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- 91** **CD4 T-cell Subsets and Tumor Immunity: The Helpful and the Not-so-Helpful**  
 Hye-Jung Kim and Harvey Cantor

## CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

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 Don M. Benson Jr and Michael A. Caligiuri

## MEETING REPORT

- 105** **The Cancer Research Institute 2013 Annual Symposium: Dynamics of Host–Tumor Interaction**

## CANCER IMMUNOLOGY MINIATURES

- 112** **Mesothelin-Specific Chimeric Antigen Receptor mRNA-Engineered T Cells Induce Antitumor Activity in Solid Malignancies**  
 Gregory L. Beatty, Andrew R. Haas, Marcela V. Maus, Drew A. Torigian, Michael C. Soulen, Gabriela Plesa, Anne Chew, Yangbing Zhao, Bruce L. Levine, Steven M. Albelda, Michael Kalos, and Carl H. June  
*Synopsis:* Beatty, Haas, and colleagues report antitumor activity in two patients treated with autologous T cells transfected with mRNA encoding a chimeric antigen receptor that recognizes mesothelin and contains the CD3- $\zeta$  and 4-1BB costimulatory domains (CART<sub>meso</sub>). The short-lived CART<sub>meso</sub> cells induced novel antiself antibodies and a broadly directed epitope spreading.

## PRIORITY BRIEFS

- 121** **Tumoral Immune Suppression by Macrophages Expressing Fibroblast Activation Protein- $\alpha$  and Heme Oxygenase-1**  
 James N. Arnold, Lukasz Magiera, Matthew Kraman, and Douglas T. Fearon  
*Synopsis:* Arnold and colleagues identify the FAP<sup>+</sup>CD45<sup>+</sup> subpopulation of M2 macrophages as the major tumoral source of heme oxygenase-1 (HO-1), the inhibition of which alleviates tumoral immune suppression and arrests tumor growth. The authors suggest that targeting HO-1 may improve cancer immunotherapy.

- 127** **Pretreatment Serum VEGF Is Associated with Clinical Response and Overall Survival in Advanced Melanoma Patients Treated with Ipilimumab**  
 Jianda Yuan, Jun Zhou, Zhiwan Dong, Sapna Tandon, Deborah Kuk, Katherine S. Panageas, Philip Wong, Xinqi Wu, Jarushka Naidoo, David B. Page, Jedd D. Wolchok, and F. Stephen Hodi  
*Synopsis:* Yuan, Zhou, and colleagues analyzed levels of serum VEGF in patients before and after ipilimumab therapy; they found that high pretreatment VEGF levels correlate with decreased overall survival. VEGF may serve as a biomarker for ipilimumab treatment.

## RESEARCH ARTICLES

- 133** **Immune Impact Induced by PROSTVAC (PSA-TRICOM), a Therapeutic Vaccine for Prostate Cancer**  
 James L. Gulley, Ravi A. Madan, Kwong Y. Tsang, Caroline Jochems, Jennifer L. Marté, Benedetto Farsaci, Jo A. Tucker, James W. Hodge, David J. Liewehr, Seth M. Steinberg, Christopher R. Heery, and Jeffrey Schlom  
*Synopsis:* Gulley and colleagues report immune responses from patients treated with PSA-TRICOM (a vaccinia prime/fowlpox boosts vaccine regimen with vectors expressing human PSA, B7.1, ICAM-1, and LFA-3), with 57% of 104 patients developing PSA-specific immune responses and 68% with antigen spreading.
- 142** **Combined Targeting of Costimulatory (OX40) and Coinhibitory (CTLA-4) Pathways Elicits Potent Effector T Cells Capable of Driving Robust Antitumor Immunity**  
 William L. Redmond, Stefanie N. Linch, and Melissa J. Kasiewicz  
*Synopsis:* Redmond and colleagues show that agonist ligation of OX40 while releasing the “brakes” on T cells via CTLA-4 blockade stimulates a unique CD4 and CD8 T-cell response that overcomes the limited efficacy of monotherapy and augments tumor immunotherapy.

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**154 Targeting Fibroblast Activation Protein in Tumor Stroma with Chimeric Antigen Receptor T Cells Can Inhibit Tumor Growth and Augment Host Immunity without Severe Toxicity**

Liang-Chuan S. Wang, Albert Lo, John Scholler, Jing Sun, Rajrupa S. Majumdar, Veena Kapoor, Michael Antzis, Cody E. Cotner, Laura A. Johnson, Amy C. Durham, Charalambos C. Solomides, Carl H. June, Ellen Puré, and Steven M. Albelda

**Synopsis:** Wang, Lo, and colleagues report the efficacy and safety of chimeric antigen receptor T cells specific for mouse fibroblast activation protein in inhibiting the growth of subcutaneously transplanted tumors when used alone and in combination with an antitumor vaccine.

**167 CD4 T Cells Require ICOS-Mediated PI3K Signaling to Increase T-Bet Expression in the Setting of Anti-CTLA-4 Therapy**

Hong Chen, Tihui Fu, Woong-Kyung Suh, Dimitra Tsavachidou, Sijin Wen, Jianjun Gao, Derek Ng Tang, Qiuming He, Jingjing Sun, and Padmanee Sharma

**Synopsis:** Chen, Fu, and colleagues show that ICOS-mediated PI3K signaling is required for the expression of transcription factor T-bet, which regulates the Th1 antitumor response elicited by anti-CTLA-4 therapy, and suggest that targeting ICOS may improve Th1 antitumor responses.

**177 Microvesicle Cargo of Tumor-Associated MUC1 to Dendritic Cells Allows Cross-presentation and Specific Carbohydrate Processing**

Aurelia Rughetti, Hassan Rahimi, Francesca Belleudi, Chiara Napoletano, Federico Battisti, Ilaria G. Zizzari, Morena Antonilli, Filippo Bellati, Hans H. Wandall, Pierluigi Benedetti Panici, Joy M. Burchell, Mara R. Torrisi, and Marianna Nuti

**Synopsis:** Rughetti and colleagues show that unlike soluble glycoprotein antigens, MUC1 carried by microvesicles translocates from the endolysosomal/HLA-II to the HLA-I compartment, deglycosylates, and generates novel glycoepitopes for presentation by dendritic cells to MUC1-specific CD8<sup>+</sup> T cells stimulating IFN $\gamma$  responses.



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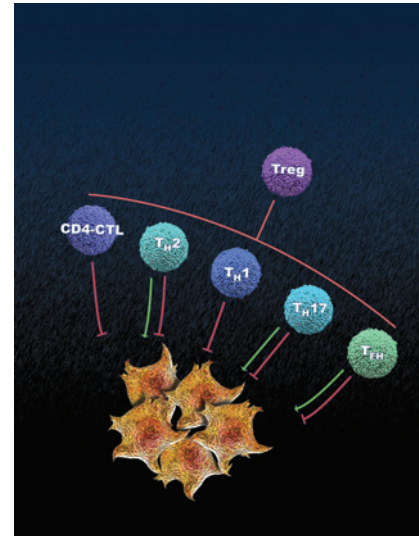
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## ABOUT THE COVER

The cover image is an artistic rendition of the complex biologic features of the CD4<sup>+</sup> T-cell lineage and their contribution to tumor immunity. In response to developmental and environmental cues, CD4<sup>+</sup> T cells differentiate into multiple subsets to orchestrate a broad range of effector activities during the initiation, expansion, and memory phase of a host immune response against pathogenic invasion, in regulating autoimmunity, and in shaping antitumor immunity.

Six major CD4<sup>+</sup> T-cell subsets have been characterized with antitumor and/or protumor activity: CD4-CTL and T<sub>H</sub>1 cells express immune molecules that promote tumor killing. T<sub>FH</sub>, T<sub>H</sub>2, and T<sub>H</sub>17 cells have both antitumor and protumor activities. FoxP3<sup>+</sup>CD4<sup>+</sup> regulatory T cells (Treg) are critically important for the maintenance of immune homeostasis and self-tolerance. However, tumor-induced factors promote the recruitment and expansion of Treg; intratumoral Treg suppress T-effector cell functions, impeding effective immunity against cancer, and high levels of CD4<sup>+</sup> Treg in tumors correlate with poor prognosis. For details, see Masters of Immunology primer by Kim and Cantor on page 91 of this issue.



## ABOUT THE MASTER

Harvey Cantor, MD, is the Baruj Benacerraf Professor of Microbiology and Immunobiology at Harvard Medical School and chair of the Department of Cancer Immunology and AIDS at the Dana-Farber Cancer Institute. Dr. Cantor's educational and practical training includes a BA from Columbia University and an MD from the New York University School of Medicine, 2 years of fellowship training at the NIH campus in Bethesda, Maryland, 2 years as an NIH Special Fellow at the National Institute for Medical Research in Mill Hill, London, and a residency in medicine at the Stanford University Hospital.

In the early 1970s, T cells were thought to be a homogenous population of lymphocytes that were not B cells. Dr. Cantor's studies indicated that the thymus gave rise to two major lineages of T cells (T-helper [T<sub>H</sub>] and T-cytotoxic [T<sub>C</sub>]), which recognized the MHC class II and class I molecules, respectively, and which were equipped to mediate distinct immunologic functions before overt encounter with antigen. These experiments were based on the idea that the pattern of proteins expressed on the cell surface could be used to separate and define the developmental and functional components of the immune system. The Cantor laboratory used this approach to dissect cell-mediated immunity into its cellular components, to isolate natural killer (NK) cells, and to correlate T-cell surface phenotype with function and MHC restriction at the clonal level.

Recent studies from the Cantor lab have begun to define a lineage of CD8<sup>+</sup> regulatory T cells (Treg) that are genetically programmed to inhibit the development of autoimmune disease and to regulate antitumor immunity via suppression of the activation and expansion of follicular helper T cells (T<sub>FH</sub>). The Cantor lab has defined an interaction between dendritic cells and T cells that regulates the differentiation of T<sub>H</sub> cell subsets after infection and have defined an inhibitory interaction between NK cells and autoreactive T cells that may regulate autoimmune disease.

Dr. Cantor is a member of the U.S. National Academy of Sciences and the American Academy of Arts and Sciences and a fellow of the American Association for the Advancement of Science. Many of the individuals he has mentored are now prominent immunologists, and several are members of the U.S. National Academy of Sciences and/or Institutes of Medicine, including Laurie Glimcher, professor of medicine and dean and provost of the Weill Cornell Medical College, Anjana Rao, professor at the La Jolla Institute for Allergy and Immunology, and Gary Nabel, past director of the NIH Vaccine Research Center and current Senior Vice President and Chief Scientific Officer of Sanofi.



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