NATIONAL INSTITUTES OF HEALTH (NIH)
SAFETY SYMPOSIUM

GENE-MODIFIED T CELLS: CHALLENGES IN CLINICAL TRIAL DESIGN

Hilton Rockville Hotel & Executive Center

June 15, 2010

8:00 AM **Welcome and Opening Remarks**

Scott E. Strome, M.D., Member, Recombinant DNA Advisory Committee
John A. Zaia, M.D., Member, Recombinant DNA Advisory Committee
Daniel Takefman, Ph.D., Federal Food and Drug Administration, Rockville, MD

8:15 AM **Evolution of Trial Design using Gene Modified T Cells**

Presenter: Richard P. Junghans, M.D., Ph.D., Roger Williams Hospital, Providence, RI
Slide Presentation

8:35 AM **Serious Adverse Events in Trials Utilizing Chimeric Antigen Receptors: Lessons for Trial Design**

Presenters: Steven A. Rosenberg, M.D., Ph.D., National Cancer Institute, NIH, Bethesda, MD
Slide Presentation

Renier J. Brentjens, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center, New York, NY
Slide Presentation

9:15 AM **Questions**

9:25 AM **Designing Novel T Cells: Balancing Efficacy and Toxicity**

Choosing an Appropriate Target and Targeting Strategy

- What criteria were used in choosing the target?
- What approach was employed in evaluating potential off target toxicities?
- How did that data inform the starting dose?
- Were there unexpected toxicities?

***Engineered T Cell Receptors*:**

Solid Tumor Antigens (MART-1, gp-100, p53, ESO-1)

Presenter: Steven A. Rosenberg, M.D., Ph.D.
Slide Presentation

9:45 AM **Break**

9:55 AM ***Chimeric Antigen Receptors (CARs)*:**

Solid Tumor Antigens (CEA, PSMA, carbonic-anhydrase IX, Lewis Y, Tag-72, Her2/neu)

Presenters: Richard P. Junghans, M.D., Ph.D.
Slide presentations: Part 1 Part 2 Part 3

Mitchell H. Finer, Ph.D., Chief Scientific Officer, Genetix Pharmaceuticals, Cambridge, MA
Slide Presentation

Stephen M. Gottschalk, M.D., Texas Children's Cancer Center, Houston, TX
Slide Presentation

Hematologic Antigens (CD19, CD20)

Presenters: Michael C.V. Jensen, M.D., City of Hope, Duarte, CA
Slide Presentation

Dario Campana, M.D., St. Jude Children's Research Hospital, Memphis, TN
Slide Presentation

11:10 AM **Discussion**

Moderator: Laurence J. Cooper, M.D., Ph.D., M.D. Anderson Cancer Center, Houston, TX

Slide Presentation

- In evaluating the potential for off-target expression, how do the experiences with anti-Her2/neu, anti-CEA, anti-CD+ 19, and anti-carbonic-anhydrase IX CARs inform the selection of future targets?
- For CARs that target antigens such as CD20, what is the effect on long term immunity if such cells persist?
- Are there additional features that can be added to enhance safety?
    - Selective Promoters
    - Suicide gene

11:55 AM **Public Comment**

12:00 PM **Lunch**

12:45 PM ***Co-signaling Moieties***

Presenter: Carl H. June, M.D., University of Pennsylvania, Philadelphia, PA

Slide Presentation

Panelists: George Coukos, M.D., Ph.D., University of Pennsylvania, Philadelphia, PA
Michel Sadelain, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center, New York, NY
Gianpietro Dotti, M.D., Baylor College of Medicine, Houston, TX

- How do co-signaling moieties change the cytokines that are released?
- What is the potential for reverse signaling through 4-1BB or B7-1 (CD80)?
- Can the strength of T cell activation and co-stimulation be titrated?
- What are the considerations in using naturally inducible versus constitutively expressed molecules?

1:30 PM **Preconditioning Regimens: Improved Engraftment vs. Systemic Toxicity**

Presenter: Steven A. Rosenberg, M.D., Ph.D.
Slide Presentation

Panelists: Laurence J. Cooper, M.D., Ph.D.
Richard E. Champlin, M.D., M.D. Anderson Cancer Center, Houston, TX

- What is the evidence for efficacy and improved engraftment with lymphodepletion?
- What is the anti-tumor effect of lymphodepletion alone?
- How does the preconditioning used for T cell protocols compare to that used for bone marrow transplantation and in particular regarding potential toxicity?
- Are there modifications to preconditioning that should be considered in initial trials with new receptors?

2:30 PM **Break**

2:45 PM **Cytokine Support for Gene Engineered T Cells**

Presenter: Cassian Yee, M.D., Fred Hutchinson Cancer Research Center, Seattle, WA *(via teleconference)*
Slide Presentation

Panelists: Michael C.V. Jensen, M.D.
Carl H. June, M.D.

- What is the optimum dose to balance T cell support and toxicity?
- How does one discern adverse events related to the cytokine support from toxicity related to the T cells?

3:15 PM **Designing Clinical Trials with New Receptors and Endodomains**

Moderator: Scott E. Strome, M.D.

Dose Escalation

- What are alternative methods of dose escalation and how should initial dose escalation be based on target antigen?
- What do we understand about persistence of cells and how should this guide dosing intervals?

Panelists: Antoni Ribas, M.D., University of California School of Medicine, Los Angeles, CA
Stephen M. Gottschalk, M.D.
Richard P. Junghans, M.D., Ph.D.

4:00 PM ***Subject Selection: Optimizing Safety***

- Should certain subjects who are at higher risk be excluded from initial trials (e.g., elderly, pulmonary disease, high disease burden)?

Panelists: Renier J. Brentjens, M.D., Ph.D.
Oliver W. Press, M.D., Ph.D., Seattle Cancer Care Alliance, Seattle, WA

4:20 PM **Public Comment**

4:30 PM ***Points to Consider for Trial Design Involving New Receptors: Initial Dose, Co-signaling Moieties, and Subject Selection***

- Choosing an Appropriate Target
- Initial Dose Selection
- Monitoring Strategies
- Preconditioning Options
- Subject Selection

All Participants

5:30 PM **Adjourn**