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RAC MEETING EXPLORES SAFETY AND DESIGN OF T CELL CANCER TRIALS USING CHIMERIC ANTIGEN RECEPTORS

(MILWAUKEE, WI – June 8, 2010) - Recent reports of serious adverse events (SAEs) from two separate clinical trials involving genetically modified T cells with chimeric antigen receptors (CARs) have prompted in-depth commentaries and review of the design of trials utilizing CARs.[1-4] The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health held a safety symposium on Tuesday, June 15, 2010 to explore implications of trial design using genetically modified T cells and approaches to balance the efficacy and safety of engineered T cells with CARs. The archived webcast of the RAC meeting will be available on the RAC website at:http://oba.od.nih.gov/rdna_rac/rac_past_meetings_2010.html in the near future.

Presenters, moderators and panelists at the RAC meeting included a number of iSBTc Members as shown in the following table. There was clear consensus to continue this area of investigation with an appreciation that, given the toxicity and the rapidity of SAE onset, suicide vectors would not provide an option to increase the safety of this approach. The accepted modification was to reduce the starting doses of transferred T cells. Several escalation schemes were discussed.

Dr. Steven A. Rosenberg suggested a trial design in which a single patient would be accrued at each dose of modified T cells until any toxicity was observed. At that point, the dose of T cells transduced with CARs would be reduced to the previous dose level and additional patients would be accrued at the lower dose. This would reduce the number of patients who might receive an ineffective (very low) dose of T cells.

In addition, Dr. Richard Paul Junghans briefly outlined a new trial design paradigm ("Strategy Escalation") to improve safety during the clinical evaluation of T cell therapies that use CARs directed at tumor antigens. This commentary is available as an Open Access article in the iSBTc Section of the *Journal of Translational Medicine* (Vol 8:55; June 10, 2010) at http://www.translational-medicine.com/series/isbtc. The iSBTc invites investigators to submit additional commentaries or post points to consider, consensus or disagreement with Dr. Junghans' manuscript. These can be appended to Dr. Junghans' manuscript posted in the iSBTc Section of the *Journal of Translational Medicine*.

iSBTc President, Dr. Bernard A. Fox, attended the June 15, 2010 RAC meeting and noted that the RAC decided that a standard starting dose of T cells used for adoptive transfer could not be defined and would be dependent on the antigen targeted and level of that antigen's expression on normal tissues. Further, Dr. Fox reported that the RAC generally agreed that adoptive transfer of CAR modified T cells should be performed in lymphodepleted individuals. Clinical studies not following this strategy would need to provide a rationale for their strategy.

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Additional clinical responses for patients receiving T cells transduced with CARs were reported at the meeting: iSBTC Member, Dr. Robert E. Hawkins, discussed his current clinical trial during the public comment period; and iSBTc Board Member, Dr. Carl H. June, mentioned that T cells transduced with CAR were surviving in some patients at "memory levels" 10 years after adoptive transfer.

iSBTc Member at June 15 RAC Meeting	Presentation/Panel Topic
Steven A. Rosenberg, MD, PhD National Cancer Institute, NIH, Bethesda, MD	SAEs in Trials Utilizing Chimeric Antigen Receptors: Lessons from Trial Design; Designing Novel T Cells: Balancing Efficacy and Toxicity; Preconditioning Regimens: Improved Engraftment vs. Systemic Toxicity
Laurence J. Cooper, MD, PhD *MD Anderson Cancer Center, Houston, TX*	CARs; Preconditioning Regimens: Improved Engraftment vs. Systemic Toxicity
Carl H. June, MD *University of Pennsylvania, Philadelphia, PA*	Co-Signaling Moieties; Cytokine Support of Gene Engineered T Cells
George Coukos, MD, PhD *University of Pennsylvania, Philadelphia, PA*	Co-Signaling Moieties
Michel Sadelain, MD, PhD *Memorial Sloan-Kettering Cancer Center, New York, NY*	Co-Signaling Moieties
Cassian Yee, MD *Fred Hutchinson Cancer Research Center, Seattle, WA*	Cytokine Support for Gene Engineered T Cells
Antoni Ribas, MD *University of California School of Medicine, Los Angeles, CA*	Designing Clinical Trials with New Receptors and Endodomains
John A. Zaia, MD *(Member, Recombinant DNA Advisory Committee)* *National Institutes of Health* *Bethesda, MD*	Designing Clinical Trials with New Receptors and Endodomains

1. Brentjens R, Yeh R, Bernal Y, Riviere I, Sadelain M. Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. Mol Ther;18(4):666-8.
2. Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther;18(4):843-51.
3. Heslop HE. Safer CARS. Mol Ther;18(4):661-2.
4. Junghans RP. Strategy Escalation: An emerging paradigm for safe clinical development of T cell gene therapies. J Transl Med;8(1):55.