

WHAT WE'RE READING

- 1383** A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

- 1384**  **Protective Innate Immune Variants in Racial/Ethnic Disparities of Breast and Prostate Cancer**
Susan T. Yeyeodu, LaCreis R. Kidd, and K. Sean Kimbro

CANCER IMMUNOLOGY MINIATURES

- 1390** **Immunologic Correlates of Pathologic Complete Response to Preoperative Immunotherapy in Hepatocellular Carcinoma**
Ahmed Omar Kaseb, Luis Vence, Jorge Blando, Shalini S. Yadav, Naruhiko Ikoma, Roberto Carmagnani Pestana, Jean Nicolas Vauthey, James P. Allison, and Padmanee Sharma
This case report of a patient with hepatocellular carcinoma highlights the immune infiltrates that correlate with the complete pathologic response achieved after preoperative anti-PD-1/CTLA-4. An increase in two distinct effector T-cell populations was observed.
- 1396** **PD-1 Inhibition Achieves a Complete Metabolic Response in a Patient with Malignant Peripheral Nerve Sheath Tumor**
Lisa E. Davis, Lauren A. Nicholls, Hani M. Babiker, Joy Liau, and Daruka Mahadevan
High-grade malignant peripheral nerve sheath tumors have a poor prognosis with limited responsiveness to systemic therapy. Treatment with pembrolizumab resulted in a complete metabolic response after four cycles of therapy.

RESEARCH ARTICLES

- 1401** **Immunologic Profiling of Mutational and Transcriptional Subgroups in Pediatric and Adult High-Grade Gliomas**
Michael Bockmayr, Frederick Klauschen, Cecile L. Maire, Stefan Rutkowski, Manfred Westphal, Katrin Lamszus, Ulrich Schüller, and Malte Mohme
Analysis of the immune phenotype of rare molecular subgroups in pediatric and adult high-grade gliomas provides information that may increase the efficacy of immunotherapeutic approaches for pediatric and adolescent high-grade gliomas.

- 1412** **Engineered Adoptive T-cell Therapy Prolongs Survival in a Preclinical Model of Advanced-Stage Ovarian Cancer**
Kristin G. Anderson, Valentin Voillet, Breanna M. Bates, Edison Y. Chiu, Madison G. Burnett, Nicolas M. Garcia, Shannon K. Oda, Christopher B. Morse, Ingunn M. Stromnes, Charles W. Drescher, Raphael Gottardo, and Philip D. Greenberg
Ovarian cancer is the most lethal gynecologic cancer. High-affinity TCR-engineered T cells targeting mesothelin effectively kill human ovarian cancer lines and prolong survival of immunocompetent mice with advanced ovarian cancer, providing the basis for a planned clinical trial.

- 1426** **TGF β Programs Central Memory Differentiation in Ex Vivo-Stimulated Human T Cells**
Amina Dahmani, Valérie Janelle, Cédric Carli, Manon Richaud, Caroline Lamarche, Myriam Khalili, Mathieu Goupil, Ksenia Bezverbnaya, Jonathan L. Bramson, and Jean-Sébastien Delisle
TGF β exposure during human T-cell stimulation ex vivo favors early memory differentiation and improves the function of adoptively transferred T cells. TGF β signaling may, thus, be harnessed to manufacture early memory T cells for cancer adoptive immunotherapy.

- 1440**  **Blockade of Immune-Checkpoint B7-H4 and Lysine Demethylase 5B in Esophageal Squamous Cell Carcinoma Confers Protective Immunity against *P. gingivalis* Infection**
Xiang Yuan, Yiwen Liu, Guifang Li, Zijun Lan, Mingyang Ma, Huaxu Li, Jinyu Kong, Jiangtao Sun, Gaochao Hou, Xurong Hou, Yingjian Ma, Feng Ren, Fuyou Zhou, and Shengan Gao
*Porphyromonas gingivalis infection can increase immunosuppression and facilitate poor immunogenicity of esophageal squamous cell carcinomas. Dual blockade of B7-H4 and a histone demethylase controls *P. gingivalis* infection and development of associated tissue neoplasia.*

- 1457**  **The Combined Effect of FGFR Inhibition and PD-1 Blockade Promotes Tumor-Intrinsic Induction of Antitumor Immunity**
Sangeetha Palakurthi, Mari Kuraguchi, Sima J. Zacharek, Enrique Zudaire, Wei Huang, Dennis M. Bonal, Jeffrey Liu, Abha Dhaneshwar, Kristin DePeaux, Martha R. Gowaski, Dyane Bailey, Samuel N. Regan, Elena Ivanova, Catherine Ferrante, Jessie M. English, Aditya Khosla, Andrew H. Beck, Julie A. Rytlewski, Catherine Sanders, Sylvie Laquerre, Mark A. Bittinger, Paul T. Kirschmeier, Kathryn Packman, Pasi A. Janne, Christopher Moy, Kwok-Kin Wong, Raluca I. Verona, and Matthew V. Lorenzi
Treatments that use a pan-FGFR (fibroblast growth factor receptor) inhibitor plus anti-PD-1 can boost antitumor responses in tumors harboring genetic mutations in driver oncogenes. The agents remodel the tumor microenvironment and enhance the expansion of T-cell clones.

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- 1472**  **MERTK Acts as a Costimulatory Receptor on Human CD8⁺ T Cells**
 Marlies J.W. Peeters, Donata Dulkeviciute, Arianna Draghi, Cathrin Ritter, Anne Rahbech, Signe K. Skadborg, Tina Seremet, Ana Micaela Carnaz Simões, Evelina Martinenaite, Hólmfrídur R. Halldórsdóttir, Mads Hald Andersen, Gitte Holmen Olofsson, Inge Marie Svane, Lene Juel Rasmussen, Özcan Met, Jürgen C. Becker, Marco Donia, Claus Desler, and Per thor Straten
Activated CD8⁺ T cells express the MERTK receptor protein kinase and its ligand PROS1. MERTK signaling acts as a late costimulatory signal, improving CD8⁺ T-cell and TIL numbers, killing efficacy, and their secretion of memory and effector cytokines.
- 1485** **SLAMF6 as a Regulator of Exhausted CD8⁺ T Cells in Cancer**
 Burcu Yigit, Ninghai Wang, Elisa ten Hacken, Shih-Shih Chen, Atul K. Bhan, Abel Suarez-Fueyo, Eri Katsuyama, George C. Tsokos, Nicholas Chiorazzi, Catherine J. Wu, Jan A. Burger, Roland W. Herzog, Pablo Engel, and Cox Terhorst
SLAMF6 can be a target for modulating T-cell exhaustion. These data highlight the potential of targeting SLAMF6, either with single agents or in combination with other inhibitors, to unleash CD8⁺ T-cell responses to improve immunotherapy efficacy.
- 1497** **Immune-Checkpoint Protein VISTA Regulates Antitumor Immunity by Controlling Myeloid Cell-Mediated Inflammation and Immunosuppression**
 Wenwen Xu, Juan Dong, Yongwei Zheng, Juan Zhou, Ying Yuan, Hieu Minh Ta, Halli E. Miller, Michael Olson, Kamalakannan Rajasekaran, Marc S. Ernstoff, Demin Wang, Subramaniam Malarkannan, and Li Wang
VISTA is an immune-checkpoint protein that can regulate the functions of MDSCs and DC subsets. Myeloid cell activation precedes T cell-mediated antitumor responses and, thus, contributes to the antitumor mechanisms of VISTA inhibition.
- 1511** **An RNA Aptamer-Based Biomarker Platform Demonstrates High Soluble CD25 Occupancy by IL2 in the Serum of Follicular Lymphoma Patients**
 Suresh Veeramani, Sue E. Blackwell, William H. Thiel, Zhi-Zhang Yang, Stephen M. Ansell, Paloma H. Giangrande, and George J. Weiner
An aptamer-based technology to measure soluble ligand-receptor complexes in patient serum was developed and demonstrated using lymphoma patients' sera to determine IL2-CD25 complexes. Similar approaches using this and other aptamer pairs could be used as a biomarker platform.
- 1523** **An Anticancer Drug Cocktail of Three Kinase Inhibitors Improved Response to a Dendritic Cell-Based Cancer Vaccine**
 Jitao Guo, Elena Muse, Allison J. Christians, Steven J. Swanson, and Eduardo Davila
Kinase inhibitors were screened for their ability to improve DC immunogenicity. Combination treatment with three such inhibitors (MK2206, NU7441, and trametinib) enhances DC immunogenicity, improving anticancer responses from patient-derived T cells and in a mouse glioblastoma model.
- 1535** **Accumulation of Tumor-Infiltrating CD49a⁺ NK Cells Correlates with Poor Prognosis for Human Hepatocellular Carcinoma**
 Haoyu Sun, Lianxin Liu, Qiang Huang, Huan Liu, Mei Huang, Jiabei Wang, Hao Wen, Renyong Lin, Kun Qu, Kun Li, Haiming Wei, Weihua Xiao, Rui Sun, Zhigang Tian, and Cheng Sun
Accumulation of CD49a⁺ NK cells in human hepatocellular carcinoma (HCC) correlates with tumor growth and poor prognosis. This NK-cell subset may negatively regulate immune responses and promote the development of HCC.
- 1547** **Natural Killer Cell Recruitment and Activation Are Regulated by CD47 Expression in the Tumor Microenvironment**
 Pulak Ranjan Nath, Dipasmita Pal-Nath, Ajeet Mandal, Margaret C. Cam, Anthony L. Schwartz, and David D. Roberts
Identification of NK-cell immune checkpoints in the tumor microenvironment could provide a basis for improving melanoma treatment. CD47 expression regulated intratumoral and systemic NK-cell function, with blockade of CD47 improving antitumor NK-cell responses in melanoma.



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ABOUT THE COVER

Ovarian tumors are difficult to treat, and more than half of patients with high-grade serous ovarian carcinoma (HGSOC) die within 5 years. Three quarters of these tumors overexpress mesothelin. Anderson et al. find that human T cells that express an engineered T-cell receptor specific for mesothelin can kill multiple HGSOC cell lines. To study the effectiveness of mesothelin-specific engineered T cells *in vivo*, a mouse model was evaluated for resemblance to human HGSOC. The mouse peritoneal-cavity metastatic tumors have a transcriptome profile similar to human metastatic tumors, including upregulation of multiple inhibitory pathways present in HGSOC. Mouse mesothelin-specific T cells recognize and kill ovarian cancer cells *in vitro* and accumulate in the tumors, and co-infusion with a mesothelin peptide vaccine promotes expansion and increases T-cell persistence. The presence of active tumor-specific engineered T cells correlates with tumor killing and prolonged mouse survival. This model is useful for testing immunologic interventions for patients with HGSOC and already serves as the basis for a clinical trial. Read more starting on page 1412. Original fluorescence micrograph of the ovarian tumor microenvironment provided by the Greenberg laboratory. Artwork by Lewis Long.

