

Expert Opinion

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Immunotherapy comes of age: overview of the 21st Annual Meeting and associated programs of the International Society for Biological Therapy of Cancer

Los Angeles, CA, USA, 27 – 29 October 2006

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This paper covers highlights from the International Society for Biological Therapy of Cancer (iSBTc) 21st Annual Meeting, including the associated iSBTc Primer on Tumor Immunology and Biological Therapy, and the iSBTc Mini-Symposium on the Biologic Effects of Targeted Therapies. The programs ran from 26 – 29 October 2006 and were held at the Hyatt Regency Century Plaza in Los Angeles, CA, USA. Focussed on the varying aspects of biological cancer therapies and tumor immunology, the iSBTc 21st Annual Meeting featured 131 scientific posters, 29 oral abstract presentations, 20 invited speaker lectures and 2 keynote addresses. The 21st Annual Meeting, Primer and Mini-Symposium were attended by > 400 clinicians and basic scientists from academia, industry and government. The iSBTc was founded in 1984 as the Society for Biological Therapy with 40 charter members. At present, the Society has > 500 members consisting primarily of MDs, PhDs, RNs and corporate representatives. Scientific and business meetings have been held annually since the Society's first Annual Meeting in 1986.

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1. International Society for Biological Therapy of Cancer 21st Annual Meeting

The International Society for Biological Therapy of Cancer (iSBTc) held its 21st Annual Meeting in Los Angeles, CA, USA on 27 – 29 October 2006. The accommodations of the Hyatt Regency Century Plaza Hotel and the warm California climate were especially conducive to the exchange of information and development of new collaborations. This meeting was attended by > 400 scientists, students, clinicians and pharmaceutical representatives from around the world. Ulrich Keilholz (Charité, CBF-Berlin) began the meeting on Friday 27 October with the President's Welcome speech that summarized the society's accomplishments in terms of meeting attendance, new members, number of posters submitted and generous external support. Also mentioned were the annual iSBTc Primer on Tumor Immunology and Biological Therapy and the iSBTc Mini-Symposium on the Biologic Effects of Targeted Therapies, which were conducted at the meeting site on

Thursday 26 October. Keilholz then introduced the meeting's first speaker and winner of the Richard V Smalley MD Memorial Award, Ron Levy MD of Stanford University. Smalley was one of the iSBTc's charter members and an ex-President who passed away in January of 2004 and whose memory is honored by this award. Levy's lecture was entitled 'Therapeutic Vaccination for Lymphoid Malignancy'. Levy reviewed his experience with the development of a vaccine that targets the idiotype of the unique immunoglobulin present on the surface of B cell malignancies. Especially impressive were the data indicating that almost half of patients in the first clinical trial of idiotype vaccination for lymphoma exhibited a significant anti-idiotype immune response that correlated with prolonged freedom from disease progression. Photographs of patients exhibiting complete clinical responses highlighted the utility and promise of this treatment strategy. Levy also detailed novel approaches to the manufacture of idiotype vaccines and recent efforts to make a commercially viable form of this vaccine for subsequent use in larger trials.

The remainder of the plenary session on the morning of the first day of the meeting was devoted to presentations on dendritic cell biology and vaccine strategies for the treatment of cancer. Larry Kwak (MD Anderson Cancer Center, TX, USA) detailed the rationale behind a unique anti-idiotype vaccination strategy for lymphoma. He described the construction of a fusion protein that consists of an idiotype fragment (sFv) linked to a pro-inflammatory chemokine moiety. He theorized that the idiotype antigen would be targeted to antigen-presenting cells via their chemokine receptors. As dendritic cells express a variety of chemokine receptors at high density, it is expected that this strategy will lead to increased uptake and processing of the antigenic portion of the fusion protein, and improved stimulation of CD4 and CD8 T cells. Craig Slingluff (University of Virginia, VA, USA) then presented data suggesting that Toll-like receptor (TLR) agonists may have utility as vaccine adjuvants. He described the results of a Phase I trial for patients with advanced melanoma in which a transdermal multi-peptide melanoma vaccine was administered in combination with imiquimod, a TLR7 agonist. Importantly, patients receiving adjuvant imiquimod developed a more robust response to the peptide vaccine. The use of dendritic cells as therapeutic vaccines in cancer was addressed by Anna Palucka of the Baylor Institute for Immunology Research, TX, USA. She related the results of a clinical trial in which IL-4-stimulated dendritic cells were loaded with killed allogeneic melanoma cells and then administered to patients with advanced melanoma. This vaccination schema led to the formation of CD8-positive T cells with specificity against the melanoma antigen recognized by T-cells-1 (MART-1) melanoma antigen. Two durable clinical responses (one complete and one partial response) were noted in the 20 patients who received this vaccine therapy.

The morning plenary session on the second day focused on regulatory mechanisms that can dampen the response to immunotherapeutic regimens. Three lectures examined the biology and immunoregulatory capacity of regulatory T (Treg) cells. These presentations revealed that:

- Treg cells can interact with cytotoxic T lymphocytes within draining lymph nodes and markedly inhibit their ability to engage in granule exocytosis
- antigen-specific Treg cells are present in the peripheral blood of patients with metastatic melanoma, but cannot be detected in the blood of normal individuals
- following IL-2 immunotherapy, numbers of circulating Treg cells were elevated in patients that exhibited progressive disease, but not in patients that experienced a clinical response

Thomas Gajewski then presented a series of well-designed experiments demonstrating that T cell anergy is reversed by active Ras and is regulated by diacylglycerol kinase- α . Gajewski showed that T cell anergy has been correlated with defective signaling by Ras GTPase, but mechanistic data linking defective Ras activity with T cell anergy have not been forthcoming. Adenoviral transduction was employed to genetically manipulate non-proliferating T cells. These experiments showed that active Ras restored IL-2 production and mitogen-activated protein kinase signaling in anergic T cells. Diacylglycerol kinases (DGKs) negatively regulate Ras activity and were found to be upregulated in anergic T cells. Importantly, treatment of anergic T cells with a DGK inhibitor led to restoration of IL-2 production. Defective translocation of the Ras guanine nucleotide-exchange factor RasGRP1 to the plasma membrane was observed both in anergic T cells and in the setting of DGK- α overexpression. These findings suggest that excess DGK activity leads to defective Ras signaling and anergy in T cells.

The definitive highlight of the meeting was the presidential session in the afternoon of day 2, in which the top four abstracts submitted by young investigators were presented to the membership of the iSBTc. Jason Zimmerer (Ohio State University, OH, USA) presented an elegant series of experiments demonstrating that proteins belonging to the suppressors of cytokine signaling (SOCS) family (SOCS1 and 3) negatively regulated the interferon (IFN)- α -induced signal transduction, gene expression and antitumor activity of immune effector cells *in vitro* and in a murine model of malignant melanoma. IFN- α treatments elicited only a 10-day increase in the survival of wild-type mice bearing B16 tumors in the intraperitoneal position. In contrast, the same dose of IFN- α led to prolonged survival in tumor-bearing SOCS1-deficient mice, an effect that was dependent on the actions of CD8-positive T cells. Yufeng Li (MD Anderson Cancer Center) then presented data demonstrating that the maintenance of CD27-positive effector memory T cells during *ex vivo* expansion of melanoma tumor-infiltrating lymphocytes was critical to the

success of adoptive T cell therapy. Furthermore, he was able to demonstrate that IL-15 was superior to IL-2 in driving the division of re-stimulated tumor-infiltrating lymphocytes. Kerrington R Molhoek (University of Virginia) then presented her exciting data concerning the effects of two targeted agents on the survival of Treg cells *in vitro*. She showed that sorafenib (a Ras kinase inhibitor also known as BAY-9006) and sirolimus (an mTOR inhibitor also known as rapamycin) were highly cytotoxic to Treg cells at sub-therapeutic doses. In contrast, CD4- and CD8-positive T cells were relatively insensitive to these compounds. Ulf Petrausch (Earle A. Chiles Research Institute, OR, USA) rounded out the session with an excellent presentation in which he demonstrated that blockade of transforming growth factor (TGF)- β signal transduction eliminated the immunosuppressive effect observed in mice bearing an experimental melanoma tumor (B16BL6-D5). This group had reported that vaccination of reconstituted, lymphopenic mice augmented the priming of tumor-specific T cells in tumor vaccine-draining lymph nodes. However, when studies were repeated with cells from systemic tumor-bearing mice, Treg cells suppressed priming of tumor-specific T cells. In a series of compelling experiments, Petrausch subsequently demonstrated that elimination of TGF- β signaling overcame the suppression observed in systemic tumor-bearing mice, resulting in improved antitumor activity in the adoptive immunotherapy model. Finally, they showed that TGF- β -insensitive Treg cells from tumor-bearing mice were unable to suppress naive T cells. After careful consideration, Petrausch was unanimously voted to be the 2006 recipient of the Presidential Award for this work.

On day 3, Ulrich Keilholz, Axel Hoos (Bristol-Myers Squibb, CT, USA) and Raj Puri (FDA, MD, USA) presented an update of the 2005 workshop on early and late clinical vaccine development. Following this, there were well-attended sessions that examined the therapeutic potential of newly developed targeted agents. These included an anti- $\alpha_v\beta_3$ antibody (MEDI-522), a peptide targeting EphA2 and a granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer vaccine (GVAX) given with an anti-CTLA antibody (MDX-010). The therapeutic potential of inhibitors of mTOR and the receptor tyrosine kinase-like orphan receptor-1 were also examined. Following this session, the annual meeting was adjourned by the incoming iSBTc President, John Wigginton, and members were informed of next year's meeting, which will take place in Boston, MA, USA on 1 – 4 November 2007.

2. Primer on Biological Therapy and Tumor Immunology

The annual iSBTc Primer on Tumor Immunology and Biological Therapy was conducted on 26 October 2006, one day prior to the Annual Meeting. The Primer provides

a one-day broad overview of immunology as it applies to tumor therapy. The Chairpersons this year were Paul Sondel MD, PhD (University of Wisconsin in Madison, WI, USA) and Mac Cheever MD (Fred Hutchinson Cancer Research Center, Seattle, WA, USA). The day was started with a talk on *Immunotherapy Perspective on Cancer Biology and Cancer Antigens* by Hans Schreiber, MD, PhD (University of Chicago, IL, USA). Schreiber reviewed the biological and historical underpinning of specific cancer immunity, with the warning that many of the systems and models in common usage today are more appropriate for evaluating tumor prevention as opposed to tumor therapy. Mary L Disis MD (University of Washington, WA, USA) reviewed *Clinical Trials of Immunotherapy with T Cells: Vaccines and Adoptive Immunotherapy*, pointing out that immunotherapy utilizing specific T cell immunity is effective, albeit in well-circumscribed circumstances, and that reagents already in hand should be able to substantially improve the efficacy of the approach. Peter McLaughlin MD (MD Anderson Cancer Center) discussed *Clinical Trials of Antibody Therapy: Hematological Malignancies*, providing a review of both the substantial efficacy of the present clinical practice of antibody therapy of hematological malignancy and also the great complexity involved in developing highly effective regimens for use in the clinic. Lewis Lanier PhD (University of California San Francisco, CA, USA) gave an incredibly comprehensive yet understandable review of *Biology of Innate Immunity: NK, Macrophage, PMN, PAMP/TLR*, despite the time limits on the individual topics imposed by having only a one-day meeting. Sherrie Morrison PhD reviewed the *Principles of Antibody Engineering and Therapy* and left the audience with great optimism that the field of antibody therapy is only in its infancy. Dennis J Slamon MD, PhD (University of California Los Angeles, CA, USA) focussed primarily on the development of Herceptin during his talk on *Clinical Trials of Antibody Therapy: Solid Tumors*, and thereby gave the audience a great view of how antibodies should be developed, also leaving the audience with both optimism about the future and sanguinity that development will now occur at an accelerated pace due to the examples of prior successes. Kim A Margolin MD (City of Hope, CA, USA) gave a comprehensive review of *Clinical Trials of Cytokines*, which left the audience with the view that only the surface of the possibilities of cytokine therapy has been seen. Finally, Theresa L Whiteside PhD (Pittsburgh Cancer Institute, PA, USA) presented *Monitoring of Cancer Immunotherapy Trials: the Methodology, Rationale and Interpretation of Standard Immunological Assays*, which ended the day with a realistic note of the technical skill and care required to not only develop immunotherapy, but to monitor and evaluate the mechanism and level of efficacy. In a survey provided by audience members, the Primer scored very high on the relevancy of the program and the methods used by the presenters. Presenting talks that are

broad, relevant and represent the present field is a difficult task that was accomplished by this year's presenters.

3. Mini-Symposium on Biological Effects of Targeted Therapeutics

In addition to the Primer, the iSBTc Annual Meeting was also preceded by a half-day Mini-Symposium focussing on the Biologic Effects of Targeted Therapeutics. The Mini-Symposium was co-chaired by Michael Atkins (Beth Israel Deaconess Medical Center, Boston, MA, USA) and Louis Weiner (Fox Chase Cancer Center, Philadelphia, PA, USA). The impetus for the Mini-Symposium was the increasing recognition that although therapies targeted at tumor or host cells have begun to revolutionize the way we view and treat cancer, such therapies are largely only palliative. Host-tumor interplay is still considered critical to achieving a durable tumor-free state. In this regard, a number of the targeted agents were felt to inhibit multiple targets, as well as similar or related pathways, within host cells, making their impact on host factors difficult to predict. Indeed, inhibition of such alternative targets within immune cells, endothelial cells and stromal components might influence the tolerability, activity, duration of benefit and ability to combine these various targeted agents. Understanding the resultant biological effects of these targeted agents was felt to be critical to their optimal application.

With this in mind, the Mini-Symposium aimed to describe the existing knowledge regarding various biological effects of existing therapies, identify the most relevant issues and gaps in the knowledge base, and discuss the optimal means of obtaining necessary missing information. Presentations by a distinguished faculty focussed on the impact of the nature of cell death on: immune function; the capacity of antibody therapy to enhance tumor antigen expression or induce a T cell-mediated immune response; the impact of chemotherapy on angiogenesis; and the impact of antiangiogenic therapy, small molecule tyrosine kinase inhibitors or epigenic modulators on immune function. A lively discussion followed the presentations, during which participants considered the ways in which the information presented could inform basic science efforts, aid in the rational design of combination treatment regimens, and influence the choice of correlative studies to be performed in the context of present and future clinical investigations. The proceedings of the workshop are being compiled with the goals of publishing them in the spring of 2007 and setting the stage for the Combination Biological Therapy Workshop to be held in conjunction with the 2007 iSBTc Annual Meeting.

4. Expert opinion and conclusion

The broad spectrum of presentations delivered at this year's program highlighted both substantial progress in the field of cancer immunotherapy and several key challenges in the years to come. New insights have further defined key determinants that will be necessary to initiate, expand and sustain a productive antitumor immune response, and have also delineated important counter-regulatory mechanisms that may compromise this response. These include immunosuppressive/counter-regulatory molecules, Treg cells and tumor-induced T-cell anergy, among several others. In addition, these presentations suggested that future progress in the field will be facilitated by an improved understanding of patient populations that are most appropriate for treatment with immunotherapy and, where appropriate, how to most effectively integrate immunotherapeutic regimens into conventional cancer treatment strategies. In turn, new evidence presented during these sessions suggests that in many cases traditional targeted agents may also have previously unrecognized effects on the immune system. An improved understanding of these mechanisms will further inform attempts to optimize the use of these drugs alone or in combination with other therapeutic agents. Finally, this year's sessions further support the notion that substantial opportunities exist for the investigation of rationally designed combinations of agents that may potentiate the host antitumor immune response in a complementary fashion. Building on this concept and dialog among the international group of basic scientists and clinical investigators representing academia, industry and regulatory agencies at this year's meeting, a formal program to assess opportunities and obstacles for the development of combination biological therapies will take place in conjunction with the 2007 iSBTc Annual Meeting.

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