2013 New Journal Targets the Immune System: *Cancer Immunology Research*

GLENN DRANOFF, MD, FOUNDING EDITOR-IN-CHIEF, 2013-2015

Best known as a master of understanding the mechanisms responsible for the generation of anti-tumor immunity, Dr. Dranoff is credited with laying the foundations for the first approved therapeutic cancer vaccine as well as the first monoclonal antibody that blocks negative immune regulation. In his current research he hopes to combine immunotherapies in the same patient by further studying the mechanisms of priming immune cells, immunomodulation, and the effect of the tumor microenvironment on immune cells. After several decades as professor of medicine at Dana Farber Cancer Institute of Harvard Medical School, Dr. Dranoff recently became Global Head of Exploratory Immuno-oncology at Novartis Institutes for BioMedical Research.

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Illuminating the Interplay of Cancer and the Immune System
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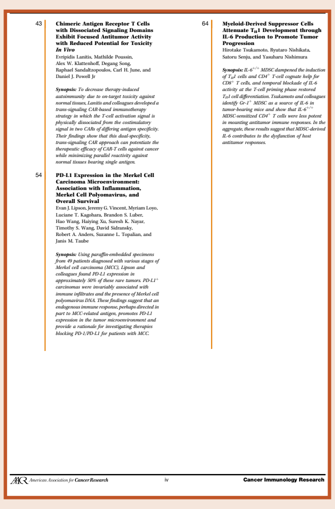

Inaugural Editorial

Editorial

Cancer Immunology Research

A Message from the Founding Editor-in-Chief

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This is an auspicious time for the AACR to launch *Cancer Immunology Research*, a new journal devoted to cancer immunology and immunotherapy. Recent clinical investigations have convincingly established that the immune system can be triggered to accomplish meaningful tumor destruction. The administration of blocking monoclonal antibodies against the negative immune checkpoints, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1), elicits remarkable antitumor effects in some patients with otherwise refractory disease. Moreover, cancer vaccines, adoptive therapy with engineered T cells, and other immunomodulatory antibodies are similarly showing promising antitumor activity. Collectively, these exciting results indicate that immunologic manipulations are likely to become a central component of cancer treatment.

In parallel to these advances in therapeutics, substantive progress in elucidating the mechanisms involved in endogenous host antitumor responses has delineated a key role for immunity in cancer pathogenesis. The principles of immunoediting have now been revealed not only in models typically used by cancer immunologists, but also in genetically engineered oncogene-driven systems that are a mainstay of investigations in cancer biology. In addition, the pivotal contribution of persistent inflammation to promoting tumor initiation and progression has now been broadly recognized, highlighting the dual roles of immunity in tumor development.

Notwithstanding these important examples of how immunology is entering the mainstream of cancer science, many cancer researchers have difficulty accessing the discipline and recognizing opportunities for productive new research directions. There are many factors that contribute to this perception of a high barrier to entry. Among the hurdles that need to be overcome are: (i) a lack of clarity regarding the logic of how immune responses work; (ii) the large number of soluble factors, surface molecules, and cell populations in the immune system that seem to be steadily increasing; (iii) a limited background in the relevant history and current literature of the field; (iv) a lack of familiarity with many immunologic techniques; (v) and uncertainty regarding how to prioritize particular areas of host–tumor cell interactions for more detailed exploration.

Cancer Immunology Research will address this important challenge through playing a leading role in educating the greater cancer research community regarding the principles and opportunities in cancer immunology. A major benefit of this investment will be to catalyze cross-disciplinary investigations, which might dramatically accelerate progress toward a deeper understanding of the host–tumor relationship, more potent therapeutics, and improved clinical outcomes. Indeed, cancer immunology is currently reaping the benefits of basic and translational studies in allied disciplines of immunology, such as autoimmunity, infectious disease, transplantation, and immunodeficiency; insights from these fields are now regularly being applied to the problems of tumor immunity.

To accomplish this educational mission, *Cancer Immunology Research* has developed several special features. The first is "Masters of Immunology," a series of primers on the fundamentals of immunology, particularly as they relate to cancer. These short pieces will be drafted by leading scholars who will present basic immunologic concepts in an accessible format that includes informative graphics. A broad spectrum of topics will be covered in the fullness of time, and the cycle will be repeated (in several iterations), allowing individual areas to be presented in increasingly greater detail and with a richer perspective on how a particular subject fits into the overall schema of tumor immunity. These primers will be organized into a virtual cancer immunology textbook on the journal website. Continuing medical education credits will also be offered for studying these primers, which should be of practical

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interest to clinicians who desire a deeper knowledge of immunology. For this inaugural issue, Hidde Ploegh has drafted an illuminating and eloquent introductory essay entitled "The Logic of the Immune System." This piece will serve as an enticing entry point to the mysteries and intricacies of immunity.

To complement these primers, *Cancer Immunology Research* will present "Cancer Immunology at the Crossroads," a series that will be devoted to exploring compelling opportunities for cross-disciplinary research. Prominent investigators will outline in short pieces specific areas where cancer immunology overlaps with other cancer research disciplines and suggest a few possibilities for fruitful collaboration. These features will highlight intersections not only with allied basic sciences such as genetics, cancer biology, metabolism, pathology, engineering, imaging, infectious disease, and population studies, but also areas relevant to translational and clinical development paths. Among these subjects will be potential synergies with targeted therapy, radiation treatment, cytotoxics, and antiangiogenic approaches; clinical trial design considerations; opportunities for new technologies; regulatory issues; immune-related patterns of tumor response; and specific clinical settings in which immunotherapy might be effectively employed. To kickoff this inspiring series, Nir Hacohen, Edward F. Fritsch, Todd A. Carter, Eric S. Lander, and Catherine J. Wu outline an intriguing approach to personalized cancer vaccinations based on next generation sequencing of individual patient tumors. The initiation of clinical testing is eagerly anticipated.

To round out the didactic components, *Cancer Immunology Research* will also include reviews of rapidly developing areas in the discipline. These pieces will probe more deeply into topics of central importance to the field and should be of great interest to both specialists and newcomers. For the inaugural issue, Bridget Keenan, Elizabeth Jaffee, and Todd Armstrong have crafted a compelling summary of the recent special AACR conference entitled "Tumor Immunology: Multidisciplinary Science Driving Basic and Clinical Advances." This article offers an exemplary analysis of ongoing work, highlighting the breadth and depth of investigation in the field.

In addition to the educational mission, *Cancer Immunology Research* will aspire to become the leading publication for original work in cancer immunology. The journal will print outstanding articles reporting major advances in cancer immunology, which may span the discipline from basic investigations in host–tumor interactions to developmental therapeutics in model systems, to early translational studies in patients, and late-stage clinical trials. These contributions may be structured as either full Research Articles or Priority Briefs. Specific topics of interest include endogenous antitumor immunity, tumor-promoting inflammation, cancer antigens, vaccines, antibodies, cellular therapy, cytokines, immune regulation, immune suppression, immunomodulatory effects of cancer treatment, emerging technologies, and clinical investigations.

Cancer Immunology Research is proud to showcase two high-impact original articles in the inaugural issue, which are both likely to advance the field significantly. Alan Korman and Mark Selby and colleagues establish the critical importance of antibody isotype to the therapeutic activity of CTLA-4 blocking antibodies in murine models. These investigators reveal the ability of anti-CTLA-4 monoclonal antibodies to trigger a striking reduction in intratumoral, but not peripheral, FoxP3$^+$ regulatory T cells, likely through Fc receptor-dependent cytotoxic mechanisms. These provocative findings uncover a new aspect of immune checkpoint blockade, with important implications for further therapeutic development and patient selection. In a second story, Daniel Powell and Evripidis Lanitis and colleagues detail an attractive strategy for improving the therapeutic index of chimeric antigen receptor-expressing T cells. By separating T-cell signaling domains in 2 chimeric antigen receptors specific for distinct targets, the investigators show that full T-cell activation requires concurrent recognition of both targets. This property may allow the use of chimeric antigen receptors that target proteins expressed on both tumor cells and normal tissues; as long as the second tumor target is not also expressed on the same normal cells as the first, the requirement for combinatorial recognition may focus T-cell responses preferentially against tumor cells.

A third type of original article that *Cancer Immunology Research* will feature is the "Cancer Immunology Miniature." These contributions may report on early clinical data or discovery-based studies that are not sufficiently developed for publication as full Research Articles, but have the potential to make a significant impact in research areas and clinical investigation or care. These pieces might include well-analyzed, provocative case reports. An outstanding example of this work is the detailed patient study of Carl June and Marcela Maus and colleagues published in this inaugural issue. The authors describe the evolution of an anaphylactic reaction in a subject treated with T cells expressing a chimeric antigen receptor incorporating a mouse monoclonal antibody as the targeting moiety. Although this class of receptors has been safely administered to a growing number of patients, this miniature sounds a cautionary note regarding antimurine immune responses and suggests that the use of fully human constructs should be carefully considered.

To advance the dual mission of *Cancer Immunology Research* in fostering education and original investigation, Elizabeth Jaffee, Stanley Riddell, and Robert Vonderheide will serve as Deputy Editors. Each is a consummate physician-scientist who has successfully developed a novel therapeutic strategy from preclinical proof-of-concept experiments through early phases of testing in patients with cancer. This rare experience coupled with a broad knowledge of the entire discipline positions the Deputy Editors as the ideal team to oversee the didactic components of the journal. Their efforts should ensure the dissemination of knowledge of cancer immunology to the larger cancer research community, thereby stimulating new investigators to enter the field.

Nineteen distinguished scientists and physicians from around the globe will serve as the Senior Editors for *Cancer Immunology Research*. Their collective knowledge spans all of the major areas of cancer immunology and immunotherapy. The Senior Editors will oversee reviews of the original articles,

assuring that they are conducted rigorously and timely; the journal will maintain the highest levels of scholarship and intellectual rigor. A vibrant and accomplished Editorial Board will assist the Senior Editors in evaluating submitted manuscripts. The broad participation of the cancer immunology community on the Editorial Board will assure that the journal helps generate new insights into the complex interplay between cancer and the immune system and accelerates the crafting of clinically efficacious immunotherapies.

The creation of *Cancer Immunology Research* reflects the many efforts of the skilled publications team at AACR, particularly Kelly Hadsell, Art Buchberg, and Diane Scott-Lichter. Connie Gee also provided invaluable assistance in launching the journal. A special thanks to Drs. Margaret Foti and Michael Caligiuri for their vision and wisdom. We hope that all of the efforts on behalf of *Cancer Immunology Research* will ensure that immunology, metaphorically and tangibly, assumes a prominent position within the heart of cancer research.

Glenn Dranoff, MD
Editor-in-Chief
Cancer Immunology Research

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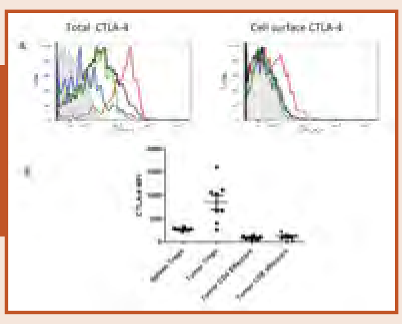
2013 CTLA-4 Blockade Works by Reducing Intratumoral Tregs and Activating Teffs

FIGURE 5. Expression of CTLA-4 on intratumoral and peripheral Tregs and Teffs. A, comparison of total CTLA-4 levels (left) or cell surface CTLA-4 levels (right) from either tumor CD4 effectors (blue histogram), tumor CD8s (green histogram), splenic Tregs (black histogram), and tumor Tregs (red histogram). Shaded gray histogram is isotype control staining. B, mean fluorescence intensity (MFI) from T-cell subsets of 8 control-IgG1 tumor-bearing mice.



HIGHLY CITED ARTICLE

Anti-CTLA-4 Antibodies of IgG2a Isotype Enhance Antitumor Activity through Reduction of Intratumoral Regulatory T Cells

Combined Local Radiotherapy and Systemic CTLA-4 Antibody Produce Sustained Remission

HIGHLY CITED ARTICLE

An Abscopal Response to Radiation and Ipilimumab in a Patient with Metastatic Non–Small Cell Lung Cancer

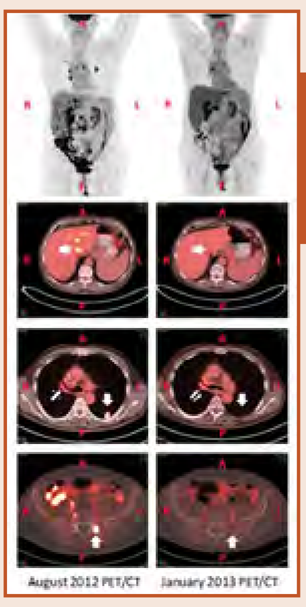


FIGURE 2. Ipilimumab and local radiotherapy result in an abscopal response. PET imaging and select fused PET/CT axial images from August 2012 (left) and January 2013 (right) are displayed. The axial images in the second row reveal the hypermetabolic liver lesion that was targeted and responded to radiotherapy (white arrows, second row). An abscopal response was seen in a left lower lobe lung lesion (white arrows, third row) and a left sacral lesion (white arrows, bottom row). A mixed response was seen in the hilar/mediastinal lymph nodes (striped arrows, third row).

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2014

Anti-mesothelin CAR-T Cells Induce Antibodies to Self Epitopes and Antitumor Activity

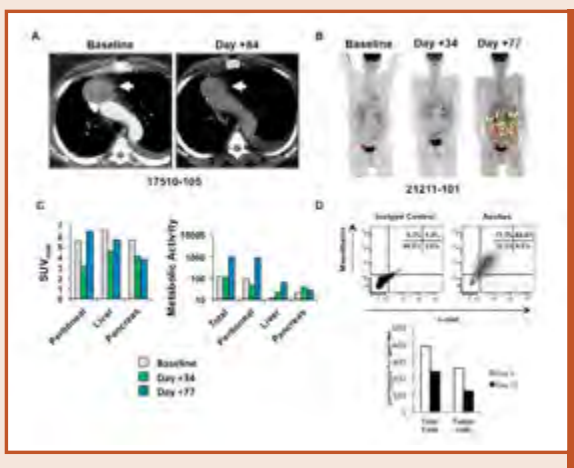

FIGURE 1. Antitumor activity of CARTmeso cells. A, CT imaging of MPM patient 17510-105 showing the patient's dominant mesothelioma mass before receiving CARTmeso infusion on schedule 1 (baseline) and 35 days after receiving the first CARTmeso infusion on schedule 2 (day +84). B, whole-body FDG PET/CT imaging of PDA patient 21211-101 obtained at baseline, day +34 after completing i.v. CARTmeso cell infusions, and day +77 after completing intratumoral CARTmeso cell infusions. C, analysis of maximum standardized uptake value (SUVmax) and mean metabolic volumetric product (MVPmean) at baseline, day +34, and day +77 is shown for all lesions (total) and individual sites of disease (peritoneal, liver, and pancreas) for PDA patient 21211-101. D, representative flow cytometric plot of ascites from PDA patient 21211-101 analyzed with isotype control antibodies versus antimesothelin and anti-c-met antibodies to identify mesothelin+ c-met+ tumor cells. Flow cytometric findings were quantified to determine the total number of cells/mL and tumor cells/μL in the ascites that is shown in the bar graph with comparison between day +3 and day +15 after beginning i.v. CARTmeso cell infusions.

Mechanisms Described for How anti-VEGF Aids CTLA-4 Blockade in Melanoma

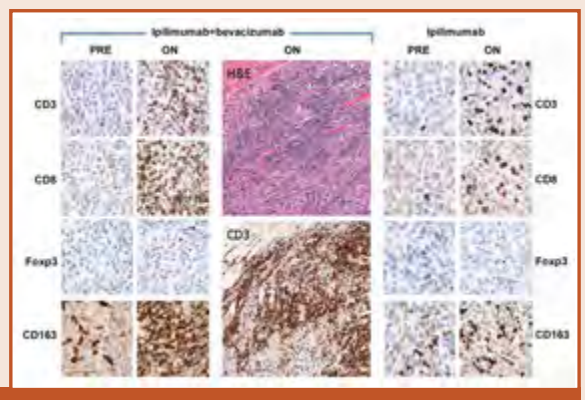

FIGURE 3. Histologic changes in tumor deposits resulting from treatment with bevacizumab plus ipilimumab. A, phenotypic characterization of immune-cell infiltrates in biopsies from responders before and after initiation of therapy. Tumors after initiation (ON) of ipilimumab–bevacizumab therapy were characterized as compared with pretreatment samples (PRE). Significant infiltration by CD3+CD8+ T cells and CD163+ macrophages with minimal change in Foxp3+ component was observed. The enlarged panels (center) emphasize the tumor-infiltrating architecture of the immune response (top left, skeletal muscle). In contrast, patients treated only with ipilimumab showed a lesser degree of immune-cell infiltration while on therapy. The two ipilimumab–bevacizumab specimens are subcutaneous tissues, and the ipilimumab-alone specimen was from the oropharyngeal submucosa.

2015

Immunology Program Heads Named Editors-in-Chief

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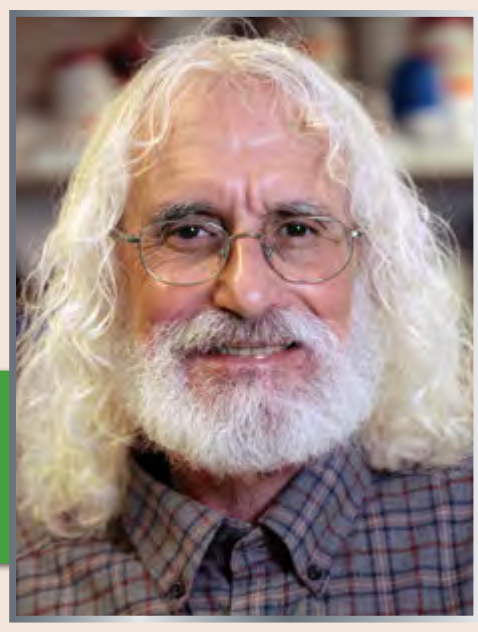
EDITOR-IN-CHIEF, 2015-PRESENT



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