

HIGHLIGHTS FROM THE LITERATURE

- 1 What We're Reading

CANCER IMMUNOLOGY AT THE CROSSROADS

- 2 **High-Dimensional Profiling of Tumor-Specific Immune Responses: Asking T Cells about What They "See" in Cancer**
Evan W. Newell and Etienne Becht

MEETING REPORT

- 10 **Translating Science into Survival: Report on the Third International Cancer Immunotherapy Conference**
Mustafa Diken, Karen K. Chu, and Arthur N. Brodsky

RESEARCH ARTICLES

- 14 **Intratumoral CD8⁺ T-cell Apoptosis Is a Major Component of T-cell Dysfunction and Impedes Antitumor Immunity**
Brendan L. Horton, Jason B. Williams, Alexandra Cabanov, Stefani Spranger, and Thomas F. Gajewski
The apoptosis of tumor-infiltrating CD8⁺ T cells was found to be a major factor inhibiting antitumor immune responses. Blocking CD8⁺ T-cell apoptosis improved tumor control and should be considered as a strategy to enhancing current immunotherapies.

- 25 **IAP Antagonists Enhance Cytokine Production from Mouse and Human iNKT Cells**
Eleanor Clancy-Thompson, Lestat Ali, Patrick T. Bruck, Mark A. Exley, Richard S. Blumberg, Glenn Dranoff, Michael Dougan, and Stephanie K. Dougan
IAP antagonists inhibit tumor growth in vivo primarily through augmentation of antitumor immunity. IAP antagonists were found to augment iNKT cell-mediated antitumor immunity in mice and were useful in expanding human IFN γ -producing iNKT cells ex vivo.

- 36 **High-Affinity GD2-Specific CAR T Cells Induce Fatal Encephalitis in a Preclinical Neuroblastoma Model**
Sarah A. Richman, Selene Nunez-Cruz, Babak Moghimi, Lucy Z. Li, Zachary T. Gershenson, Zissimos Mourelatos, David M. Barrett, Stephan A. Grupp, and Michael C. Milone
GD2 is a ganglioside on neuroblastomas and is expressed in certain brain regions. Severe and fatal neurotoxicity resulted from the use of T cells bearing an enhanced chimeric antigen receptor to GD2, indicating a narrow immunotherapeutic window.

- 47 **Reversible Transgene Expression Reduces Fratricide and Permits 4-1BB Costimulation of CAR T Cells Directed to T-cell Malignancies**
Maksim Mamonkin, Malini Mukherjee, Madhuwanti Srinivasan, Sandhya Sharma, Diogo Gomes-Silva, Feiyan Mo, Giedre Krenciute, Jordan S. Orange, and Malcolm K. Brenner
CAR T cells targeting malignant T cells can form unwanted cytotoxic immunologic synapses between themselves, impairing their survival. CAR-derived 4-1BB costimulation stabilized these synapses, and reversing CAR expression overcame unwanted fratricide while retaining antitumor activity.

- 59 **Soluble CD80 Protein Delays Tumor Growth and Promotes Tumor-Infiltrating Lymphocytes**
Lucas A. Horn, Tiha M. Long, Ryan Atkinson, Virginia Clements, and Suzanne Ostrand-Rosenberg
Therapeutic strategies that simultaneously neutralize PD-1 suppressive mechanisms while activating tumor-reactive T cells are needed. The use of soluble CD80 in mice achieved both of these goals, which supports its potential usefulness as an immunotherapeutic for cancer patients.

- 69 **CD137 (4-1BB) Costimulation Modifies DNA Methylation in CD8⁺ T Cell-Relevant Genes**
M. Angela Aznar, Sara Labiano, Angel Diaz-Lagares, Carmen Molina, Saray Garasa, Arantza Azpilikueta, Iñaki Etxeberria, Alfonso R. Sanchez-Paulete, Alan J. Korman, Manel Esteller, Juan Sandoval, and Ignacio Melero
CD137(4-1BB) ligation with agonist monoclonal antibodies used in immunotherapy induces long-term sequence-specific CpG DNA-methylation patterns in human CD8⁺ T lymphocytes. These epigenetic changes give rise to mRNA and protein expression changes in key T-cell genes and regulatory factors.

- 79 **A Serum Protein Signature Associated with Outcome after Anti-PD-1 Therapy in Metastatic Melanoma**
Jeffrey S. Weber, Mario Sznol, Ryan J. Sullivan, Shauna Blackmon, Genevieve Boland, Harriet M. Kluger, Ruth Halaban, Antonietta Bacchiocchi, Paolo A. Ascierto, Mariaelena Capone, Carlos Oliveira, Krista Meyer, Julia Grigorieva, Senait G. Asmellash, Joanna Roder, and Heinrich Roder
A proteomic signature in serum identifies melanoma patients who will experience long or short survival after checkpoint inhibition therapy. The signature, determined by mass spectrometry and machine learning, may predict patients who would benefit most from immunotherapy.

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87 **Impact of Tumor Purity on Immune Gene Expression and Clustering Analyses across Multiple Cancer Types**

Je-Keun Rhee, Yu Chae Jung, Kyu Ryung Kim, Jinseon Yoo, Jeeyoon Kim, Yong-Jae Lee, Yoon Ho Ko, Han Hong Lee, Byoung Chul Cho, and Tae-Min Kim

The impact of tumor purity on assessing relationships between gene expression and clinicopathological features is unclear. With the use of TCGA data, less pure samples could confound correlations with gene expression, mutation burdens, gene clustering, and molecular taxonomy.

98 **β -Adrenergic Signaling Impairs Antitumor CD8⁺ T-cell Responses to B-cell Lymphoma Immunotherapy**

Michael D. Nissen, Erica K. Sloan, and Stephen R. Mattarollo

β -adrenergic receptor (β AR) signaling regulates cancer growth and metastasis as well as normal physiology. In a mouse model of B-cell lymphoma, elevated β AR signaling suppressed proliferation and function of CD8⁺ T cells, resulting in reduced efficacy of immunotherapy.

110 **A Transgenic Dual-Luciferase Reporter Mouse for Longitudinal and Functional Monitoring of T Cells *In Vivo***

Martin Szyska, Stefanie Herda, Stefanie Althoff, Andreas Heimann, Josefine Russ, Daniele D'Abundo, Tra My Dang, Isabell Durieux, Bernd Dörken, Thomas Blankenstein, and Il-Kang Na

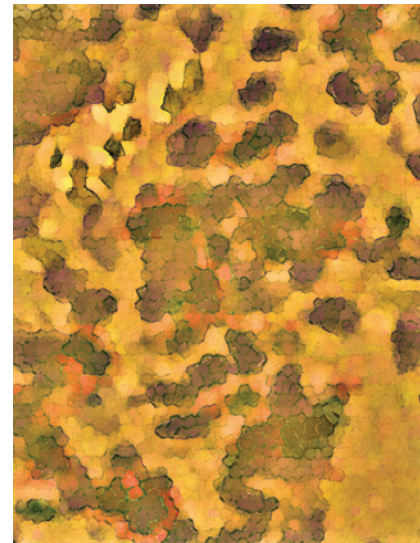
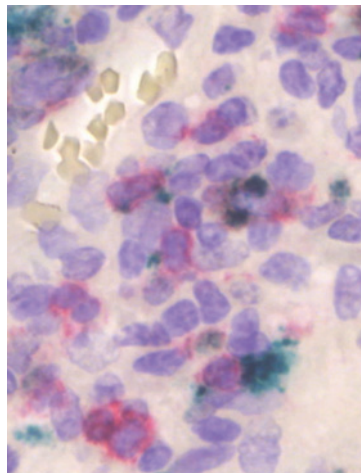
Longitudinal and functional monitoring of T cells in vivo could improve our understanding of immune functions. A transgenic mouse expressing dual-luciferase reporters was tested in tumor models to assess immune reconstitution, graft-versus-host disease, and adoptive T-cell therapy.

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ABOUT THE COVER

Many tumors are infiltrated by tumor-specific T cells. However, because the T cells often express the inhibitory marker PD-1, and the ligand for PD-1 is readily expressed within tumor sites, it has been assumed that the infiltrating T cells are inert or exhausted, basically unable to mount an effective immune response against the tumor. However, evidence suggests that tumor-specific T cells in tumors are activated, so why are they unable to overcome tumors? The Gajewski laboratory has found that a major factor hindering a T cell-mediated immune response is that these activated T cells readily apoptose, that is, die by programmed cell death. By preventing apoptosis, or combining strong costimulation with blockade of inhibitory checkpoints, T cells that expressed PD-1 were able to control tumors. Read more in Horton et al., starting on page 14 of this issue of *Cancer Immunology Research*. Immunohistochemistry image from the Gajewski lab shows Caspase-3 in aqua and CD8⁺ T cells in pink, within a melanoma metastasis. Artwork by Lewis Long.



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