

## MASTERS OF IMMUNOLOGY

- 305**  $\alpha\beta$  TCR-Mediated Recognition: Relevance to Tumor-Antigen Discovery and Cancer



Immunotherapy

Ellis L. Reinherz

## CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 313** The Emerging Understanding of Myeloid Cells as Partners and Targets in Tumor Rejection

Miranda L. Broz and Matthew F. Krummel

## CANCER IMMUNOLOGY MINIATURES

- 320** Severe Adverse Immunologic Reaction in a Patient with Glioblastoma Receiving Autologous Dendritic Cell Vaccines Combined with GM-CSF and Dose-Intensified Temozolomide

Duane A. Mitchell, Elias J. Sayour, Elizabeth Reap, Robert Schmittling, Gabriel DeLeon, Pamela Norberg, Annick Desjardins, Allan H. Friedman, Henry S. Friedman, Gary Archer, and John H. Sampson  
*Synopsis:* Mitchell and colleagues report the induction of a grade 3 immunologic reaction in a patient with glioblastoma receiving autologous RNA-pulsed dendritic-cell vaccines admixed with GM-CSF and coordinated cycles of temozolomide, highlighting the capacity for potent immunologic induction with this regimen.

## RESEARCH ARTICLES

- 326** PD-L1 Expression Correlates with Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy in Breast Cancer

Hallie Wimberly, Jason R. Brown, Kurt Schalper, Herbert Haack, Matthew R. Silver, Christian Nixon, Veerle Bossuyt, Lajos Pusztai, Donald R. Lannin, and David L. Rimm

*Synopsis:* Wimberly and colleagues analyzed pretreatment biopsies and outcomes from 105 breast cancer patients; they report the association of PD-L1 expression with hormone receptor–negative and triple-negative status and pathologic complete response and suggest that PD-L1 expression is a biomarker in this treatment cohort.

- 333** Targeting CD20<sup>+</sup> Aggressive B-cell Non-Hodgkin Lymphoma by Anti-CD20 CAR mRNA-Modified Expanded Natural Killer Cells *In Vitro* and in NSG Mice

Yaya Chu, Jessica Hochberg, Ashlin Yahr, Janet Ayello, Carmella van de Ven, Matthew Barth, Myron Czuczman, and Mitchell S. Cairo

*Synopsis:* Chu and colleagues show that K562-mbIL15-41BBL-expanded peripheral blood NK cells, modified with mRNA nucleofection of an anti-CD20 CAR, significantly enhanced cytotoxicity against CD20<sup>+</sup>B-cell non-Hodgkin lymphoma, extended survival time, and reduced tumor size in xenografted NSG mice.

- 345** Stereotactic Radiation Therapy Augments Antigen-Specific PD-1–Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen

Andrew B. Sharabi, Christopher J. Nirschl, Christina M. Kochel, Thomas R. Nirschl, Brian J. Francica, Esteban Velarde, Theodore L. Deweese, and Charles G. Drake

*Synopsis:* Sharabi and colleagues show in two mouse tumor models that radiotherapy combined with PD-1 blockade or Treg depletion improves local tumor control by increasing antigen-experienced and effector-memory T cells, antigen-MHC complexes, and T-cell infiltration into tumors via antigen cross-presentation in the tumor-draining lymph node.

- 356** Identification of Chimeric Antigen Receptors That Mediate Constitutive or Inducible Proliferation of T Cells

Matthew J. Frigault, Jihyun Lee, Maria Ciocca Basil, Carmine Carpenito, Shinichiro Motohashi, John Scholler, Omkar U. Kawalekar, Sonia Guedan, Shannon E. McGettigan, Avery D. Posey Jr, Sonny Ang, Laurence J.N. Cooper, Jesse M. Platt, F. Brad Johnson, Chrystal M. Paulos, Yangbing Zhao, Michael Kalos, Michael C. Milone, and Carl H. June

*Synopsis:* Frigault, Lee, and colleagues compared chimeric antigen receptors (CAR) encoding signaling domains comprising CD28, ICOS, and 4-1BB and found that some CD28 CAR-T cells have antigen-independent constitutive proliferation and cytokine secretion when highly expressed, leading to inferior antitumor effects.

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- 368**    **Functional Tuning of CARs Reveals Signaling Threshold above Which CD8<sup>+</sup> CTL Antitumor Potency Is Attenuated due to Cell Fas–FasL-Dependent AICD**  
Annette Künkele, Adam J. Johnson, Lisa S. Rolczynski, Cindy A. Chang, Virginia Hoglund, Karen S. Kelly-Spratt, and Michael C. Jensen  
*Synopsis:* Künkele and colleagues demonstrate in a solid tumor model that CARs with the highest in vitro activity exhibit attenuated antitumor potency in vivo as CTLs expressing hyperactive CARs are susceptible to activation-induced cell death; CARs tuned for moderate signaling outputs mediate effective tumor eradication.
- 380**    **Genetic Evidence That Intratumoral T-cell Proliferation and Activation Are Associated with Recurrence and Survival in Patients with Resected Colorectal Liver Metastases**  
Ajay V. Maker, Hiromichi Ito, Qianxing Mo, Elliot Weisenberg, Li-Xuan Qin, Simon Turcotte, Shishir Maithel, Jinru Shia, Leslie Blumgart, Yuman Fong, William R. Jarnagin, Ronald P. DeMatteo, and Michael I. D'Angelica  
*Synopsis:* Maker and colleagues analyzed liver tumor specimens and outcomes from 96 patients with colorectal cancer liver metastases and report that genetic evidence of T-cell activation/proliferation in liver tumors, specifically the increased expression of TNFSF14/LIGHT, is associated with longer overall and disease-free survival.
- 389**    **Three Steps to Breaking Immune Tolerance to Lymphoma: A Microparticle Approach**  
Amani Makkouk, Vijaya B. Joshi, Caitlin D. Lemke, Amaraporn Wongrakpanich, Alicia K. Olivier, Sue E. Blackwell, Aliasger K. Salem, and George J. Weiner  
*Synopsis:* Makkouk and colleagues show that intratumoral delivery of doxorubicin in polylactide-co-glycolide microparticles combined with antibodies against OX40 and CTLA-4 induced T cell–dependent systemic responses that enhanced T-cell infiltration into and eradication of distant tumors and improved survival in mouse models of lymphoma.
- 399**    **Induction of T-cell Immunity Overcomes Complete Resistance to PD-1 and CTLA-4 Blockade and Improves Survival in Pancreatic Carcinoma**  
 Rafael Winograd, Katelyn T. Byrne, Rebecca A. Evans, Pamela M. Odorizzi, Anders R.L. Meyer, David L. Bajor, Cynthia Clendenin, Ben Z. Stanger, Emma E. Furth, E. John Wherry, and Robert H. Vonderheide  
*Synopsis:* Winograd and colleagues used an engineered KPC mouse model of pancreatic ductal adenocarcinoma (PDA) reflecting that of human PDA to show that baseline refractoriness to checkpoint inhibitors can be rescued by priming a T-cell response with αCD40 plus chemotherapy with gemcitabine and nab-paclitaxel.
- 412**    **Galectin-3 Shapes Antitumor Immune Responses by Suppressing CD8<sup>+</sup> T Cells via LAG-3 and Inhibiting Expansion of Plasmacytoid Dendritic Cells**  
 Theodore Kouo, Lanqing Huang, Alexandra B. Pucsek, Minwei Cao, Sara Solt, Todd Armstrong, and Elizabeth Jaffee  
*Synopsis:* Kouo and colleagues report the development of neutralizing Abs to galectin-3 in PDA patients who showed improved survival in response to a GM-CSF–secreting allogeneic tumor vaccine, and they propose that carbohydrate signaling be considered as "signal 4" of immune-cell programming and differentiation.

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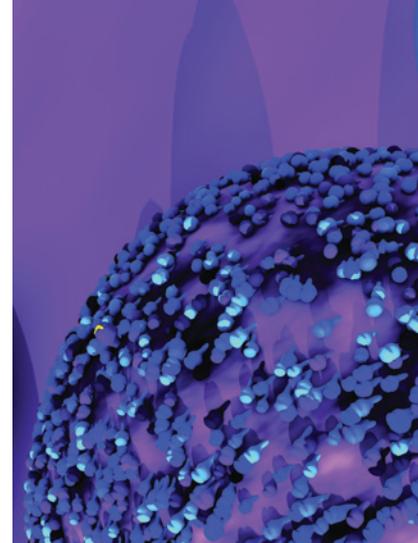
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## ABOUT THE COVER

The surface of an antigen-presenting cell (APC) displays a large array of peptides bound to a major histocompatibility molecule (pMHC). Yet, the specific pMHC against which a T cell is directed is often displayed at a very low (i.e., even single digit) copy number among 50,000 to 100,000 other pMHC molecules. These pMHC complexes comprise the same MHC molecule and similarly sized but distinct peptides. How can a T-cell scan and use its T-cell receptor (TCR) machinery to find a "needle in a haystack"? The solution has been achieved through the evolution of the  $\alpha\beta$  TCR as a mechanosensor. As a result, CD8 cytotoxic T lymphocytes (CTL) and CD4 helper T cells manifest extraordinary ligand sensitivity and specificity. This cover image offers an artist's rendition of MHC molecules projecting from the plasma membrane of an APC. In this case, only one peptide, represented by the small dot in yellow near the periphery of the circle, is the target of that TCR's specificity. Thus, the TCR must mediate T-cell recognition in a chemically complex environment with the ability to finely discriminate among peptides of like size and charge, including tumor antigens for effective elimination of cancers. This figure was rendered by Steve Moskowitz of Advanced Medical Graphics, Boston, MA. For details, see the Masters of Immunology article by Ellis L. Reinherz that begins on page 305 of this issue.



## ABOUT THE MASTER

Ellis L. Reinherz, MD, is a professor of medicine at Harvard Medical School (HMS) and chief of the Laboratory of Immunobiology and codirector of the Cancer Vaccine Center at the Dana-Farber Cancer Institute (DFCI). Dr. Reinherz is known for his basic research that has revealed key functional and structural discoveries about TCRs, including their CD3 signaling subunit components, and how the TCRs, along with the CD4 and CD8 coreceptor molecules that he identified, bind to the pMHC. More recently he and his colleagues have defined the TCR as an anisotropic mechanosensor, offering a physical solution to the longstanding question of how T cells can achieve rapid and specific sensing of a single peptide bound to an MHC molecule among a sea of unrelated peptides arrayed on the surface of an antigen-presenting cell with exquisite specificity and dynamic range. His findings on the molecular basis of adaptive immunity have implications for rational vaccine design and human immunotherapy efforts in the clinic. He has authored more than 400 research publications in human and murine immunology, spanning areas in basic and translational research. The development of OKT3, the first FDA-approved monoclonal antibody (mAb) in humans, resulted from his studies demonstrating the ability of the mAb to inhibit antigen-specific T-cell responses.

Dr. Reinherz was born in Malden, MA, and is a distinguished alumnus of the Middlesex School in Concord, MA. He entered Harvard College in 1968 and graduated *summa cum laude* in 1971 with an AB degree. He received his medical degree from HMS in 1975. After completing his internship and residency at the Massachusetts General Hospital and a hematology fellowship at the Brigham and Women's Hospital, Dr. Reinherz pursued research training as a postdoctoral fellow in the laboratory of Stuart Schlossman. Subsequently he was recruited to join the faculty of DFCI and HMS as an assistant professor of medicine, and he has held the rank of HMS professor of medicine since 1994. Dr. Reinherz is a member of the editorial boards of several basic and clinical immunology journals; he is the coeditor of the T-cell biology section of *Frontiers in Immunology*. Currently he chairs the steering committee of the NIH Human Immunology Project Consortium. Dr. Reinherz is a member of the American Federation for Clinical Research, the American Society of Hematology, the American Society of Clinical Investigation, and the American Association of Immunologists (AAI). He is the recipient of the 2011 AAI Human Immunology Award.

