


## HIGHLIGHTS FROM THE LITERATURE

- 425** What We're Reading

## CANCER IMMUNOLOGY AT THE CROSS-ROADS

- 426**  Novel "Elements" of Immune Suppression within the Tumor Microenvironment  
Devikala Gurusamy, David Clever, Robert Eil, and Nicholas P. Restifo


## MEETING REPORT

- 434** Cancer Immunology and Immunotherapy: Taking a Place in Mainstream Oncology  
Keystone Symposia Meeting Summary  
Matthew M. Gubin

## CANCER IMMUNOLOGY MINIATURES

- 439** 4-1BB-Enhanced Expansion of CD8<sup>+</sup> TIL from Triple-Negative Breast Cancer Unveils Mutation-Specific CD8<sup>+</sup> T Cells  
Michiko Harao, Marie-Andrée Forget, Jason Roszik, Hui Gao, Gildy V. Babiera, Savitri Krishnamurthy, Jessica A. Chacon, Shumin Li, Elizabeth A. Mittendorf, Sarah M. DeSnyder, Korrene F. Rockwood, Chantale Bernatchez, Naoto T. Ueno, Laszlo G. Radvanyi, Luis Vence, Cara Haymaker, and James M. Reuben  
*Triple-negative breast cancers have low somatic mutational loads. By culturing tumor-infiltrating lymphocytes with agonistic 4-1BB mAb, tumor-specific T cells were expanded and the mutations to which they responded identified, providing a rationale for adoptive T cell therapy.*

## RESEARCH ARTICLES

- 446** Combined Anti-VEGF and Anti-CTLA-4 Therapy Elicits Humoral Immunity to Galectin-1 Which Is Associated with Favorable Clinical Outcomes  
Xinqi Wu, Jingjing Li, Erin M. Connolly, Xiaoyun Liao, Jing Ouyang, Anita Giobbie-Hurder, Donald Lawrence, David McDermott, George Murphy, Jun Zhou, Matthias Piesche, Glenn Dranoff, Scott Rodig, Matthias Piesche, Glenn Dranoff, Scott Rodig, Margaret Shipp, and F. Stephen Hodi  
*Galectin-1 is often produced by tumors and is protumoral, proangiogenic, and immunosuppressive. Ipilimumab plus bevacizumab induced production of neutralizing antibodies to galectin-1, which correlated with better clinical outcomes in metastatic melanoma patients, highlighting its utility as a therapeutic target.*
- 455** RIG-I Resists Hypoxia-Induced Immunosuppression and Dedifferentiation  
Christina Engel, Grethe Brüggmann, Silke Lambing, Larissa H. Mühlenbeck, Samira Marx, Christian Hagen, Dorottya Horváth, Marion Goldeck, Janos Ludwig, Anna-Maria Herzner, Jan W. Drijfhout, Daniela Wenzel, Christoph Coch, Thomas Tüting, Martin Schlee, Veit Hornung, Gunther Hartmann, and Jasper G. Van den Boom  
*Solid tumors are generally hypoxic. RIG-I, but not IFN $\alpha$ , still functioned under hypoxia. Activating RIG-I and using vitamin C to scavenge free radicals in a melanoma model augmented NK and CD8<sup>+</sup> T cell antitumor functions and prolonged survival.*
- 468** A STING Agonist Given with OX40 Receptor and PD-L1 Modulators Primes Immunity and Reduces Tumor Growth in Tolerized Mice  
Jeremy B. Foote, Marlene Kok, James M. Leatherman, Todd D. Armstrong, Bridget C. Marcinkowski, Lauren S. Ojalvo, David B. Kanne, Elizabeth M. Jaffee, Thomas W. Dubensky Jr, and Leisha A. Emens  
*The efficacy and immune dynamics of STING modulation in the toleragenic tumor microenvironment were examined. Combining a STING agonist, PD-L1 blockade, and OX40R stimulation created an inflamed tumor microenvironment that recruited T cells and activated tumor-specific immunity.*
- 480**  Soluble PD-L1 as a Biomarker in Malignant Melanoma Treated with Checkpoint Blockade  
Jun Zhou, Kathleen M. Mahoney, Anita Giobbie-Hurder, Fengmin Zhao, Sandra Lee, Xiaoyun Liao, Scott Rodig, Jingjing Li, Xinqi Wu, Lisa H. Butterfield, Matthias Piesche, Michael P. Manos, Lauren M. Eastman, Glenn Dranoff, Gordon J. Freeman, and F. Stephen Hodi  
*Melanoma cells could secrete several splice variants of PD-L1. Secretion differed among patients, and was affected by checkpoint therapy, with some changes associated with progressive disease, and others with favorable outcomes, suggesting circulating PD-L1 as a dynamic biomarker.*

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**493** Tumor-Derived  $\alpha$ -Fetoprotein Directly Drives Human Natural Killer-Cell Activation and Subsequent Cell Death

Lazar Vujanovic, Elizabeth C. Stahl, Angela D. Pardee, David A. Geller, Allan Tsung, Simon C. Watkins, Gregory A. Gibson, Walter J. Storkus, and Lisa H. Butterfield

*Low NK cell numbers, function, and infiltration into tumors predict poor outcomes for patients with hepatocellular carcinoma (HCC). Tumor-derived  $\alpha$ -fetoprotein (AFP) from HCCs directly impacted NK cell function and viability, through both the AFP protein and AFP's low-molecular-mass cargo.*

**503** Combining DNA Vaccine and AIDA-1 in Attenuated *Salmonella* Activates Tumor-Specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell Responses

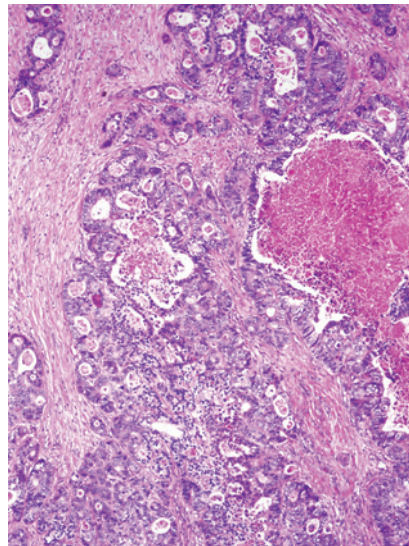
Yu Mei, Lixiang Zhao, Yonghao Liu, Huanle Gong, Yuan Song, Lei Lei, Ying Zhu, Ziqi Jin, Shoubao Ma, Bo Hu, Qing Sun, and Haiyan Liu  
*Effective tumor vaccines activate both CD4<sup>+</sup> and CD8<sup>+</sup> T cells. A melanoma DNA vaccine delivered by a bacterial system that ensured presentation of both class I and class II peptides activated both arms of the adaptive immune response.*

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## ABOUT THE COVER

This issue of *Cancer Immunology Research* includes a Cancer Immunology at the Crossroads article that highlights two of the many ways in which tumors can evade immune surveillance. Both of these “tricks” employ the repurposing of how two elements, oxygen and potassium, engage with the tumor microenvironment and the resultant suppression of antitumor immune responses. Read more in Gurusamy et al., beginning on page 426. The original image is of a resected metastatic colon tumor stained with hematoxylin and eosin. Photo from the Restifo laboratory. Artwork by Lewis Long.



# Cancer Immunology Research

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