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The 13th Annual Meeting of the Translational Research Cancer Centers Consortium (TrC3); Immune Suppression and the Tumor Microenvironment, Columbus, Ohio; March 1–2, 2010

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Summary

The Translational Research Cancer Centers Consortium (TrC3) is a cancer immunotherapy network, established to promote biologic therapeutics in the Midwestern and Northeastern regions of The United States. The 13th Annual Meeting of the TrC3 was hosted by The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute and took place at The Blackwell Hotel and Conference Center in Columbus, OH on March 1–2, 2010 (<http://www.osuccc.osu.edu/TrC3/index.htm>). This year's theme was "Immune Suppression and the Tumor Microenvironment." The meeting consisted of 21 oral presentations, a roundtable discussion focused on enhancing collaborative relationships within the consortium, and a poster session with 54 abstracts from predoctoral or postdoctoral researchers. This annual meeting brought together more than 170 investigators from 9 regional cancer centers including: Abramson Cancer Center at The University of Pennsylvania, Barbara Ann Karmanos Cancer Institute at Wayne State University, Case Comprehensive Cancer Center, Cleveland Clinic Taussig Cancer Center, James P. Wilmot Cancer Center, Mary Babb Randolph Cancer Center at West Virginia University, The Ohio State University Comprehensive Cancer Center, Penn State Cancer Institute, Roswell Park Cancer Institute, and University of Pittsburgh Cancer Institute. The proceedings of this year's meeting are summarized in this report.

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Biologics have assumed a major role in existing and emerging cancer therapies. Indeed, many biologic therapies are derived from cellular or molecular components of the host immune system, and include tumor or stroma-targeted antibodies, recombinant cytokines, vaccines, engineered cells, viral vectors, and other small molecule therapeutic agents.¹ These agents have great promise owing to their ability to elicit, on occasion, dramatic clinical responses in patients and are now being explored in combination with other standard and experimental therapies. One major challenge that remains for improving the response to biologic therapy of cancer in general, is overcoming immune suppression that is associated with cancer.² Tumor cells and their associated stromal tissue can produce a variety of factors which directly inhibit the host immune response to cancer. In fact, various cellular and metabolic factors are altered in a tumor-bearing host which can inhibit both innate and adaptive immunologic processes in cancer.³⁻⁵ Experimental models have demonstrated that these many layers of immune suppression can inhibit the action of biologic therapy, and promote cancer progression.^{6,7} With these challenges in mind, the goals of this collaborative meeting were to gain a greater understanding of interactions between the immune system, cancer development, and biologic-based therapy amongst a consortium of regional cancer centers (Fig. 1).

CELLULAR MEDIATORS OF IMMUNE SUPPRESSION

The heterogeneous nature of myeloid, lymphoid, or other stromal-derived cells that suppress host immune responses to tumors were a prominent topic of discussion. Dr Hans Schreiber (University of Chicago) served as the keynote speaker to open the sessions, and presented provocative data regarding the role of stromal cells in the maintenance and progression of cancer. Dr Schreiber also provided the audience with an accurate historical review of many sentinel studies documenting the antigenicity of tumors and the recognition that antibodies directed against the Gr1 antigen could neutralize cells with a granulocytic phenotype and augment antitumor immune responses.⁸⁻¹¹

The first session concluded with a series of presentations on the basic biology of T regulatory cells (Treg). Using a murine tumor model along with RMA-S lymphoma cells, Dr Xuefang Cao (Roswell Park) showed that tumor-induced Treg cell expansion could occur only in the presence of non-T accessory cells. Furthermore, Dr Cao demonstrated that treatment with proinflammatory cytokine, interleukin-12 blocked tumor-induced expansion of Treg cells. The focus on cytokines as mediators of Treg cell biology continued as Dr Venuprasad Poojary (Karmanos) provided evidence that transforming growth factor- β signaling in naive T cells regulates Foxp3 expression and Treg development. Studies from Dr Poojary's laboratory showed that T cells deficient for the ubiquitin ligase "Itch" are resistant to transforming growth factor- β treatment and defective in Foxp3 expression. It is interesting to note that Itch-mediated monoubiquitination also results in transforming growth factor- β -inducible early gene1 nuclear translocation and Foxp3 expression.

In addition to Dr Schreiber's keynote lecture, other investigators presented original data on the biologic properties of myeloid-derived suppressor cells (MDSC) and their ability to inhibit antitumor immune responses. A presentation by Ms Bethany Mundy from the laboratory of Dr William E. Carson, III (Ohio State), showed that immune cells from tumor-bearing mice had a decreased response to interferon stimulation and elevated levels of MDSC. Analysis of spleens from these mice revealed elevated levels of nitric oxide, and

increased nitration on tyrosine residues of the signal transducer and activator of transcription (STAT)1 protein. When MDSC were depleted from tumorbearing animals, interferon responsiveness was restored, indicating a direct association between MDSC and interferon signaling in immune cells of tumor-bearing mice. Other work presented by Mr Matthew Farren from the laboratory of Dr Kelvin Lee (Roswell Park) highlighted novel findings in regard to the mechanisms by which tumors inhibit dendritic cell (DC) differentiation. They showed that protein kinase C- β , which plays a crucial role in DC differentiation, was downregulated by tumor driven signaling. Importantly, these findings suggest that this process is mediated by tumor-driven STAT3 hyperactivation.

TUMOR MICROENVIRONMENT AND IMMUNE SUPPRESSION

The next session of the meeting was centered on understanding how various factors within the tumor microenvironment might contribute to tumor development. For example, both clinical and experimental data demonstrate that tumor-associated macrophages (TAMs) contribute to breast cancer metastasis, but relatively little is known of the genes and pathways that contribute to this function.¹² Dr Michael Ostrowski (Ohio State) used mouse genetic models to ablate the transcription factor Ets2 in TAMs, demonstrating a profound affect on breast tumor metastasis to the lung. Ets2 regulates a gene expression program in TAMs that selectively affects angiogenesis and growth of metastatic tumors. This gene signature was found to be conserved in human patient samples and to retrospectively predict patient survival. A subsequent presentation from Dr Heather O'Leary (Mary Babb Randolph Cancer Center) showed the unexpected expression of vascular endothelial (VE)-cadherin on both cell lines and patient samples of Philadelphia chromosome positive acute lymphoblastic leukemia. In addition she determined that Abelson tyrosine kinase, as well as VE-cadherin and β -catenin, could be stabilized by the bone marrow microenvironment during chemotherapy treatment. Inhibition of VE-cadherin signaling could render the Philadelphia chromosome positive acute lymphoblastic leukemia tumor cells more sensitive to chemotherapy even in the presence of bone marrow stromal cell derived cues warranting further investigation of VE-cadherin as a therapeutic target.

Dr Angelika Burger (Karmanos) also reported on the influence of the tumor microenvironment on the function of the insulin-like growth factor binding protein-related protein 1 (IGFBP-rP1). IGFBP-rP1 is a secreted protein that regulates insulin and insulin growth factor I/II bio-availability in the circulation. This protein is also found in the cytoplasm of many normal tissues including breast tissue. Intracellular IGFBP-rP1 was downregulated during disease progression of breast cancer. However, in the normal mammary gland IGFBP-rP1 is expressed in cells with self-renewal properties and is critical in maintaining normal mammary gland architecture. The rP1 knockout mice showed a progressive loss of mammary gland structures with tissue remodeling and aging. Similarly, breast cancer-initiating cells express high levels of rP1. Experiments using cocultures of breast cancer cells and tumor stromal cells showed that intracellular rP1 was strongly decreased, reflective of potential events in the tumor microenvironment.

Dr Joe Palumbo (Cincinnati Children's Hospital/Ohio State) supported the hypothesis that hemostatic factors such as thrombin and fibrinogen are determinants of inflammation-induced colitis-associated colon cancer (CAC). In murine models of CAC, Dr Palumbo found that fibrinogen was mechanistically coupled to CAC by the engagement of integrin $\alpha_5\beta_1$, and that these interactions supported the growth of CAC. Fibrinogen-mediated $\alpha_5\beta_1$ engagement could also drive early inflammatory events important in adenoma initiation and/or promotion. Together these presentations represented the diverse factors that are operative within the tumor microenvironment and identified novel pathways that deserve further investigation as prognostic or therapeutic targets.

STRATEGIES AND BARRIERS TO OVERCOMING IMMUNE SUPPRESSION

The remainder of the meeting emphasized other clinically relevant immunosuppressive barriers and various strategies which could be used to overcome this suppression associated with advanced malignancy. After a discussion by Dr Steve Bernstein (Wilmot Cancer Center) on anti-idiotypic vaccines, Dr Shannon Hilchey (Wilmot Cancer Center) described the phenomenon by which follicular lymphoma (FL) infiltrating T cells are hyporesponsive to CD3/CD28 costimulation. This is in part, owing to increased proportions of CD39⁺ T cells (which includes Treg cells) within the FL microenvironment as compared with that of normal or reactive lymph nodes. CD39⁺ T cells contribute to T-cell hyporesponsiveness through an adenosine-dependent mechanism. It is interesting to note that, comparison of the CD4⁺ T helper cell subsets, both phenotypically and functionally, demonstrated no skewing of Th1, Th2, Th17 etc subsets when comparing FL to normal or reactive nodes. These findings have significant implications for therapy of patients with FL, as the effector T cells within the tumor microenvironment appear functionally similar to those from nonmalignant lymph nodes.

Although immune suppression in cancer is heavily regulated by specific cell populations, other components of the host immune system are gaining increased attention as key mediators of this process. Dr Andrea Faccibene from the Abramson Cancer Center described the role of complement in T-cell adhesion to endothelium and homing to tumors. These studies indicated that C3, a component of the complement system, was overexpressed in the endothelium of tumors with T-cell infiltrates and that complement activation in host tissues was required for T-cell engraftment and tumor rejection. It is interesting to note that, complement hyperactivation led to enhanced T-cell engraftment in tumors and could facilitate rejection by suboptimal numbers of tumor-specific T cells.

Therapeutic strategies for overcoming immune suppression in the tumor microenvironment were also highlighted in the scientific sessions. Dr Rosa Lapalombella (Ohio State) described how clinically relevant concentrations of the immunomodulatory drug, lenalidomide could promote time-dependent CD154 transmembrane protein expression through 2 distinct mechanisms of transcriptional activation and posttranscriptional mRNA stabilization. She demonstrated that lenalidomide could produce an *in vivo* humoral response to tumor cells. Oncolytic virus (OV) strategies also received considerable attention as a promising biologically focused antitumor strategy. Dr Balveen Kaur (Ohio State) described the utility of OV as a therapeutic strategy, specifically for intracranial tumors. Data from Dr Kaur's laboratory showed a significant increase in vascular permeability in intracranial tumors treated with oncolytic herpes simplex virus-1-derived viruses compared with phosphate buffered-saline-treated animals. This vascular leakage correlated with increased tumor inflammation. Reduction of tumor vasculature using antiangiogenic agents led to a reduction in OV-induced vessel permeability and antiviral inflammation, resulting in increased OV propagation and efficacy. This inflammation caused increased angiogenesis in the tumor that regrew after oncolysis. Based on these results, Dr Kaur closed by describing the creation of an OV armed with antiangiogenic gene therapy which was found to increase therapeutic efficacy of intracranial tumors in nude mice.

The critical role for effective T-cell costimulation and interactions with DC which present tumor antigens was also represented at this meeting. Dr Jianxun Song (Penn State) described his work focused on understanding whether various targets of T-cell costimulation have overlapping or synergistic functions. Dr Song used retrovirusmediated transduction to introduce bcl-xL and survivin linked by a 2A peptide, into antigen-responding CD8⁺ T cells. His group found that bcl-xL and survivin (2 targets of costimulation) both contributed in a synergistic, nonredundant, manner to augment the accumulation and persistence of CD8⁺ T

cells after encounter with antigen. Most significantly, the cointroduction of these molecules into CD8 T cells resulted in their ability to fully protect against tumor growth.

DC have considerable potential as a therapeutic strategy for patients with advanced malignancy.¹³ An increased understanding of immunosuppressive factors limiting their efficacy, was considered by Dr Julie Urban (Université Pierre et Marie Curie). She presented the notion that the efficacy of DC vaccines may be limited by endogenous cytotoxic lymphocytes which eliminate them at the site of injection after in vivo administration. Dr Urban also shared her group's findings demonstrating the rationale for interfering with the cytotoxic lymphocytes activity as a means of improving the outcomes of therapeutic cancer vaccines. Complex and critical interactions between T cells and DC influence both tumor rejection and effective responses to vaccines intended to promote antitumor immunity.

Natural killer (NK) cells, a component of the innate immune system were also a focus of discussion owing to their ability to regulate stressed and malignant cells.¹⁴ Dr Don Benson (Ohio State) showed that NK cells mediated cytotoxicity against multiple myeloma (MM) tumor cell targets through the balance of activating and inhibitory signaling initiated via killer immunoglobulin-like receptors (KIR). MM uses a variety of immunoevasive strategies against NK cells, including increased expression of ligands for inhibitory KIR. Preclinical data from Dr Benson's group showed that IPH-2101, a novel anti-inhibitory KIR blocking antibody, could enhance NK cell function against MM. Furthermore, this novel agent was reported to appear safe and well tolerated in a phase clinical I trial. This exciting work may have applications for a variety of tumors other than MM.

Dr Abbe deVallejo (Université Pierre et Marie Curie) introduced the concept that the aging process may lead to dynamic changes in T-cell repertoire and function. He presented evidence that as immunity is a determinant of individual fitness and survival, further understanding the nature and extent of immune repertoire remodeling will be important in the design of alternative strategies to improve immune protection for the elderly. In the setting of biologic therapy for cancer, it was suggested that exploration of agetargeted therapies may be warranted.

EMERGING TOPICS AND OPPORTUNITIES FOR COLLABORATION

Of great importance to the consortium has been identifying critical ways to collaborate amongst the member institutions. With this in mind, the meeting continued with a presentation by Dr Pui-Kai Li (Ohio State) who discussed the multi-disciplinary, Molecular Targeted Therapy drug development group. Dr Li highlighted the various STAT3 pathway and survivin small molecule inhibitors that are currently being developed and tested preclinically by the group. Next, Dr Cheryl London, from The Ohio State University Department of Veterinary Biosciences summarized the tremendous potential for implementing comparative oncology trials that cross from the veterinary clinic to the phase I human clinical trial setting. This concept was of great interest and was discussed further as a novel means to bring forward anticancer vaccine or targeted-antibody therapy trials.

This year's meeting came to a close with a panel discussion that featured Dr Soldano Ferrone (Université Pierre et Marie Curie), Dr Elizabeth Repasky (Roswell Park), Dr Carl June (Abramson), Dr William Petros (Mary Babb Randolph), Dr Gregory Lesinski (OSU), and Dr Wei-zen Wei (Karmanos). This group of consortium representatives discussed future funding opportunities for maintaining the consortium and its mission, the prospects of implementing a comparative oncology trial of an antibody targeting the high molecular weight melanoma antigen for canine melanoma,¹⁵ and documenting the collaborative relationships between consortium members.

The next, 14th Annual Meeting of the TrC3 will take place in February, 2011 at The Seven Springs Mountain Resort, in Seven Springs, PA and will be hosted by The University of Pittsburgh Cancer Institute. There, we will focus on strategies of autophagy, miRNA, the role of innate immune cells, and the development of novel biomarkers associated with these important factors in the biologic therapy of cancer.^{16–20}

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References

1. Cheever MA, Schlom J, Weiner LM, et al. Translational Research Working Group developmental pathway for immune response modifiers. *Clin Cancer Res.* 2008; 14:5692–5699. [PubMed: 18794077]
2. de Souza AP, Bonorino C. Tumor immunosuppressive environment: effects on tumor-specific and nontumor antigen immune responses. *Expert Rev Anticancer Ther.* 2009; 9:1317–1332. [PubMed: 19761435]
3. Norian LA, Rodriguez PC, O'Mara LA, et al. Tumor-infiltrating regulatory dendritic cells inhibit CD8+ T-cell function via L-arginine metabolism. *Cancer Res.* 2009; 69:3086–3094. [PubMed: 19293186]
4. Prendergast GC. Immune escape as a fundamental trait of cancer: focus on IDO. *Oncogene.* 2008; 27:3889–3900. [PubMed: 18317452]
5. Srivastava MK, Sinha P, Clements VK, et al. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. *Cancer Res.* 2010; 70:68–77. [PubMed: 20028852]
6. Petrausch U, Poehlein CH, Jensen SM, et al. Cancer immunotherapy: the role regulatory T cells play and what can be done to overcome their inhibitory effects. *Curr Mol Med.* 2009; 9:673–682. [PubMed: 19689294]
7. Ugel S, Delpozzi F, Desantis G, et al. Therapeutic targeting of myeloid-derived suppressor cells. *Curr Opin Pharmacol.* 2009; 9:470–481. [PubMed: 19616475]
8. Mullen CA, Urban JL, Van Waes C, et al. Multiple cancers. Tumor burden permits the outgrowth of other cancers. *J Exp Med.* 1985; 162:1665–1682. [PubMed: 3877140]
9. Pekarek LA, Starr BA, Toledano AY, et al. Inhibition of tumor growth by elimination of granulocytes. *J Exp Med.* 1995; 181:435–440. [PubMed: 7807024]
10. Seung LP, Rowley DA, Dubey P, et al. Synergy between T-cell immunity and inhibition of paracrine stimulation causes tumor rejection. *Proc Natl Acad Sci U S A.* 1995; 92:6254–6258. [PubMed: 7603979]
11. Seung LP, Seung SK, Schreiber H. Antigenic cancer cells that escape immune destruction are stimulated by host cells. *Cancer Res.* 1995; 55:5094–5100. [PubMed: 7585557]
12. Zabuawala T, Taffany DA, Sharma SM, et al. An ets2-driven transcriptional program in tumor-associated macrophages promotes tumor metastasis. *Cancer Res.* 2010; 70:1323–1333. [PubMed: 20145133]
13. Kalinski P. Dendritic cells in immunotherapy of established cancer: roles of signals 1, 2, 3 and 4. *Curr Opin Investig Drugs.* 2009; 10:526–535.
14. Becknell B, Caligiuri MA. Natural killer cells in innate immunity and cancer. *J Immunother.* 2008; 31:685–692. [PubMed: 18779751]
15. Goto Y, Ferrone S, Arigami T, et al. Human high molecular weight-melanoma-associated antigen: utility for detection of metastatic melanoma in sentinel lymph nodes. *Clin Cancer Res.* 2008; 14:3401–3407. [PubMed: 18519770]

16. Chavez AR, Buchser W, Basse PH, et al. Pharmacologic administration of interleukin-2. *Ann N Y Acad Sci.* 2009; 1182:14–27. [PubMed: 20074271]
17. Livesey KM, Tang D, Zeh HJ, et al. Autophagy inhibition in combination cancer treatment. *Curr Opin Investig Drugs.* 2009; 10:1269–1279.
18. Lotfi R, Schrezenmeier H, Lotze MT. Immunotherapy for cancer: promoting innate immunity. *Front Biosci.* 2009; 14:818–832.
19. Okada H, Kohanbash G, Lotze MT. MicroRNAs in immune regulation-Opportunities for cancer immunotherapy. *Int J Biochem Cell Biol.* 2010 Feb 6. Epub ahead of print.
20. Tahara H, Sato M, Thurin M, et al. Emerging concepts in biomarker discovery; the US-Japan Workshop on Immunological Molecular Markers in Oncology. *J Transl Med.* 2009; 7:45. [PubMed: 19534815]

FIGURE 1.
Geographic distribution of Translational Research Cancer Centers Consortium member institutions.