

EDITORIAL

- 925 **A New *Cancer Immunology Research* Special Feature: Perspective from a Master of Immunology**

PERSPECTIVE FROM A MASTER OF IMMUNOLOGY

- 926 **The Path to Reactivation of Antitumor Immunity and Checkpoint Immunotherapy**
Hye-Jung Kim and Harvey Cantor

CANCER IMMUNOLOGY AT THE CROSSROADS: MICROBIOLOGY

- 937 **HPV Infection–Associated Cancers: Next-Generation Technology for Diagnosis and Treatment**
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PRIORITY BRIEF

- 943 **Assessment of MAGE-A Expression in Resected Non–Small Cell Lung Cancer in Relation to Clinicopathologic Features and Mutational Status of *EGFR* and *KRAS***
Maha Ayyoub, Lorenzo Memeo, Emilio Álvarez-Fernández, Cristina Colarossi, Rosario Costanzo, Eleonora Aiello, Daniela Martinetti, and Danila Valmori
Synopsis: Ayyoub and colleagues show that MAGE-A expression occurs primarily in squamous tumors and is correlated with high tumor grade and poorer survival, whereas *EGFR* and *KRAS* mutations occur in adenocarcinomas but not in squamous tumors, with *KRAS* mutations associated with early-stage disease and better survival.

RESEARCH ARTICLES

- 949 **A Feasibility Study of Cyclophosphamide, Trastuzumab, and an Allogeneic GM-CSF–Secreting Breast Tumor Vaccine for HER2⁺ Metastatic Breast Cancer**
Gang Chen, Richa Gupta, Silvia Petrik, Marina Laiko, James M. Leatherman, Justin M. Asquith, Maithili M. Daphtary, Elizabeth Garrett-Mayer, Nancy E. Davidson, Kellie Hirt, Maureen Berg, Jennifer N. Uram, Tianna Dausies, John Fetting, Elizabeth M. Duus, Saadet Atay-Rosenthal, Xiaobu Ye, Antonio C. Wolff, Vered Stearns, Elizabeth M. Jaffee, and Leisha A. Emens
Synopsis: Chen and colleagues show in patients and in a mouse model of HER2⁺ breast cancer that abrogating immune suppression with low-dose cyclophosphamide along with administration of an allogeneic GM-CSF–secreting HER2⁺ tumor vaccine and trastuzumab weekly augmented HER2-specific T-cell responses and survival.
- 962 **Association Studies of Fcγ Receptor Polymorphisms with Outcome in HER2⁺ Breast Cancer Patients Treated with Trastuzumab in NCCTG (Alliance) Trial N9831**
Nadine Norton, Rebecca M. Olson, Mark Pegram, Kathleen Tenner, Karla V. Ballman, Raphael Clynes, Keith L. Knutson, and Edith A. Perez
Synopsis: Norton, Olson, and colleagues found no differences in disease-free survival in trastuzumab-treated patients regardless of their FCGR2A and FCGR3A genotypes, but a significant difference between patients with FCGR2B variants, suggesting the functionality of FCGR2B may predict benefit to trastuzumab.
- 970 **Cytotoxic T Lymphocyte Antigen-4 Blockade Enhances Antitumor Immunity by Stimulating Melanoma-Specific T-cell Motility**
Tsvetelina Pentcheva-Hoang, Tyler R. Simpson, Welby Montalvo-Ortiz, and James P. Allison
Synopsis: Pentcheva-Hoang and colleagues analyzed melanoma-specific T-cell dynamics in tumors and tumor-draining lymph nodes before and after immune checkpoint blockade, and their study demonstrates that successful immunotherapy correlates with greater T-cell motility and reversal of the T-cell paralysis in growing tumors.

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- 981 Adjuvant Vaccine Immunotherapy of Resected, Clinically Node-Negative Melanoma: Long-term Outcome and Impact of HLA Class I Antigen Expression on Overall Survival**
William E. Carson III, Joseph M. Unger, Jeffrey A. Sosman, Lawrence E. Flaherty, Ralph J. Tuthill, Mark J. Porter, John A. Thompson, Raymond A. Kempf, Megan Othus, Antoni Ribas, and Vernon K. Sondak
Synopsis: A final report of trial S9035 by Carson and colleagues indicates a significant overall benefit from the lysed adjuvant vaccine melacrine for patients with stage II to IV melanoma with HLA A2 and/or HLA Cw3 serotypes, implicating interactions between HLA haplotype and clinical outcome.
- 988 A Transient Increase in Eosinophils Is Associated with Prolonged Survival in Men with Metastatic Castration-Resistant Prostate Cancer Who Receive Sipuleucel-T**
Douglas G. McNeel, Thomas A. Gardner, Celestia S. Higano, Philip W. Kantoff, Eric J. Small, Mark H. Wener, Robert B. Sims, Todd DeVries, Nadeem A. Sheikh, and Robert Dreicer
Synopsis: McNeel and colleagues demonstrate that a transient increase in eosinophil counts following sipuleucel-T treatment was associated with therapy-induced immune responses and longer prostate cancer survival, suggesting this could be prospectively evaluated as a biomarker in clinical trials.
- 1000 Phenotypic and Functional Activation of Hyporesponsive KIR^{neg}NKG2A^{neg} Human NK-Cell Precursors Requires IL12p70 Provided by Poly(I:C)-Matured Monocyte-Derived Dendritic Cells**
Shane A. Curran, Emanuela Romano, Michael G. Kennedy, Katharine C. Hsu, and James W. Young
Synopsis: Curran and colleagues show that IL12p70 from human DCs induces NK-cell precursors to transition from KIR/NKG2A-negative to positive and become functionally active, providing a rationale for generating donor NK cells against missing KIR ligands to enhance the graft-versus-leukemia effect after allogeneic HSCT.
- 1011 TGF β Inhibition Prior to Hypofractionated Radiation Enhances Efficacy in Preclinical Models**
Kristina H. Young, Pippa Newell, Benjamin Cottam, David Friedman, Talicia Savage, Jason R. Baird, Emmanuel Akporiaye, Michael J. Gough, and Marka Crittenden
Synopsis: Young and colleagues demonstrate in syngeneic mouse models of colorectal and pancreatic cancers that TGF β inhibition with the oral, small-molecule inhibitor SM16 enhanced adaptive immunity in the tumor microenvironments and significantly improved the efficacy of subsequent radiotherapy.

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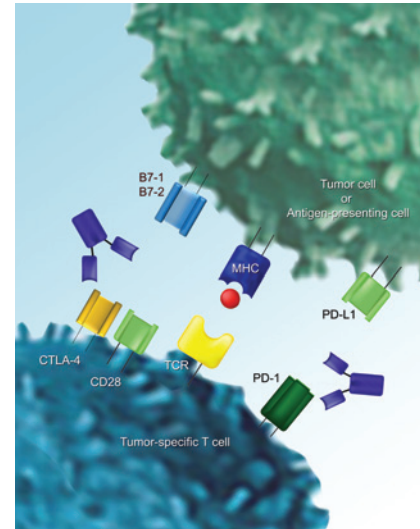
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ABOUT THE COVER

Cancer immunology research on the fundamental elements of T-cell and NK-cell biology, including the mechanistic basis of antigen recognition, activation, proliferation, and survival, and the signaling pathways that govern immunity against tumors, has informed the design of therapeutic approaches to augment the body's natural anticancer immune response. Each T cell expresses a unique receptor that recognizes a specific antigen in the context of a specific MHC on a target cell. Engagement of a TCR by an MHC-peptide complex transmits a signal (signal 1) that is not sufficient to promote an effective T-cell response. Sensitivity of T-cell recognition is refined by binding of CD4 and CD8 coreceptors expressed by two major T-cell lineages: CD4 expressed by T-helper cells and CD8 expressed by cytotoxic T cells. However, coreceptor engagement is necessary but not sufficient to provoke full T-cell activation and acquisition of effector function, which requires signals transduced by costimulatory receptors (signal 2). CD28-B7-1/B7-2 interaction delivers an activation signal while CTLA-4-B7-1/B7-2 interaction delivers an inhibitory signal, and the balance of these signals is critical for the development and function of both CD4 T-effector cells and T-regulatory (Treg) cells. Inflammatory signals often induce upregulation of cell surface receptors including PD-1 (signal 3). Integration of a complex set of signals delivered by costimulatory and coinhibitory receptors expressed by T cells is essential for robust and appropriate T-cell responses. Expression of PD-1 by T-effector cells is associated with an exhausted phenotype in T cells during infection and cancer, while PD-1/PD-L1 interactions have been implicated in the generation of peripherally derived Treg. Preclinical and clinical data from checkpoint blockade using anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies suggest that increased antitumor immunity may be achieved by the combined effects of enhanced T-effector activity and depletion of suppression by CD4 Treg. The cover shows some of the key components regulating T-cell antitumor immunity that have provided the foundation for current strategies of checkpoint immunotherapy. For details see the Perspective from a Master of Immunology by Hye-Jung Kim and Harvey Cantor on page 926 of this issue.



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