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CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 598 **Hostile, Hypoxia–A2-Adenosinergic Tumor Biology as the Next Barrier to Overcome for Tumor Immunologists**
 Michail V. Sitkovsky, Stephen Hatfield, Robert Abbott, Bryan Belikoff, Dmitriy Lukashev, and Akio Ohta

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- 606 **The Second Annual AACR–Cancer Research Institute Lloyd J. Old Award in Cancer Immunology**

PRIORITY BRIEF

- 610 **A Soluble Form of CD80 Enhances Antitumor Immunity by Neutralizing Programmed Death Ligand-1 and Simultaneously Providing Costimulation**
 Samuel T. Haile, Lucas A. Horn, and Suzanne Ostrand-Rosenberg
Synopsis: Haile and colleagues report that CD80-Fc effectively maintained PD-1⁺ T-cell activation and IFN γ production by blocking PD-L1-mediated immune suppression and costimulating CD28, and suggest the development of CD80-Fc as a therapeutic agent.

RESEARCH ARTICLES

- 616 **Immunotherapy Converts Nonimmunogenic Pancreatic Tumors into Immunogenic Foci of Immune Regulation**


Eric R. Lutz, Annie A. Wu, Elaine Bigelow, Rajni Sharma, Guanglan Mo, Kevin Soares, Sara Solt, Alvin Dorman, Anthony Wamwea, Allison Yager, Daniel Laheru, Christopher L. Wolfgang, Jiang Wang, Ralph H. Hruban, Robert A. Anders, Elizabeth M. Jaffee, and Lei Zheng
Synopsis: Lutz and colleagues show that an allogeneic vaccine given with or without low-dose cyclophosphamide converted pancreatic cancer into an immunogenic cancer with infiltrating effector lymphocytes and formation of tertiary lymphoid aggregates that are regulatory structures of adaptive immunity.

- 632 **Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma**

F. Stephen Hodi, Donald Lawrence, Cecilia Lezcano, Xinqi Wu, Jun Zhou, Tetsuro Sasada, Wanyong Zeng, Anita Giobbie-Hurder, Michael B. Atkins, Nageatte Ibrahim, Philip Friedlander, Keith T. Flaherty, George F. Murphy, Scott Rodig, Elsa F. Velazquez, Martin C. Mihm Jr, Sara Russell, Pamela J. DiPiro, Jeffrey T. Yap, Nikhil Ramaiya, Annick D. Van den Abbeele, Maria Gargano, and David McDermott
Synopsis: Hodi and colleagues report the safety and efficacy of targeting angiogenesis and CTLA-4 in a phase I trial of 46 patients with metastatic melanoma, which revealed the influence of VEGF-A blockade on inflammation, lymphocyte trafficking, and immune regulation, and their synergistic therapeutic effects.

- 643 **Response to BRAF Inhibition in Melanoma Is Enhanced When Combined with Immune Checkpoint Blockade**

Zachary A. Cooper, Vikram R. Juneja, Peter T. Sage, Dennie T. Frederick, Adriano Piris, Devarati Mitra, Jennifer A. Lo, F. Stephen Hodi, Gordon J. Freeman, Marcus W. Bosenberg, Martin McMahon, Keith T. Flaherty, David E. Fisher, Arlene H. Sharpe, and Jennifer A. Wargo
Synopsis: Cooper, Juneja, Sage, and colleagues show that combining BRAF and PD-1/PD-L1 blockade slowed tumor growth and prolonged survival in a melanoma mouse model, with increased number and activity of tumor-infiltrating lymphocytes similar to that in a human melanoma patient treated with this regimen.

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- 655** **The Tumor Microenvironment Shapes Lineage, Transcriptional, and Functional Diversity of Infiltrating Myeloid Cells**
 Kutlu G. Elpek, Viviana Cremasco, Hua Shen, Christopher J. Harvey, Kai W. Wucherpennig, Daniel R. Goldstein, Paul A. Monach, and Shannon J. Turley
Synopsis: Elpek and colleagues analyzed the developmental and transcriptomic signatures of infiltrating myeloid cells in three mouse tumor models and report that tumor-associated macrophages and neutrophils exhibited different frequencies, gene expression profiles, and functions dependent on cancer types but not locations.
- 668** **Intralesional Treatment of Stage III Metastatic Melanoma Patients with L19–IL2 Results in Sustained Clinical and Systemic Immunologic Responses**
Benjamin Weide, Thomas K. Eigentler, Annette Pflugfelder, Henning Zelba, Alexander Martens, Graham Pawelec, Leonardo Giovannoni, Pier Adelchi Ruffini, Giuliano Elia, Dario Neri, Ralf Gutzmer, Jürgen C. Becker, and Claus Garbe
Synopsis: Weide and colleagues show that intralesional therapy using the immunocytokine L19–IL2 elicited a high rate of clinical and systemic immune responses in patients with stage III melanoma and report their observation of favorable distant metastasis-free and overall survival in these patients after treatment.
- 679** **ERK-Dependent Downregulation of the Atypical Chemokine Receptor D6 Drives Tumor Aggressiveness in Kaposi Sarcoma**
Benedetta Savino, Nicoletta Caronni, Achille Anselmo, Fabio Pasqualini, Elena Monica Borroni, Gianluca Basso, Giuseppe Celesti, Luigi Laghi, Athanasia Tournalaki, Vinicio Boneschi, Lucia Brambilla, Manuela Nebuloni, Gianluca Vago, Alberto Mantovani, Massimo Locati, and Raffaella Bonecchi
Synopsis: Savino, Caronni, and colleagues report that D6 expression was inversely correlated with increased tumor-associated M2-macrophages and aggressiveness in ERK pathway-activated Kaposi sarcoma (KS), and suggest targeting of CCR2 and the ERK pathway as a therapeutic option for patients with KS.
- 690** **Programmed Cell Death Ligand 1 Expression in Osteosarcoma**
Jacson K. Shen, Gregory M. Cote, Edwin Choy, Pei Yang, David Harmon, Joseph Schwab, G. Petur Nielsen, Ivan Chebib, Soldano Ferrone, Xinhui Wang, Yangyang Wang, Henry Mankin, Francis J. Hornicek, and Zhenfeng Duan
Synopsis: Shen, Cote, and colleagues developed a quantitative RNA-based PD-L1 assay and report PD-L1 expression in 84% of human osteosarcomas, of which 24% were at high levels and correlated with TILs, indicating that this subset of patients may benefit from anti-PD-L1 immunotherapy.
- CORRECTION**
- 699** **Correction: Oncolytic Viruses and Their Application to Cancer Immunotherapy**

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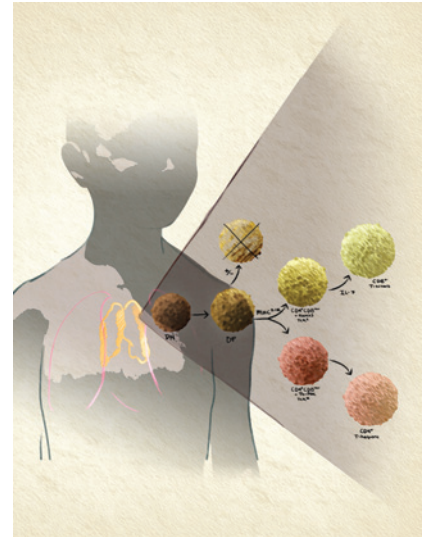
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ABOUT THE COVER

The thymus is required for the generation of a normal adaptive immune system; thymocyte development and selection are essentially complete prior to sexual maturity. T cells that leave the thymus can recognize peptides presented by the body's class I or class II major histocompatibility complex (MHC^{I/II}). The ordered stages of intrathymic T-cell development include double negative (DN; CD4⁻CD8⁻) → double positive (DP; CD4⁺CD8⁺) → transitional (CD4⁺CD8^{low}) → CD8⁺ T-killer cells or CD4⁺ T-helper cells. T-cell receptors for MHC^{I/II} (TCR^I or TCR^{II}) are expressed on DP thymocytes, which are selected upon encounter with the appropriate MHC molecules. DP cells with TCRs that are not selected for binding to the body's peptides plus MHC^{I/II} die from "neglect" in the cortex. Thymocytes with too high an affinity for peptides plus MHC^{I/II} die from "negative selection" in the cortex and medulla. In a healthy person, only ~2% of newly generated thymocytes exit the thymus daily; the rest die *in situ* during various stages of development. If the transitional (CD4⁺CD8^{low}) thymocyte expresses TCR^{II}, interaction with CD4 and MHC^{II} will activate transcription factor Th-POK to generate CD4⁺ T-helper cells. If the transitional (CD4⁺CD8^{low}) thymocyte expresses TCR^I, the weak binding of TCR^I and downregulated CD8 with thymic MHC^I in the presence of IL7 will cause coreceptor reversal, i.e. the cell expresses transcription factor RUNX3, which silences the transcription of CD4 and antagonizes Th-POK, enabling the development of CD8⁺ T-killer cells. For details of thymocyte development, see the Masters of Immunology primer by Harald von Boehmer on page 592 of this issue.



ABOUT THE MASTER

Harald von Boehmer, MD, PhD, is a professor emeritus at the Dana-Farber Cancer Institute (DFCI) and Harvard Medical School (HMS), an adjunct professor at the University of Florida, and a visiting professor in the Institute for Immunology at the Ludwig-Maximilian University of Munich, Germany, where he received his MD in 1968. He subsequently earned a PhD in 1974 from the University of Melbourne, Australia, under the tutelage of Dr. Ken Shortman. Dr. von Boehmer was a member of the Basel Institute for Immunology in Switzerland until 1996, before becoming the director of Unité INSERM 373 at the René Descartes University in Paris, France. He was recruited to join the faculty at DFCI-HMS in 1999, where he served as chief of the Laboratory for Lymphocyte Biology in the DFCI Department of Cancer Immunology and AIDS and a faculty member of the HMS Department of Microbiology and Immunobiology.

The von Boehmer laboratory has contributed significantly to our understanding of T-cell development and its roles in immune responses. Dr. von Boehmer discovered the pre-TCR, cloned the pre-TCR α gene, and defined its role in TCR β allelic exclusion. Using gene transfer of the TCR, he characterized TCR contribution to recognition by T cells of peptide-MHC complexes. Through analysis of TCR transgenic mice, his favorite experiments, he delineated the role of negative selection in the thymus of developing T cells by peptide-MHC complexes to generation of self-tolerance. He elucidated mechanisms of positive selection in intrathymic generation of CD8⁺ killer cells, CD4⁺ helper cells, and FoxP3-expressing CD4⁺ regulatory cells. His studies on TCR-signaling pathways that permit conversion of naïve T cells into regulatory T cells *in vivo* have been used to establish antigen-specific tolerance to insulin and prevention of type 1 diabetes. He described the contribution of T-cell development to acute lymphoblastic T-cell leukemia. In particular, his studies of TCR signaling and Notch signaling revealed that T-cell lineage commitment is instructed by the intensity of TCR signals, and that Notch signaling is mandatory for the generation of $\alpha\beta$ but not $\gamma\delta$ lineage T cells.

Dr. von Boehmer was born in Guben, Germany; he is an accomplished cellist and has performed with orchestras in Goettingen and Freiburg. His many honors include the Louis-Jeantet Prize for Medicine, jointly with Nicole Le Douarin and Gottfried Schatz (1990), the Avery-Landsteiner prize of the German Society for Immunology (1990), the Paul Ehrlich and Ludwig Darmstadter Prize for Immunology (1993), the Kurt A. Korber Prize for European Science (1997), and most recently the Helmholtz International Fellow Award (2013). He also received an honorary medical degree from the Technical University of Munich (2002). Dr. von Boehmer is an elected member of the Academia Europaea (1990), the Institut Universitaire de France (1997), and the German Academy of Sciences Leopoldina (2003).



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