



## **2007 iSBTc “Primer on Tumor Immunology and Biological Therapy” Program Summary**

*by Kim A. Margolin, MD, Meeting Organizer*

The International Society for Biological Therapy of Cancer (iSBTc) “Primer on Tumor Immunology and Biological Therapy” was organized by Martin “Mac” A. Cheever, MD, of the Fred Hutchinson Cancer Research Center, and Kim A. Margolin, MD, from the City of Hope. The Primer was held at the Seaport Convention Center in Boston, Massachusetts on November 1, 2007 and was well attended, drawing an audience of 137 people.

The introductory talk was given by Carmen Scheibenbogen, MD, from the Institut Für Medical Immunologie Charité in Berlin, Germany, whose talk was titled, “Cancer Vaccines, 2007.” Dr. Scheibenbogen provided a comprehensive introduction to the field of preventive and therapeutic cancer vaccines, along with basic concepts of the development of antigen-specific T-cells in response to vaccinations based on tumor antigens. She then went on to describe the essential components of effective tumor vaccines and to summarize the clinical experience to date on vaccine trials in human malignancy.

The second talk was given by Patrick Hwu, MD, from the MD Anderson Cancer Center in Houston, Texas, which was called, “Basic Concepts of T-Cell Responses to Tumor Cells in the Therapeutic Manipulation of Cytotoxic T-Cells with Cytokines and Various Adoptive Cell Therapy Strategies.” Dr. Hwu summarized those strategies that involved active immunization against melanoma antigens and then went on to talk about the physiologic immunoregulatory molecules that have recently been recognized as targets for immunoregulatory blockade in the development of T-cell-based therapies. Examples of clinical responses to adoptive T-cell therapy in viral diseases as well as a variety of hematologic malignancies, with the relationships between graft-versus-host and graft-versus-malignancy, were also described. Recent improvements in adoptive cell therapy based on lymphodepletion, with its potential for enhancing homeostatic re-population of antigen-specific T-cells, were also mentioned.

Francesco “Franco” Marincola, MD, from the Department of Transfusion Medicine at the National Institute of Health in Bethesda, Maryland, spoke next on the topic of “Host-Tumor Interactions.” Dr. Marincola proposed two different models of anti-tumor immunity that may elucidate the interactions among elements of immunosurveillance, the innate immune system, inflammation, the development of malignancy, and ultimately the design of effective immunotherapy against tumor antigens. He concluded with a proposed algorithm for tumor immune responsiveness that depicts possible sites for therapeutic intervention in the future.

The next speaker, Polly Matzinger, PhD, of the National Institute of Allergy and Infectious Disease in Bethesda, Maryland, spoke of “*In Vivo* Immunity: Integrating Innate and Adaptive Immunity - The Role of Danger.” This topic was based on her work in the area of self/non-self discrimination and the importance of “danger” signals in controlling the immune response to autologous antigens, inflammation, and tumor antigens. She concluded with a strong admonition that boosting must be repeated in therapeutic tumor vaccination and reiterated the importance of the tumor microenvironment as the focus for the optimization of these therapeutic immune responses.

Rakesh K. Jain, PhD, from Harvard Medical School spoke on the “Normalization of the Tumor Micro Environment by Antiangiogenic Therapy.” Dr. Jain’s talk focused on the importance of tumor-associated vasculature in the tumor acting as an organ rather than a uniform collection of tumor cells. He showed data from intra-vital microscopy that can be used to image tumor vasculature in different components of the tumor

and in response to various therapeutic interventions. He elaborated on the data behind the concept that anti-angiogenetic therapy may not be simply angiogenesis blockade but more likely an induced normalization of the aberrant tumor blood vessels, which facilitates the delivery of therapeutic molecules to the sites of their tumor target. In association with these experiments, Dr. Jain described some of the important blood biomarkers of angiogenesis that have been used and should be considered for correlative assays in future trials of anti-angiogenetic agents.

The next talk was given by Judah Folkman, MD, from the Children's Hospital in Boston, Massachusetts, and was titled, "Angiogenesis as an 'Organizing Principle' in Biology." Dr. Folkman began with a comment linking the earlier workshop on combinations of anti-angiogenic therapies and immunotherapy and moved into his own discussion about the importance of angiogenesis in tumor biology and therapy. He summarized the early studies of assay development for angiogenic endpoints in his own and other laboratories, as well as the early days of research on now-approved agents that have anti-angiogenetic properties, including thalidomide, bevacizumab, and sunitinib. Some of these drugs are used in diseases of pathologic angiogenesis not associated with malignancy, such as macular degeneration. The vast array of physiological molecules that have now been studied and have angiogenic or angiostatic properties was reviewed, and the association between various tumors and the production of those molecules was summarized. Dr. Folkman concluded with two important points. The first was that the approved angiogenesis inhibitors currently target only one of the myriad of tumor-derived molecules that promote angiogenesis and may be involved in compensatory feedback loops that lead to increased levels of pro-angiogenic molecules during blockade of one. The second point was the importance of targeting molecules that are direct components of the vascular endothelium rather than the "indirect" effect of blocking substances produced by tumors and acting on the vasculature.

Paul M. Sondel, MD, PhD, from the University of Wisconsin, gave the first talk that focused on antibody-based strategies in cancer therapy. His session was titled, "Antibody Therapy, Biology, Immunocytokines and Hematologic Malignancy." Dr. Sondel provided an introduction to antibodies and went on to describe engineering of antibodies that can optimize their function in tumor immunotherapy, including the delivery of toxins, radioactive emitters other functional molecules such as cytokines to the tumor site. Mechanisms of antibody function distinct from complement-dependent and antibody-dependent cellular cytotoxicity were also detailed.

The second talk on the use of antibodies in the therapy of solid tumors, titled, "Antibody Therapy of Solid Tumors," was given by Louis M. Weiner, MD, from Fox Chase Cancer Center in Washington, D.C., who began with some descriptions of antibody function and structure. He went on to describe various manipulations of antibody structure that could be associated with the enhancement of their efficacy. Dr. Weiner then focused on therapeutic antibodies that block receptor molecules associated with intracellular signaling essential to tumor cell survival and talked about studies of resistance to these antibodies. He concluded with some sobering thoughts about current challenges to the successful development of therapeutic antibodies but followed this with suggestions for future work in this area.

The next talk was given by Ira H. Pastan, MD, from the National Institute of Health in Bethesda, Maryland, whose talk was titled, "Immunotoxin Therapy of Cancer: Successes and Challenges." Dr. Pastan's talk was focused on the variety of immunoconjugates that have been developed to deliver potent toxins in a tumor-specific fashion while maintaining an acceptably low level of toxicity to normal organs. He detailed the use of the pseudomonas exotoxin conjugated to an antibody against the B-cell determinant CD22, describing its pre-clinical development and clinical data in human patients with a variety of B-cell malignancies. He then turned to a new immunotoxin against the tumor-derived molecule mesothelin, describing a newly developed immunotoxin that has shown synergy with chemotherapy based on the ability of chemotherapy to alter the dynamics of tumor and shed tumor antigen. He emphasized the importance of treating tumors that are most chemo-sensitive together with the immunotoxins to achieve the best results.

The final talk, "Cytokines in Malignancy," was given by Kim A. Margolin, MD, from the City of Hope in Duarte, California, who covered a series of cytokines that have either been used clinically or have implications for future clinical use. These included an update on the preclinical and clinical uses for interleukin- 2, and a summary of the current status of several other cytokines that are not yet marketed for clinical use, including free and transgenically-expressed GM-CSF for tumor vaccines, IL-4 and IL-13 for dendritic cell preparation, IL-7 and IL-15 for supporting lymphopoiesis and antigen-specific responses, and IL-12 and IL-18 for their adjuvant roles and position linking innate and adaptive immunity.

The audience was extremely attentive and interactive, and the invited speakers who were not previously familiar with the society stayed for the entire event and complimented the Society on the high quality of the Primer.

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The iSBTc Primer provided an overview of tumor immunology and biological therapy by leaders in the field to educate attendees on both the biologic underpinnings of the field, as well as recent basic science and clinical developments.

The program was recorded for use as a Webinar and is available for viewing online on the iSBTc website at [www.iSBTc.org](http://www.iSBTc.org). A CD-ROM version of the webinar is also available for purchase. The webinar consists of video-taped presentations by each speaker synchronized to their slide-set as it appeared during the program. Please contact the iSBTc executive office for details by calling (414) 276-2456.