

MASTERS OF IMMUNOLOGY

- 1023** **The Immunological Synapse**
Michael L. Dustin



CANCER IMMUNOLOGY AT THE CROSSROADS: PUBLIC/PRIVATE PARTNERSHIP

- 1034** **Prostate Cancer Immunotherapy: Beyond Immunity to Curability**
Jonathan W. Simons

PRIORITY BRIEF

- 1044** **BRAF Inhibition Alleviates Immune Suppression in Murine Autochthonous Melanoma**
Shannon M. Steinberg, Peisheng Zhang, Brian T. Malik, Andrea Boni, Tamer B. Shabaneh, Katelyn T. Byrne, David W. Mullins, Constance E. Brinckerhoff, Marc S. Ernstoff, Marcus W. Bosenberg, and Mary Jo Turk
Synopsis: Steinberg and colleagues show that the BRAF-inhibitor PLX4720 enhanced intratumoral Treg apoptosis and decreased both the proportion and the per-cell immunosuppressive function of MDSCs, thus informing the design of combinatorial therapies for melanoma.

CANCER IMMUNOLOGY MINIATURES

- 1051** **Immune Activation and a 9-Year Ongoing Complete Remission Following CD40 Antibody Therapy and Metastasectomy in a Patient with Metastatic Melanoma**
David L. Bajor, Xiaowei Xu, Drew A. Torigian, Rosemarie Mick, Laura R. Garcia, Lee P. Richman, Cindy Desmarais, Katherine L. Nathanson, Lynn M. Schuchter, Michael Kalos, and Robert H. Vonderheide
Synopsis: Bajor and colleagues used next-generation sequencing of TCRs in the tumor and blood to identify the emergence and persistence of a de novo T-cell repertoire following agonistic CD40 therapy, highlighting the potential of immune agonists in therapy and TCR deep sequencing in immune assessment.

RESEARCH ARTICLES

- 1059** **Nature of Tumor Control by Permanently and Transiently Modified GD2 Chimeric Antigen Receptor T Cells in Xenograft Models of Neuroblastoma**
Nathan Singh, Xiaojun Liu, Jessica Hulitt, Shuguang Jiang, Carl H. June, Stephan A. Grupp, David M. Barrett, and Yangbing Zhao
Synopsis: Singh and colleagues show that RNA-CAR T cells mediate rapid and long-term tumor destruction when delivered locally but not when delivered systemically due to the inability of RNA-CAR T cells to penetrate the tumor microenvironment.



- 1071** **Downregulation of MHC-I Expression Is Prevalent but Reversible in Merkel Cell Carcinoma**
Kelly G. Paulson, Andrew Tegeder, Christoph Willmes, Jayasri G. Iyer, Olga K. Afanasiev, David Schrama, Shinichi Koba, Renee Thibodeau, Kotaro Nagase, William T. Simonson, Aaron Seo, David M. Koelle, Margaret Madeleine, Shailender Bhatia, Hideki Nakajima, Shigetoshi Sano, James S. Hardwick, Mary L. Disis, Michele A. Cleary, Jürgen C. Becker, and Paul Nghiem
Synopsis: Paulson and colleagues report that 84% of Merkel cell carcinoma (MCC) tumors downregulated MHC-I expression, and MCC patients treated with intralesional IFNs had increased MHC-I expression on their tumor cells, thus promoting the use of immune-stimulating therapies for MCC.

- 1080** **Selective Inhibition of Regulatory T Cells by Targeting the PI3K-Akt Pathway**
Rasha Abu-Eid, Raed N. Samara, Laurent Ozburn, Maher Y. Abdalla, Jay A. Berzofsky, Kevin M. Friedman, Mikayel Mkrtichyan, and Samir N. Khleif
Synopsis: Abu-Eid, Samara, and colleagues used PI3K-Akt pathway inhibitors to selectively disrupt homeostasis of immunosuppressive Tregs in naïve and tumor-bearing mice, and to enhance vaccine-induced antitumor immune responses, highlighting the therapeutic potential of these inhibitors as Treg-depleting reagents.



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1090 Immune Consequences of Decreasing Tumor Vasculature with Antiangiogenic Tyrosine Kinase Inhibitors in Combination with Therapeutic Vaccines

Benedetto Farsaci, Renee N. Donahue, Michael A. Coplin, Italia Grenga, Lauren M. Lepone, Alfredo A. Molinolo, and James W. Hodge
Synopsis: Farsaci, Donahue, and colleagues show that combining antiangiogenic tyrosine kinase inhibitors with vaccines increased tumor-infiltrating lymphocytes, decreased tumor density, and enhanced tumor oxygenation, indicating the potential of altering tumor architecture in cancer therapy.

1103 IL4 Limits the Efficacy of Tumor-Targeted Antibody Therapy in a Murine Model

Rishi Surana, Shangzi Wang, Wei Xu, Sandra A. Jablonski, and Louis M. Weiner
Synopsis: Surana and colleagues report that neutralizing IL4 altered the tumor microenvironment (TME) and enhanced the efficacy of the HER2-directed antibody trastuzumab, thus providing a rationale for targeting soluble mediators in the TME to enhance antitumor antibody therapy.

1113 Murine Splenic CD4⁺ T Cells, Induced by Innate Immune Cell Interactions and Secreted Factors, Develop Antileukemia Cytotoxicity

Megan E. Nelles, Joshua M. Moreau, Caren L. Furlonger, Alexandra Berger, Jeffrey A. Medin, and Christopher J. Paige
Synopsis: Nelles and colleagues show in a murine model of leukemia that each of the cytokines IL12, IFN γ , and MCP-1 has a role in guiding a cellular cascade of contact-dependent cooperation of NKT cells and DCs that leads to activation of CD4⁺ cytotoxic T cells and elimination of leukemia.

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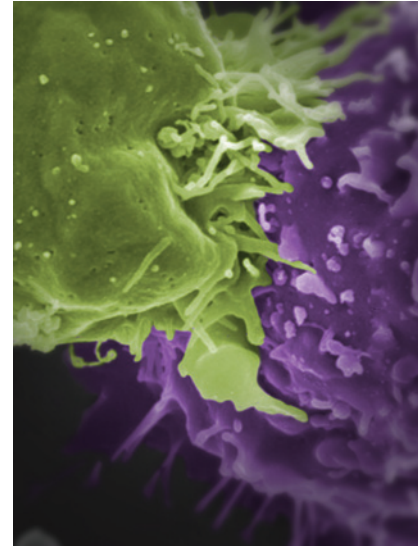
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ABOUT THE COVER

The T-cell immunological synapse is a specialized junction formed between a T cell and an antigen-presenting cell. It comprises molecular interactions for antigen recognition regulating the immune response. The immunological synapse integrates three broad categories of receptors: antigen recognition (TCR), adhesion, and costimulatory/checkpoint. The organization of these receptors in the interface has an impact on the way they function. Antigen recognition begins with engagement of a TCR by an MHC-peptide complex. Adhesion molecules provide the energy needed to pull cells together, allowing sustained antigen recognition and precise execution of effector functions. Finally, costimulatory and checkpoint receptors alter the functional outcome of immunological synapse formation and signaling. The cover image is a scanning electronic micrograph showing the interaction between a CD4⁺ T cell (green) and an antigen-presenting cell (lilac). The image was adapted from Biggs et al., "High-resolution imaging of the immunological synapse and T-cell receptor microclustering through microfabricated substrates" (*J R Soc Interface* 2011;8:1462-71, by permission of the Royal Society and Dr. S.J. Wind), using an artificial antigen-presenting cell generated by Thomas et al. (*Clin Immunol* 2002;105:259-72). For details see the Master of Immunology primer by Michael L. Dustin on page 1023 of this issue.



ABOUT THE MASTER

Michael L. Dustin, PhD, is a professor of molecular immunology at the Nuffield Department of Orthopedic, Rheumatology and Musculoskeletal Sciences, and the head of immunology at the Kennedy Institute of Rheumatology at the University of Oxford, UK. He was born in Poughkeepsie, NY, where he was inspired to study biology by looking at pond water through a microscope. He received a BA in biology with honors from Boston University and a PhD in cell and developmental biology from Harvard University. After his PhD work on T-cell adhesion molecules in Timothy Springer's lab, Dr. Dustin joined the laboratory of Stuart Kornfeld at the Washington University School of Medicine, St. Louis (WUSTL) to expand his studies in cell biology and microscopy. In 1993, he established his independent laboratory as Assistant Professor of Pathology at WUSTL, where he led a collaborative group in discovering the requirements for the T-cell immunological synapse. He moved to the Skirball Institute of Biomolecular Medicine at the New York University School of Medicine in 2001 as the Irene Diamond Professor in Immunology, and then the Muriel G. and George W. Singer Chair Professor of Molecular Immunology. In 2013, Dr. Dustin joined the University of Oxford as a Wellcome Trust Principal Research Fellow.



The Dustin laboratory has made substantial contributions to our understanding of T-cell surface molecules, the mechanism and regulation of T-cell migration in the lymph node and spleen, the mechanism of T-cell tolerance and activation *in vivo* by dendritic cells, and the modulation of T-cell immunological synapses. He has collaborated on intravital microscopy studies on breast and pancreatic cancers. The Dustin team in Oxford is developing new approaches to harness the immunological synapse as a therapeutic target in autoimmune disease and cancer.

Dr. Dustin has served on various scientific advisory boards and journal editorial boards. He is a fellow of the American Association for the Advancement of Sciences. He has received numerous awards, including a Presidential Early Career Award in Science and Engineering and the DART-NYU Biotechnology Award. He was also included in *Esquire* magazine's Best and Brightest in 2001. Dr. Dustin has organized various conferences on imaging of immunoreceptors and the immune system and authored over 250 peer-reviewed, original research papers, review articles, and book chapters. He is an enthusiastic teacher and has mentored over 40 graduate and postgraduate trainees. In addition, His lab has hosted over 20 visiting scientists from around the world. In keeping with his upbringing in the picturesque Hudson Valley, Dr. Dustin enjoys birding, cycling, and nature photography.

Cancer Immunology Research

2 (11)

Cancer Immunol Res 2014;2:1023-1124.

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