

GTSAB REPORT

Recombinant DNA Advisory Committee

September 14, 2011



Protocols Submitted for 3rd Quarter 2011

- ▶ **14 submissions total**

- 11 Protocols Not Selected:**

- **10 for cancer**
- **1 for hemophilia**

- Vectors:**
 - **7 plasmid**
 - **2 vaccinia virus**
 - **2 lentivirus**

MIC1 Submissions

3rd Quarter 2011

- ▶ **11 Protocols notified OBA of enrollment (M1C1 submission).**
 - ▶ **Two protocols that were reviewed at a public meeting provided responses to recommendations.**
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Adoptive Immunotherapy for CD19+ B-Lymphoid Malignancies Using Sleeping Beauty Transposition to Express a CD19-specific Chimeric Antigen Receptor in Autologous Ex Vivo Expanded T Cells (OBA Protocol #922 reviewed June 2008)

- ▶ A recommendation was made that given the possibility that the transposon system could cause insertional mutagenesis an evaluation for clonal expansion should be undertaken.**
- ▶ At the time of cryopreservation of cells for culture (21 days after electroporation) 2×10^6 cells will be cultured for 14 days to evaluate for clonal expansion using flow cytometry**
- ▶ Changes also made to the definition of dose limiting toxicity and the informed consent in response to RAC discussions.**

A Phase II Study to Determine the Efficacy and Safety of Allogeneic Human Chondrocytes Expressing TGF- β 1 in Patients with Grade 3 Chronic Degenerative Joint Disease of the Knee (OBA Protocol #1016 reviewed March 2010)

- ▶ **The RAC discussions raised a concern regarding the lack of data on whether the gene modified cells would remain in the joint, adhere to the cartilage and secrete the TGF- β 1 in the joint.**
- ▶ **New data submitted from *ex vivo* cell adhesion studies in rabbit and human knee tissue demonstrating that transduced cells adhere to the cartilage surface. In human cartilage tissue obtained from arthroplasty surgery, 40-60% of cells remain on the knee tissue.**

A Phase II Study to Determine the Efficacy and Safety of Allogeneic Human Chondrocytes Expressing TGF- β 1 in Patients with Grade 3 Chronic Degenerative Joint Disease of the Knee (OBA Protocol #1016 reviewed March 2010)

- ▶ A concern was raised during the RAC discussion regarding the number of deaths observed in preclinical animal studies. In response, further analysis of long-term mice, rabbit, and goat studies was undertaken and this analysis did not reveal a difference in mortality between control and injected animals.**

A Phase II Study to Determine the Efficacy and Safety of Allogeneic Human Chondrocytes Expressing TGF- β 1 in Patients with Grade 3 Chronic Degenerative Joint Disease of the Knee (OBA Protocol #1016 reviewed March 2010)

- ▶ It was noted during the RAC discussions that the two allogeneic lines could have the potential to induce an immune response and that this was not modeled in the preclinical studies, which used xenogenic rather than allogeneic cells. A recommendation was made to monitor for an immune response by evaluating for pre-existing antibodies and T cells and performing serial blood samples.**

A Phase II Study to Determine the Efficacy and Safety of Allogeneic Human Chondrocytes, cont...

- ▶ To address this concern, additional analyses were done on data from the U.S. Phase I study to examine the HLA antigen expression levels of the allogeneic chondrocytes cells and the subjects' immune responses:**
 - The chondrocytes exhibit significantly decreased levels of class I HLA antigens compared to control peripheral blood mononuclear cells**
 - Antibody analysis from subjects in the Phase I study did not show an increase in antibodies against donor-specific HLA antigens**

A Phase II Study to Determine the Efficacy and Safety of Allogeneic Human Chondrocytes, cont...

- In addition, cytokine analysis showed increased cytokine levels in half the patients at various time points, but given the inconsistent trends in the onset, duration and levels of cytokine increase, these data do not support a conclusion that the cytokine elevations indicate an immune response to the gene modified allogeneic chondrocytes.**

**Cytokines analyzed GM-CSF, IL-1 α , IL4,
IL-6, IL-10, TNF- α**

RNA Oligonucleotides: Emerging Clinical Applications

**Hilton Hotel, Rockville, Maryland
December 15-16, 2011**

- ▶ **The meeting is open to the public and an agenda for this meeting can be found on OBA's Website at the following URL:**

http://oba.od.nih.gov/rdna/rdna_symposia.html#CONF_001

Serious Adverse Events

- ▶ **18 serious adverse events were reviewed by the GTSAB from 14 protocols, including initial and follow-up reports. One event will be briefly discussed.**

Recent Adverse Event Description

- ▶ **OBA was informed of an unexpected toxicity in a trial that uses a leukemia vaccine consisting of 1) irradiated K562 cells transduced by a plasmid encoding the transgene for GM-CSF and 2) irradiated autologous leukemia cells.**
 - ▶ **The trial is a Phase I trial for patients with hematologic malignancies in the setting of allogeneic transplant.**
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Recent Adverse Event Description

- ▶ **The toxicity involved an unexpected sustained and severe leukocytosis and several months after this leukocytosis was first detected the subject died of what appears to have been possible complications of infection/sepsis.**
- ▶ **Analyses regarding the etiology of the leukocytosis and any contribution of the gene transfer vaccine to the leukocytosis and the subsequent clinical events is ongoing.**
 - **No conclusions are available at this time and the trial remains on clinical hold**

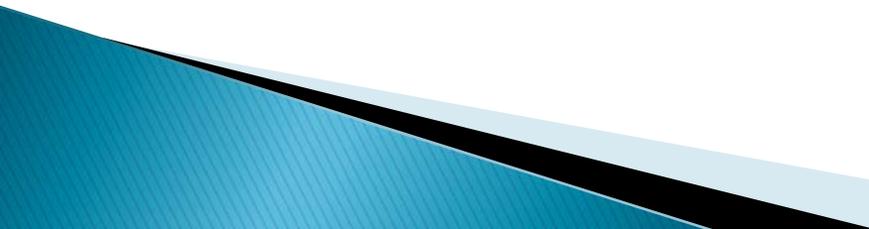
NIH/OBA Analysis

- ▶ **Using OBA's Genetic Modification Clinical Research Information System (GeMCRIS), 24 studies that employ a tumor vaccine using irradiated GM-CSF secreting K562 cells were identified:**
 - **At least 20 trials reported enrollment of subjects and are complete**
 - **Approximately 300 subjects have been dosed**
- ▶ **44 studies that use a tumor vaccine consisting of irradiated tumor cells transduced with GM-CSF were identified:**
 - **At least 34 trials reported enrollment of subjects and are complete**
 - **Approximately 1500 subjects have been dosed**

NIH/OBA Analysis

- ▶ **OBA screened GeMCRIS for serious adverse events submitted on these protocols in which the subject developed an unexpected leukocytosis after receiving one or more vaccinations.**
 - ▶ **This analysis identified one event reported in a trial using autologous irradiated tumor cells that expressed GM-CSF for metastatic lung cancer.**
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NIH/OBA Analysis

- ▶ **In the previous event on a lung cancer trial, the leukocytosis was self-limiting and subject clinically did well.**
 - ▶ **Cytokine analysis indicated a rise in GM-CSF levels after the vaccination at the time the leukocytosis developed.**
 - ▶ **GM-CSF is a licensed product used to increase the white blood cell count in the setting of chemotherapy.**
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Next Steps

- ▶ **Sponsor will present his assessment of the case at the December 12-14, 2011, meeting of the NIH Recombinant DNA Advisory Committee.**
 - ▶ **OBA will inform investigators working with similar products and their Institutional Biosafety Committees of any new information.**
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Recent Notable Results

The NEW ENGLAND JOURNAL *of* MEDICINE

BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D.,
Adam Bagg, M.D., and Carl H. June, M.D.

This article (10.1056/NEJMoa1103849) was
published on August 10, 2011, at NEJM.org.

Recent Notable Results

RESEARCH ARTICLE

LEUKEMIA

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos,^{1,2*} Bruce L. Levine,^{1,2*} David L. Porter,^{1,3} Sharyn Katz,⁴ Stephan A. Grupp,^{5,6}
Adam Bagg,^{1,2} Carl H. June^{1,2†}

www.ScienceTranslationalMedicine.org
10 August 2011 Vol 3 Issue 95 pp1-11

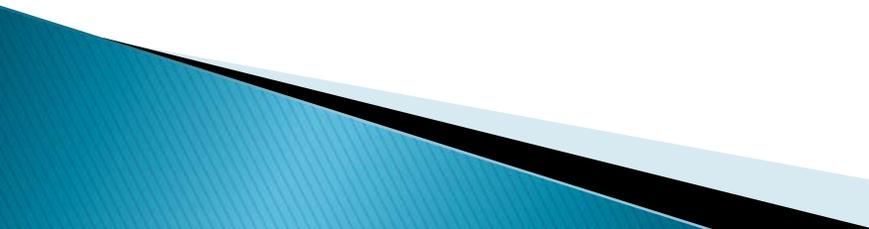
Chimeric Antigen Receptor (CAR) T cells for Chronic Lymphoid Leukemia (CLL) (OBA Protocol # 0607-793)

- ▶ **Protocol administers autologous T cells modified to express an anti-CD19 CAR that contains the 4-1BB signaling domain with the CD3-zeta (2nd generation CAR).**
 - ▶ **Lentiviral vector used to transduce the cells.**
 - ▶ **Cells administered after lymphodepleting chemotherapy.**
 - ▶ **IL-2 is not administered.**
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Chimeric Antigen Receptor (CAR) T cells for Chronic Lymphoid Leukemia (OBA Protocol # 0607-793)

- ▶ **Subject with advanced refractory, p53 deficient CLL received 1.5×10^5 cells/kg.**
- ▶ **The T cells expanded to a level that was more than 1000 times the initial engraftment, at one time accounted for 20% of circulating cells.**
- ▶ **There was delayed development of tumor lysis syndrome that was managed.**
- ▶ **Engineered T cells persisted for 6 months in the blood and bone marrow.**

Chimeric Antigen Receptor (CAR) T cells for Chronic Lymphoid Leukemia

- ▶ **Subject achieved a complete remission that was ongoing at 10 months after infusion.**
 - ▶ **Subject experienced loss of normal B cells, which also express CD19. This was managed with intravenous immune globulin.**
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Chimeric Antigen Receptor (CAR) T cells for Chronic Lymphoid Leukemia

- ▶ **In their article published in *Science Translational Medicine*, investigators provide additional data on expansion, persistence and function of the CAR modified T cells in all three subjects dosed to date.**
- ▶ **Their studies indicated that the persisting CAR-modified T cells consist of both central and effector memory T cells.**
- ▶ **Dr. Carl June, University of Pennsylvania, has been invited to present his findings at the December 12-14, 2011, meeting.**



Update on OBA Protocol # 0610-809
**A Phase 1/2 Randomized, Double-Blinded,
Placebo-Controlled Dose Escalation Trial of
Intracoronary Administration of MYDICAR™
(AAV1/SERCA2a) in Subjects with Heart
Failure**

Presenter: Krisztina Zsebo, Ph.D.
Chief Executive Officer
President and Director
Celladon Corporation
La Jolla, CA

