

# Gene Transfer Safety Assessment Board (GTSAB) REPORT

## Recombinant DNA Advisory Committee June 21-22, 2016



# *Charge to the GTSAB*

- 1) Review in closed session as appropriate safety information from gene transfer trials for the purpose of assessing toxicity and safety data across gene transfer trials**
- 2) Identify significant trends or significant single events**
- 3) Report significant findings and aggregated trend data to the RAC**

**Process enhances review of new protocols, improves the development, design, and conduct of human gene transfer trials, promotes public understanding and awareness of the safety of human gene transfer research studies, and informs decision-making of potential research participants**

# GTSAB Roster

**Hans Peter Kiem, MD, PhD** (*Chair*)

**Michael Atkins, MD**

**William Curry, MD**

**J. Kevin Donahue, MD**

**Howard Kaufman, MD**

**Dean Lee, MD, PhD**

**Joseph Pilewski, MD**

**Richard Whitley, MD**

**Denise Gavin, PhD** (*FDA Representative*)

**Ramjay Vatsan, PhD** (*FDA Representative*)

# Protocols Submitted for Second Quarter 2016

- 26 total submissions (4 selected for public review; review of one was deferred from March; 5 will be reviewed at this meeting)
- 22 protocols not selected this quarter include:

Diseases	
19 Oncology	1 Peripheral artery disease
1 Monogenic disease	1 Infectious disease

Vectors		
5 Lentivirus	3 Vaccinia virus/Fowlpox	1 AAV
4 Retrovirus	2 HSV	1 Listeria
4 Plasmid	1 Adenovirus	1 RNA

# Serious Adverse Events

**24** serious adverse events were reviewed by the GTSAB from **15** protocols, including initial and follow-up reports

# Protocol Update: Delayed Listeriosis

In response to a recent SAE of delayed listeriosis the protocol was further amended. The revised protocol:

- adds new and prolonged antibiotic regimens for eradication of the attenuated *Listeria monocytogenes* (*Lm*) strain,
- adds blood cultures for monitoring persistent *Lm* infections,
- excludes subjects with implants and hardware that are not easily removable,
- adds potential risks of delayed listeriosis to IB & ICD,
- excludes subjects who have used certain immunosuppressive agents,
- and extends follow-up of study participants for delayed listeriosis to 3 years.

*Protocol 1082*



# Protocol Update: Prolonged Pancytopenia

In response to recent SAEs of **Prolonged Pancytopenia** this TCR immunotherapy protocol was further amended to evaluate alternative lymphodepletion (LD) regimens, including Cohorts with high tumor antigen expression to receive LD chemotherapy with only Cyclophosphamide (Cy), or a reduced dose of Fludarabine and Cy.

*Protocol 1071*



# TCR & CAR Trials with CRS-related SAEs

Several SAEs were reported in a single CD19 CAR T cell trial, which is currently in Phase 2. A number of these involved severe CRS and **neurotoxicity** (e.g., including confusion and seizures).

One SAE involved CRS and early neurotoxicity complicated by multiple lab abnormalities and later **cardiac arrest**.

Another SAE involved a Grade 3 neurotoxicity complicated by multiple lab abnormalities and eventually **hemophagocytic lymphohistiocytosis (HLH)**.

Another SAE involved a Grade 4 neurotoxicity complicated by **leukoencephalopathy** on CNS imaging and extremity weakness.

*Protocol 1339*



# TCR & CAR Trials with CRS-related SAEs (Cont.)

- A CD19 CAR T cell trial targeting B cell Lymphoma met their criteria for stopping rules due to toxicities. As per PI **neurotoxicity** was the most important toxicity experienced by subjects in this study.

## *Protocol 940*

- A Phase 2 CD19 CAR T cell trial reported an SAE involving severe CRS complicated by **hypernatremia** and later an **encephalopathy of unclear etiology**.

## *Protocol 1351*

- Another Phase 2 CD19 CAR T cell trial reported an SAE with severe CRS, which was later complicated by **encephalopathy**, seizures, **cerebral edema**, and **severe hypernatremia**.

## *Protocol 1419*

# Opening of New Protocols Second Quarter 2016

- **Fifteen protocols notified NIH/OSP of enrollment (MIC1 submission)**
- **Two were publicly reviewed**

**Protocol 1404-1307** A Phase I Clinical Trial of Cyclophosphamide Followed by Intravenous and Intraperitoneal Infusion of Autologous T cells Genetically Engineered to Secrete IL-12 and to Target the MUC16ecto Antigen in Patients with Recurrent MUC16ecto+ Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

**Protocol 1508-1455** The Effect of Vorinostat and AGS-004 on Persistent HIV-1 Infection (The VOR VAX Study)

# Research Update (Meetings)

**CAR T-CELL THERAPY: GETTING A HANDLE ON TOXICITY.** [Medscape](#) (6/14, Johnson, 302K) reports that “chimeric antigen receptor (CAR) T-cell therapies are causing a stir in leukemia and lymphoma circles, with impressive response rates and sustained remission in patients with advanced, chemorefractive disease.”

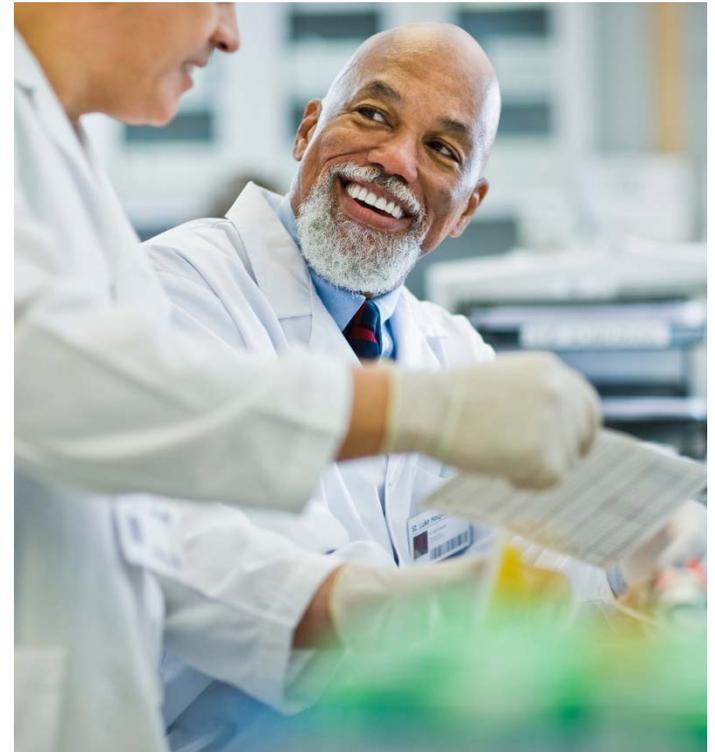
According to Medscape, “With more than 20 American trials looking at the anti-CD19 CAR T-cell space, treatment toxicity is emerging as a major focus.” Catherine Bollard, MD, who “acted as discussant for a series of three studies on CAR-CD19 T-cell therapy” at the ASCO Annual Meeting, said, “There is no gain without pain, and the ‘cytokine release syndrome’ [CRS] does remain a problem, although multiple groups are looking at ways of preventing it.” Medscape points out that “in one study...James Kochenderfer, MD, from the Experimental Transplantation and Immunology Branch of the National Cancer Institute, showed that **lightening up on pretreatment conditioning chemotherapy can cut toxicity without sacrificing efficacy.**”



# Research Updates (Approvals) (cont.)

The first gene therapy for children and second gene therapy in Europe (after Glybera, which was approved in 2014) was approved by EMA late last month for children with ADA-SCID.

The product (Strimvelis) was developed by investigators at Vita-Salute San Raffaele Univ. collaborating with the Italian Biotech MolMed & GSK licensed the IP in 2010. It involves autologous CD34+ cells transduced to express the ADA gene.



# Research Updates (Publication) (cont.)

## PERSPECTIVE

### AAV2 and Hepatocellular Carcinoma

Jean-Charles Nault, Shalini Datta, Sandrine Imbeaud, Andrea Franconi, Maxime Mallet, Gabrielle Couchy, Eric Letouze´, Camilla Pilati, Benjamin Verret, Jean-Fre´de´ric Blanc, Charles Balabaud, Julien Calderaro, Alexis Laurent, Me´lanie Letexier, Paulette Bioulac-Sage, Fabien Calvo, and Jessica Zucman-Rossi\* HUMAN GENE THERAPY, VOLUME 27 NUMBER 3 DOI: 10.1089/hum.2016.002

- Response to K. Berns & colleagues, who refuted the Nault JC, Datta S, Imbeaud S, et al. article “Recurrent AAV2-related insertional mutagenesis in human hepatocellular carcinomas”. *Nat Genet* 2015;47:1187–1193.
- Agreed with the conclusion by Russell & Grompe in their editorial to the above article, that “Close follow-ups of patients treated with AAV vectors will shed light on some of these issues, and renewed research into the potential oncogenicity of AAV vectors is now more important than ever.”

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# Additional Resources



Bringing Science Policy Into Focus

Learn more about the Office of Science Policy  
from our blog “Under the Poliscope”

<http://osp.od.nih.gov/under-the-poliscope>

(A recent blog was posted about this RAC Meeting)

# Additional Resources

- For General Inquiries:

[SciencePolicy@od.nih.gov](mailto:SciencePolicy@od.nih.gov)

- Subscribe to the OSP listserv

Send and email to: [listserv@list.nih.gov](mailto:listserv@list.nih.gov)

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