

## WHAT WE'RE READING

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## BOOK REVIEW

- 718 From Bratislava to New York: A Scientist's Tale  
Sir Marc Feldmann


## IN THE SPOTLIGHT

- 719 Zeroing in on Tumor-Reactive TILs  
Pamela S. Ohashi  
*See related article, p. 734.*

## MASTERS OF IMMUNOLOGY

- 720 About the Master
- 721 Regulatory T Cells: Differentiation and Function  
George Plitas and Alexander Y. Rudensky

## CANCER IMMUNOLOGY MINIATURES

- 726  The Intratumoral Balance between Metabolic and Immunologic Gene Expression Is Associated with Anti-PD-1 Response in Patients with Renal Cell Carcinoma  
Maria Libera Ascierto, Tracee L. McMiller, Alan E. Berger, Ludmila Danilova, Robert A. Anders, George J. Netto, Haiying Xu, Theresa S. Pritchard, Jinshui Fan, Chris Cheadle, Leslie Cope, Charles G. Drake, Drew M. Pardoll, Janis M. Taube, and Suzanne L. Topalian  
*Tumor cell-intrinsic metabolic factors, a hallmark of kidney cancer, may contribute to anti-PD-1 treatment resistance. This intersection between cancer immunology and metabolism supports an emerging theme of discovery for tumor type-specific biomarkers for immune checkpoint blocking therapies.*

## RESEARCH ARTICLES

- 734 Tumor- and Neoantigen-Reactive T-cell Receptors Can Be Identified Based on Their Frequency in Fresh Tumor  
Anna Pasetto, Alena Gros, Paul F. Robbins, Drew C. Deniger, Todd D. Prickett, Rodrigo Matus-Nicodemos, Daniel C. Douek, Bryan Howie, Harlan Robins, Maria R. Parkhurst, Jared Gartner, Katarzyna Trebska-McGowan, Jessica S. Crystal, and Steven A. Rosenberg  
*Effective adoptive T-cell therapy requires multiple tumor-epitope reactive T-cell clones. Fresh TILs were found to frequently contain such cells. Their TCRs were rapidly isolated based only on their frequency and could be used for personalized TCR-gene therapy. See related Spotlight, p. 719.*
- 744 Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma  
Sebastian Theurich, Sacha I. Rothschild, Michael Hoffmann, Mario Fabri, Andrea Sommer, Maria Garcia-Marquez, Martin Thelen, Catherine Schill, Ramona Merki, Thomas Schmid, Dieter Koeberle, Alfred Zippelius, Christian Baues, Cornelia Mauch, Christian Tigges, Alexander Kreuter, Jan Borggrefe, Michael von Bergwelt-Baildon, and Max Schlaak  
*Too few patients benefit from immune checkpoint inhibition alone. However, patients with melanoma receiving systemic anti-CTLA-4 plus localized treatments had significantly prolonged overall survival. In a multivariate analysis, adding local treatment was an independent factor for improved survival.*
- 755 Analyses of Pretherapy Peripheral Immunoscore and Response to Vaccine Therapy  
Benedetto Farsaci, Renee N. Donahue, Italia Grenga, Lauren M. Lepone, Peter S. Kim, Brendan Dempsey, Janet C. Siebert, Nuhad K. Ibrahim, Ravi A. Madan, Christopher R. Heery, James L. Gulley, and Jeffrey Schlom  
*Refined subsets of peripheral blood immune cells were assessed prior to therapy in two clinical trials. The resultant "peripheral immunoscores," compiled through methodology potentially generalizable to other trials, were correlated with clinical benefit in patients receiving vaccine therapy.*

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**766** Gp96-Ig/Costimulator (OX40L, ICOSL, or 4-1BBL) Combination Vaccine Improves T-cell Priming and Enhances Immunity, Memory, and Tumor Elimination



George Fromm, Suresh de Silva, Louise Giffin, Xin Xu, Jason Rose, and Taylor H. Schreiber  
*Local anticancer therapies can increase antitumor efficacy while reducing toxicities. Cellular vaccines that locally secreted costimulation ligands produced stronger, more specific T-cell activation and tumor rejection with lower ligand concentrations than did vaccines combined with systemic antibody agonists.*

**779** Myeloma Drug Resistance Induced by Binding of Myeloma B7-H1 (PD-L1) to PD-1

Mariko Ishibashi, Hideto Tamura, Mika Sunakawa, Asaka Kondo-Onodera, Namiko Okuyama, Yasuko Hamada, Keiichi Moriya, Inhak Choi, Koji Tamada, and Koiti Inokuchi  
*B7-H1 suppresses T cells by binding to PD-1, but it is unclear how binding to B7-H1 on cancer cells affects tumors. "Reverse signaling" of B7-H1 on myeloma cells was found to induce drug resistance through the Akt-signaling pathway.*

**789** Mutation Drivers of Immunological Responses to Cancer

Eduard Porta-Pardo and Adam Godzik  
*Tumor mutations create neoantigens that increase their immunogenicity but also enable new avenues of immune escape. DomainXplorer analyzes distributions of mutations in cancer genomes searching for correlations with immune response that are not seen by gene level methods.*

**799** Molecular Programming of Tumor-Infiltrating CD8<sup>+</sup> T Cells and IL15 Resistance

Andrew L. Doedens, Mark P. Rubinstein, Emilie T. Gross, J. Adam Best, David H. Craig, Megan K. Baker, David J. Cole, Jack D. Bui, and Ananda W. Goldrath  
*Tumor-infiltrating CD8<sup>+</sup> T cells were profoundly resistant to IL15 complexes, so could not induce tumor regression. Their gene-expression signature was compared with that of productive cytotoxic responses and known differentiation states to determine how to restore antitumor function and cytokine responsiveness.*

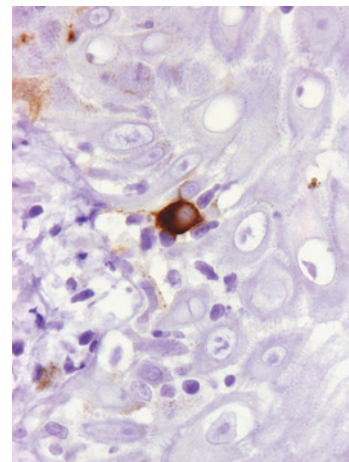
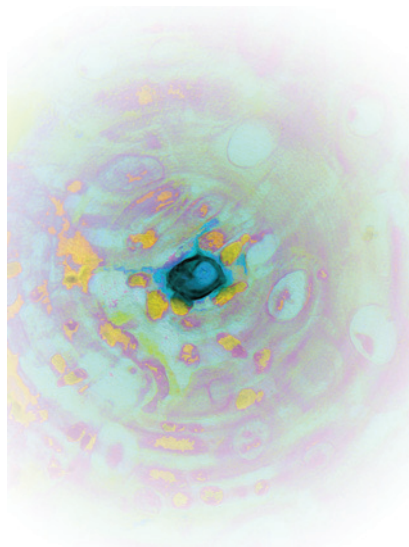


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## ABOUT THE COVER

Intensive research into the intertwined relationship of the immune system with tumors is yielding new therapies that rely on managing a patient's immune system to promote long-term tumor destruction. Melanoma is the poster child for immunotherapies, with many clinical trials first tested in patients with this tumor. The Rosenberg lab has been treating patients with improved versions of the patient's own cells that recognize and kill melanoma cells. Their latest study identifies T-cell receptors (TCRs) that recognize a patient's tumor antigens based on the frequency of TCR usage among the T cells present in the patient's tumors. The original micrograph (right) depicts a melanin-filled antigen-presenting cell (brown) surrounded by T cells, in the midst of a melanoma tumor. Read more in the article by Pasetto et al., starting on page 734 of this issue. The micrograph (right) is from the Steven Rosenberg laboratory. Artwork is by Lewis Long.



# Cancer Immunology Research

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