

MASTERS OF IMMUNOLOGY

- 1** **Eosinophils and Cancer**
Benjamin P. Davis and Marc E. Rothenberg



CANCER IMMUNOLOGY AT THE CROSSROADS: MICROBIOLOGY

- 9** **Pathogen-Driven Cancers and Emerging Immune Therapeutic Strategies**
Natalie Vandeven and Paul Nghiem

CANCER IMMUNOLOGY MINIATURE

- 15** **Anti-PD1 Following Ipilimumab for Mucosal Melanoma: Durable Tumor Response Associated with Severe Hypothyroidism and Rhabdomyolysis**
Le Min and F. Stephen Hodi
Synopsis: Min and Hodi report that a patient with metastatic mucosal melanoma that was resistant to temozolomide and ipilimumab has experienced a durable near complete response to MK-3475 anti-PD1 therapy with associated autoimmune-related adverse events.

PRIORITY BRIEF

- 19** **Role of Crosslinking for Agonistic CD40 Monoclonal Antibodies as Immune Therapy of Cancer**
Lee P. Richman and Robert H. Vonderheide
Synopsis: In a comprehensive analysis of the agonistic activity of anti-human CD40 mAb CP-870,893, Richman and Vonderheide show that Fc-crosslinking of CP-870,893 is not required. In contrast, the therapeutic potency is more dependent on the CD40 epitopes recognized.

RESEARCH ARTICLES

- 27** **Regression of Metastatic Merkel Cell Carcinoma Following Transfer of Polyomavirus-Specific T Cells and Therapies Capable of Reinducing HLA Class-I**
Aude G. Chapuis, Olga K. Afanasiev, Jayasri G. Iyer, Kelly G. Paulson, Upendra Parvathaneni, Joo Ha Hwang, Ivy Lai, Ilana M. Roberts, Heather L. Sloan, Shailender Bhatia, Kendall C. Shibuya, Ted Gooley, Cindy Desmarais, David M. Koelle, Cassian Yee, and Paul Nghiem
Synopsis: Chapuis, Afanasiev, and colleagues show that the combined regimen of local tumor-targeted preconditioning and systemic immune therapies elicited a durable complete response in two of three lesions with a prolonged period without development of additional distant metastasis.
- 37** **Epigenetic Potentiation of NY-ESO-1 Vaccine Therapy in Human Ovarian Cancer**
Kunle Odunsi, Junko Matsuzaki, Smitha R. James, Paulette Mhaweche-Faucegla, Takemasa Tsuji, Austin Miller, Wa Zhang, Stacey N. Akers, Elizabeth A. Griffiths, Anthony Miliotto, Amy Beck, Carl A. Batt, Gerd Ritter, Shashikant Lele, Sacha Gnjatich, and Adam R. Karpf
Synopsis: Odunsi and colleagues show that the DNA methyltransferase inhibitor decitabine augmented the efficacy of the NY-ESO-1 vaccine and doxorubicin treatment of patients with refractory epithelial ovarian cancer, demonstrating the potential of the combined chemo-immunotherapy regimen.
- 50** **Myeloid-Derived Suppressor Cells in the Development of Lung Cancer**
Myrna L. Ortiz, Lily Lu, Indu Ramachandran, and Dmitry I. Gabrilovich
Synopsis: Using mouse models of lung cancer, Ortiz and colleagues show that immature myeloid cells with the phenotype of myeloid-derived suppressive cells but lacking immune suppressive activity accumulate during lung inflammation and may contribute to cancer development.
- 59** **iNKT Cell Cytotoxic Responses Control T-Lymphoma Growth *In Vitro* and *In Vivo***
Hamid Bassiri, Rupali Das, Peng Guan, David M. Barrett, Patrick J. Brennan, Pinaki P. Banerjee, Susan J. Wiener, Jordan S. Orange, Michael B. Brenner, Stephan A. Grupp, and Kim E. Nichols
Synopsis: Bassiri and colleagues demonstrate that the cytotoxic responses of invariant natural killer T (iNKT) cells are sufficient to limit the growth of T lymphomas, highlighting the potential utility of iNKT cells in the immunotherapy of CD1d⁺ cancers.

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TUMOR EOSINOPHILIA

70 Paradoxical Activation of T Cells via Augmented ERK Signaling Mediated by a RAF Inhibitor

Margaret K. Callahan, Gregg Masters, Christine A. Pratilas, Charlotte Ariyan, Jessica Katz, Shigehisa Kitano, Valerie Russell, Ruth Ann Gordon, Shachi Vyas, Jianda Yuan, Ashok Gupta, Jon M. Wigginton, Neal Rosen, Taha Merghoub, Maria Jure-Kunkel, and Jedd D. Wolchok

Synopsis: Callahan and colleagues show that RAF inhibitors can potentiate T-cell activation by increasing T-cell expansion and ERK signaling, and when combined with CTLA-4 blockade show superior tumor control in two transplantable mouse tumor models.

80 Locally Delivered CD40 Agonist Antibody Accumulates in Secondary Lymphoid Organs and Eradicates Experimental Disseminated Bladder Cancer

Linda C. Sandin, Anna Orlova, Erika Gustafsson, Peter Ellmark, Vladimir Tolmachev, Thomas H. Tötterman, and Sara M. Mangsbo

Synopsis: Comparing the efficacy and biodistribution of local and systemic delivery of anti-CD40 agonistic antibodies, Sandin and colleagues show that local low-dose antibody therapy is effective against disseminated bladder cancer with reduced toxic side effects.



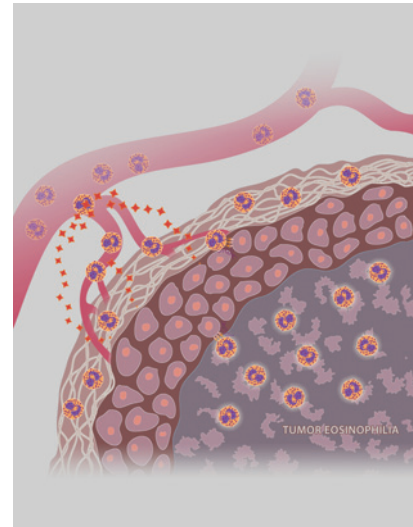
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ABOUT THE COVER

The cover image is an artistic rendition of tumor eosinophilia. Eosinophils are granulocytic leukocytes derived from bone marrow hematopoietic progenitors. Mature eosinophils, characterized by their large cytoplasmic secretory granules, are stimulated by inflammatory mediators and tumor-associated cytokines and chemokines (orange stars/diamonds). Upon activation, they enter the blood stream, migrate to, and infiltrate both the necrotic core (lower right) and fibrous capsules of tumors. Known tumor-associated cytokines and chemokines related to eosinophil accumulation include IL-2, IL-3, IL-5, IL-25, GM-CSF, eotaxin-1, and HMGB1. Cellular contact is mediated by CD11a/CD18 and 2B4 and likely by NKG2D. Eosinophils secrete a wide variety of molecules important for their function, including cytokines, chemokines, lipid mediators, neurotransmitters, DNA traps, and cytotoxic granule proteins ECP, EDN, EPO, and MBP. For details, see the Masters of Immunology primer by Davis and Rothenberg on page 1 of this issue.



ABOUT THE MASTER

Marc E. Rothenberg, MD, PhD, is a professor of pediatrics at the University of Cincinnati College of Medicine and the director of the Division of Allergy and Immunology at the Cincinnati Children's Hospital Medical Center. He graduated summa cum laude in chemistry and biochemistry from Brandeis University and received his MD/PhD degree from Harvard Medical School (HMS). His PhD thesis work was on eosinophil hematopoiesis in Dr. Frank Austen's laboratory, where he developed the first culture system for human eosinophils. Dr. Rothenberg completed residency training in pediatrics and a combined fellowship in allergy/immunology and hematology at the Boston Children's Hospital and HMS. His postdoctoral training was in Dr. Philip Leder's laboratory, where he cloned the gene encoding the eotaxin chemokine. At the University of Cincinnati Children's Hospital, he has helped to build a premier program in pediatric research, with his division a leader in pediatric allergy and immunology. Dr. Rothenberg's research program is focused on the molecular mechanisms of allergic disorders. He directs the Cincinnati Center for Eosinophilic Disorders, where he sees patients with allergic and immunologic diseases from around the world.

Dr. Rothenberg has received many honors, including the Pharmacia Allergy Research Foundation Award for the best young investigator in the allergy field; the American Academy of Allergy, Asthma, and Immunology Young Investigator and Scholar in Allergy Awards; the Ohio Governor's Recognition Award; and the 2007 Society of Pediatric Research E. Mead Johnson Award. He is an elected member of the American Society of Clinical Investigation, the Association of American Physicians, and the Society for Pediatric Research and a Diplomate of the American Academy of Allergy, Asthma, and Immunology. Dr. Rothenberg has published over 250 articles on the molecular mechanisms of allergic responses and edited a book entitled *Chemokines in Allergic Disease*. He has served on various review panels for journals and funding agencies, including the Advisory Council of the NIAID, the Burroughs Trust, and the Medical Research Council of the UK. His research has been supported by the NIH, the U.S. Department of Defense, the Human Frontier Science Program Organization, the Burroughs Wellcome Fund, the Dana Foundation, and the Food Allergy and Anaphylaxis Network.



Cancer Immunology Research

2 (1)

Cancer Immunol Res 2014;2:1-90.

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