


MASTERS OF IMMUNOLOGY

- 575** NKG2D Receptor and Its Ligands in Host Defense
 Lewis L. Lanier

CANCER IMMUNOLOGY AT THE CROSSROADS: COMPLEMENTARY THERAPEUTIC MODALITIES

- 583** Targeting Heat-Shock Protein 90 (HSP90) as a Complementary Strategy to Immune Checkpoint Blockade for Cancer Therapy
 David A. Proia and Gunnar F. Kaufmann

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- 590** Special Conference on Tumor Immunology and Immunotherapy: A New Chapter
 Katelyn T. Byrne, Robert H. Vonderheide, Elizabeth M. Jaffee, and Todd D. Armstrong

CANCER IMMUNOLOGY MINIATURES

- 598** Ipilimumab-Induced Encephalopathy with a Reversible Splenic Lesion
 Robert M. Conry, Joseph C. Sullivan, and Louis B. Nabors III
Synopsis: Conry and colleagues report two novel immune-related adverse events—encephalopathy with a reversible splenic lesion and neurogenic bladder—in a patient with stage IV melanoma treated with ipilimumab, which were resolved completely with high-dose methylprednisolone.




PRIORITY BRIEF

- 602** BRAF^{V600E} Co-opts a Conserved MHC Class I Internalization Pathway to Diminish Antigen Presentation and CD8⁺ T-cell Recognition of Melanoma
 Sherille D. Bradley, Zeming Chen, Brenda Melendez, Amjad Talukder, Jahan S. Khalili, Tania Rodriguez-Cruz, Shujuan Liu, Mayra Whittington, Wanleng Deng, Fenge Li, Chantale Bernatchez, Laszlo G. Radvanyi, Michael A. Davies, Patrick Hwu, and Gregory Lizée
Synopsis: Bradley, Chen, and colleagues show that BRAF^{V600E}-induced internalization of MHC class I and its sequestration within endolysosomal compartments can be reversed by MAP kinase inhibitors, demonstrating a direct link between oncogenic activation of the MAPK pathway and MHC class I trafficking and localization.

RESEARCH ARTICLES

- 610** PD-1 Restrains Radiotherapy-Induced Abscopal Effect
 Sean S. Park, Haidong Dong, Xin Liu, Susan M. Harrington, Christopher J. Krco, Michael P. Grams, Aaron S. Mansfield, Keith M. Furutani, Kenneth R. Olivier, and Eugene D. Kwon
Synopsis: Park, Dong, and colleagues show in mouse models of melanoma and renal cell carcinoma that stereotactic ablative radiotherapy synergized with PD-1 blockade to induce near-complete regression of the irradiated tumors, and a tumor-specific 66% reduction in the nonirradiated tumors outside the radiation field.
- 620** PD-1⁺Tim-3⁺ CD8⁺ T Lymphocytes Display Varied Degrees of Functional Exhaustion in Patients with Regionally Metastatic Differentiated Thyroid Cancer
 Jill J. Severson, Hilary S. Serracino, Valerica Mateescu, Christopher D. Raeburn, Robert C. McIntyre Jr, Sharon B. Sams, Bryan R. Haugen, and Jena D. French
Synopsis: Severson and colleagues show that exhaustion of PD-1⁺ T cells in tumor-involved lymph nodes from patients with metastatic differentiated thyroid cancer was not complete. While PD-1⁺CD8⁺ T cells were variably dysfunctional in their ability to produce cytokines, their proliferative capacity was maintained, and PD-1⁺CD4⁺ T cells remained functional.
- 631** Robust Antitumor Effects of Combined Anti-CD4-Depleting Antibody and Anti-PD-1/PD-L1 Immune Checkpoint Antibody Treatment in Mice
 Satoshi Ueha, Shoji Yokochi, Yoshiro Ishiwata, Haru Ogiwara, Krishant Chand, Takuya Nakajima, Kosuke Hachiga, Shigeyuki Shichino, Yuya Terashima, Etsuko Toda, Francis H.W. Shand, Kazuhiro Kakimi, Satoru Ito, and Kouji Matsushima
Synopsis: Ueha, Yokochi, Ishiwata, and colleagues show in three mouse tumor models that CD4 depletion led to tumor-specific CTL proliferation in the draining lymph node and increased tumor infiltration of PD-1⁺CD8⁺ T cells; it also synergized with PD-1/PD-L1 blockade to suppress tumor growth and prolong survival.

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- 641** **A Rapid Embryonic Stem Cell–Based Mouse Model for B-cell Lymphomas Driven by Epstein–Barr Virus Protein LMP1**
 Zhaoqing Ba, Fei-Long Meng, Monica Gostissa, Pei-Yi Huang, Qiang Ke, Zhe Wang, Mai N. Dao, Yuko Fujiwara, Klaus Rajewsky, Baochun Zhang, and Frederick W. Alt
Synopsis: Ba, Meng, Gostissa, and colleagues developed an ES cell/RAG2-deficient blastocyst complementation-based model for Epstein–Barr virus protein LMP1-driven B-cell lymphomas that allows rapid analyses of genetic alterations that cooperate with LMP1 to promote lymphomagenesis and immunotherapeutic strategies.
- 650** **Mass Cytometry Analysis Shows That a Novel Memory Phenotype B Cell Is Expanded in Multiple Myeloma**
 Leo Hansmann, Lisa Blum, Chia-Hsin Ju, Michaela Liedtke, William H. Robinson, and Mark M. Davis
Synopsis: Hansmann and colleagues used cytometry by time-of-flight (CyTOF) and next-generation sequencing to detect cancer-associated immune phenotypes in human peripheral blood on a single-cell level, leading to identification of an expanded novel memory B-cell phenotype in multiple myeloma.
- 661** **Fine-tuning Tumor Immunity with Integrin Trans-regulation**
Joseph M. Cantor, David M. Rose, Marina Slepak, and Mark H. Ginsberg
Synopsis: Cantor and colleagues created an $\alpha 4$ (S988A) integrin-bearing mouse, which precludes PKA-mediated $\alpha 4$ phosphorylation, and showed that manipulating the signaling properties of $\alpha 4$ integrins can selectively enhance T-cell entry, but not myeloid-cell entry, into B16 melanomas, thereby limiting tumor growth.
- 668** **Generation of Mouse Pluripotent Stem Cell–Derived Proliferating Myeloid Cells as an Unlimited Source of Functional Antigen-Presenting Cells**
Rong Zhang, Tian-Yi Liu, Satoru Senju, Miwa Haruta, Narumi Hirotsawa, Motoharu Suzuki, Minako Tatsumi, Norihiro Ueda, Hiroyuki Maki, Ryusuke Nakatsuka, Yoshikazu Matsuoka, Yutaka Sasaki, Shinobu Tsuzuki, Hayao Nakanishi, Ryoko Araki, Masumi Abe, Yoshiki Akatsuka, Yasushi Sakamoto, Yoshiaki Sonoda, Yasuharu Nishimura, Kiyotaka Kuzushima, and Yasushi Uemura
Synopsis: Zhang and colleagues transduced c-Myc into mouse iPSC (induced pluripotent stem cells) to generate proliferating myeloid cells that propagate in a cytokine-dependent manner while retaining their potential to differentiate into functional antigen-presenting cells that stimulate tumor antigen-specific T-cell responses.
- 678** **Cross-Presentation of the Oncofetal Tumor Antigen 5T4 from Irradiated Prostate Cancer Cells—A Key Role for Heat-Shock Protein 70 and Receptor CD91**
Josephine Salimu, Lisa K. Spary, Saly Al-Taei, Aled Clayton, Malcolm D. Mason, John Staffurth, and Zsuzsanna Tabi
Synopsis: Salimu and colleagues show that preexisting tumor antigen-specific T cells can be reactivated as a consequence of radiotherapy and demonstrate the crucial role that Hsp70, rather than TLR4, plays in antigen cross-presentation from irradiated tumor cells.
- 689** **Antibody Blockade of Semaphorin 4D Promotes Immune Infiltration into Tumor and Enhances Response to Other Immunomodulatory Therapies**
 Elizabeth E. Evans, Alan S. Jonason Jr, Holm Bussler, Sebold Torno, Janaki Veeraraghavan, Christine Reilly, Michael A. Doherty, Jennifer Seils, Laurie A. Winter, Crystal Mallow, Renee Kirk, Alan Howell, Susan Giralico, Maria Scrivens, Katya Klimatcheva, Terrence L. Fisher, William J. Bowers, Mark Paris, Ernest S. Smith, and Maurice Zauderer
Synopsis: Evans and colleagues describe a novel immunomodulatory function of semaphorin 4D (SEMA4D) and show that blocking SEMA4D enhances immune infiltration into tumor and increases antitumor activity in synergy with other immunomodulatory therapies.

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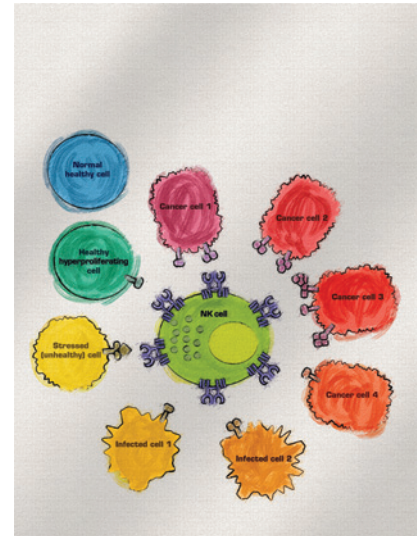
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ABOUT THE COVER

NKG2D is an activating receptor expressed on the surface of natural killer (NK) cells, CD8⁺ T cells, subsets of CD4⁺ T cells, invariant NKT cells, and $\gamma\delta$ T cells. NKG2D transmits signals by its association with the adapter subunits. Although NKG2D is encoded by a highly conserved gene (*KLRK1*) with limited polymorphism, the receptor recognizes an extensive repertoire of molecules, including eight ligands in humans, some of which exhibit extensive allelic polymorphism, and nine ligands in mice. In general, healthy adult tissues do not express NKG2D ligands on the cell surface, but these ligands can be induced by hyperproliferation, transformation, and infection. Thus, the NKG2D pathway serves as a mechanism for the immune system to detect and eliminate cells that have undergone "stress." Viruses and tumor cells have devised strategies to evade detection by the NKG2D surveillance system, and diversification of the NKG2D ligand genes likely has been driven by selective pressures imposed by pathogens. For details, see the Masters of Immunology article by Lewis L. Lanier that begins on page 575 of this issue.



ABOUT THE MASTER

Lewis L. Lanier, PhD, is an American Cancer Society Professor and the J. Michael Bishop Distinguished Professor and chair of Microbiology and Immunology at the University of California San Francisco (UCSF). He leads the Cancer, Immunity, and Microenvironment Program of the UCSF Helen Diller Comprehensive Cancer Center. Dr. Lanier is a pioneer in the study of natural killer (NK) cells. He identified a subset of human lymphocytes with the innate capacity to kill tumor cells and infected cells, which he hypothesized as a third lymphocyte lineage, and began to study their biology before NK cells were fashionable. He showed that these cells express surface markers CD56 and CD16, and that the CD16 Fc receptor mediates antibody-dependent cellular cytotoxicity. The Lanier group has identified and characterized many of the activating and inhibitory NK-cell surface receptors and their ligands. In addition, they discovered the immunotyrosine-based activation motif (ITAM)-bearing DAP12 adaptor molecule that signals for NK-cell receptors and the NKG2D/DAP10 receptor complex in mice and humans. They also showed that many of these NK receptors are present on T cells and modulate T-cell function. Dr. Lanier and his research group continue to study NK cells, a component of innate immune surveillance that recognizes and eliminates cells that have become transformed or infected by viruses.



In recognition of his scientific contributions, Dr. Lanier was awarded the William B. Coley Award for Distinguished Research in Basic Tumor Immunology from the Cancer Research Institute in 2002. In 2005 he received the Rose Payne Award for his contributions to immunogenetics from the American Society for Histocompatibility and Immunogenetics. In 2010 he was elected to the U.S. National Academy of Sciences; in 2011 he became a fellow of the American Academy of Microbiology and was elected to the American Academy of Arts and Sciences. He received the 2001 Distinguished Service Award from the American Association of Immunologists (AAI) and served as AAI president from 2006 to 2007. He has published more than 400 scientific articles and is on the editorial boards of leading peer-reviewed journals. Dr. Lanier serves on the Scientific Advisory Board of several pharmaceutical and biotechnology companies and research institutes. (Continued on the following page.)

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ABOUT THE MASTER

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Dr. Lanier was born in Memphis, Tennessee. He graduated with high honors in biology (microbiology) from Virginia Polytechnic Institute and State University and received his PhD in microbiology and immunology from the University of North Carolina (UNC) Chapel Hill. He began his postdoctoral training at the Lineberg Cancer Center at UNC Chapel Hill and continued as a Damon Runyon-Walter Winchell Cancer Research Fellow at the University of New Mexico. He joined the Research and Development Department at the Becton Dickinson Monoclonal Center in Mountain View, California, where he advanced to Associate Director of Research. In 1990, he joined the DNAX Research Institute of Molecular and Cellular Biology in Palo Alto and later became its Director of Immunobiology. In 1999, he joined the faculty of UCSF, where he became chair of Microbiology and Immunology in 2010. Dr. Lanier is an avid sailor who skippers a sailboat racing team on San Francisco Bay. He is also a music aficionado. As the keynote speaker at the Harvard Medical School (HMS) Immunology program retreat in 2014, he impressed young immunologists with his performance of a rap version of The Band's 1968 classic hit song "The Weight" accompanied by the HMS Immunology house band, Captain Fred and The Pogies.

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