nodes will be evaluated to assess cellular infiltration by T cells, and immunostaining will be used to identify CD4+ and CD8+ effector cells and T-reg subsets in the tumor and mean levels of hIL-12 and T cells will be compared among cohorts.**

Protocol # 0710-881 continued

- **Study amended to single dose study and the number of subjects to be enrolled will be 16 rather than 40. Further details on the analyses for each cohort provided.**
- **Suggested changes to the informed consent, including clarification of the financial relationship between the Pittsburgh Medical Center and the sponsor have been made.**

Phase I/IIa, Dose Escalation, Safety, Pharmokinetic, and Preliminary Efficacy Study of Intraperitoneal Administration of DTA-H19 in Subjects with Advanced Ovarian Cancer (OBA #0901-967 March 2009)

- **Data presented using DNA microarrays in 79 human tissues and cells to document the lack of H-19 expression in the overwhelming majority of normal tissues and when expressed is at least 5-12x less than what is seen in fetal tissue. This was contrasted with data from multiple tumor cells including ovarian cancer cells in ascites fluid.**
 - **Low level H19 Expression in Normal Tissues: uterine endometrium in secretory phase of menstrual cycle, rheumatoid arthritis synovial tissue, airway epithelium of smokers, tongue, skeletal muscle, adrenal gland, appendix, liver and adipocytes**

Phase I/IIa, Dose Escalation, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Intraperitoneal Administration of DTA-H19 in Subjects with Advanced Ovarian Cancer (OBA #0901-967 March 2009)

- **In response to concerns about potential H-19 expression at the site of the catheter due to inflammation and possible adverse impacts on wound healing, data summarized on examination of injection sites in mice and from a compassionate use case in which the vector did not impact wound healing from invasive procedures and biopsies. However, the catheter site will be monitored.**

AMENDMENTS

- ***Amendment to Protocol 923: A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement in Hereditary Inclusion Body Myopathy-2***
- ***Principal Investigator:*** ***Dr. Joseph Kuhn***
- ***Sponsor:*** ***Gradalis Inc.***
- ***Sponsor Representative:*** ***Dr. John Nemunaitis***

A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement in Hereditary Inclusion Body Myopathy-2 (OBA # 0807-923 Rv'd Sept. 2008)

- **Hereditary Inclusion Body Myopathy – 2 (HIBM2) is a disease which causes severe skeletal muscle wasting, and leads to almost complete disability as early as ages 35 to 45. There are no proven treatments for HIBM2.**
- **GNE gene encodes a rate limiting enzyme that catalyzes the first 2 steps of sialic acid biosynthesis. Decreased sialic acid production consequently leads to decreased sialylation of a variety of glycoproteins including critical muscle protein alpha-dystroglycan (α -DG). This in turn severely cripples muscle function and leads to the onset of the syndrome.**

A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement . . . Cont.

- **Single subject protocol submitted June 2008 for intramuscular administration of liposomal encapsulated plasmid containing transgene for GNE.**
- **Patient is a 41 year old female with HIBM2 mutation and advanced disease. Subject in robotic wheelchair with wrist extensor muscle functional capacity decreased 95% from normal.**
- **Initial FDA approval on 7/24/08, OBA allowed IBC to approve protocol prior to RAC review and first IM dose given to subject on 8/19/08.**
- **Results of initial injections reviewed at September 2008 meeting (L Extensor Carpi Radialis Longus & L Biceps).**

A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement . . . Cont.

■ RAC Recommendations

■ Preclinical studies to:

- Determine if increased production of sialylated proteins could lead to immunological reactions due to new glycopeptides
- Elucidate the dose relationship and why increasing amount of vector in preclinical studies does not appear to affect expression

■ Clinical recommendations:

- Determine if GNE open reading frames will alter the anticipated clinical effects in future trials
- Consider control injections to determine the role of the injection itself versus transgene expression

■ Ethical

- Minimize conflicts of interest, perceived and real, and further explain these conflicts in the consent document

A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement . . . Cont.

- **Original protocol: 4 evenly divided injections into two muscles, left biceps and left ECRL**
- **Amended in October 2008: re-dose every 60 days x 3 injections into right ECRL after no toxicity with first injection and improved left ECRL function**
- **Amended in May/June 2009: test the safety and efficacy via IV administration (enhanced or stabilized muscle function) of GNE gene replacement in HIBM2. FDA approved amendment and subject was given first dose on 7/17/09.**

A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement . . . Cont.

■ Dose Design

- 5 dose levels are proposed.
- The cumulative dose, if all five levels are administered, will be 35.4mg.
- The 0.4mg dose is 1/400th of the IV NOAEL in mice.

Dose Level	Dose (mg/ inj)	Volume (mL)*
Level 1	0.4	0.8
Level 2	1	2
Level 3	4	8
Level 4	10	20
Level 5	20	40

* Volume of lipoplex in 400mL total volume (D5W diluent)