

CANCER IMMUNOLOGY RESEARCH

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WHAT WE'RE READING

- 557** **A Sampling of Highlights from the Literature**

PRIORITY BRIEF

- 558** **Microparticle-Delivered Cxcl9 Prolongs Braf Inhibitor Efficacy in Melanoma**

Gabriele Romano, Francesca Paradiso, Peng Li, Pooja Shukla, Lindsay N. Barger, Olivia El Naggar, John P. Miller, Roger J. Liang, Timothy L. Helms, Alexander J. Lazar, Jennifer A. Wargo, Francesca Taraballi, James C. Costello, and Lawrence N. Kwong

The authors show that microparticle-mediated delivery of Cxcl9 recruits effector T cells to the tumor site and delays relapse. The data suggest an adjuvant approach to boost the immune response in combination with targeted therapy or immunotherapy.

RESEARCH ARTICLES

- 570** **Low TCR Binding Strength Results in Increased Progenitor-like CD8⁺ Tumor-Infiltrating Lymphocytes**
Zachary L.Z. Hay, Jennifer R. Knapp, Roman E. Magallon, Brian P. O'Connor, and Jill E. Slansky

Transcriptional profiling reveals that tumor-infiltrating lymphocytes (TILs) with low TCR affinity to a tumor-associated antigen exhibit progenitor-like phenotypes and increased quiescence, whereas higher affinity TCR TILs exhibit more cell division and faster progression to T-cell exhaustion programs.

- 583** **Discovery of Podofilox as a Potent cGAMP-STING Signaling Enhancer with Antitumor Activity**
Jing Han, Shuiqing Hu, Yawei Hu, Yifang Xu, Yanfei Hou, Yinlong Yang, Huili Su, Zhengyin Zhang, Peng Liu, Xuxu Sun, and Conggang Zhang

The authors identify podofilox as an enhancer of the cGAMP-STING signaling pathway. By altering STING trafficking, podofilox promotes STING activation and antitumor responses *in vitro* and *in vivo*, suggesting an approach to enhance STING agonist cancer immunotherapy.

- 600** **Netrin-1 Promotes the Immunosuppressive Activity of MDSCs in Colorectal Cancer**

Xueli Xia, Zhenwei Mao, Wenxin Wang, Jie Ma, Jie Tian, Shengjun Wang, and Kai Yin

Tumor-derived netrin-1 enhances the immunosuppressive function of myeloid-derived suppressor-cell (MDSC) via interaction with A2BR, facilitating the development of tumors. These findings highlight netrin-1 as a regulator of antitumor immune responses and potential therapeutic target in colorectal cancer.

- 614** **Myeloid-Derived Suppressor-Cell Dynamics Control Outcomes in the Metastatic Niche**

Jesse Kreger, Evanthia T. Roussos Torres, and Adam L. MacLean

Mathematical modeling of myeloid-derived suppressor-cell (MDSC) dynamics reveals MDSC-NK cell interactions as a crucial predictor of outcomes in breast-to-lung metastasis and a possible therapeutic target.

- 629** **Driver Mutations Dictate the Immunologic Landscape and Response to Checkpoint Immunotherapy of Glioblastoma**

Alan T. Yeo, Rushil Shah, Konstantinos Aliazis, Rinku Pal, Tuoye Xu, Piyan Zhang, Shruti Rawal, Christopher M. Rose, Frederick S. Varn, Vicky A. Appleman, Joon Yoon, Hemant Varma, Steven P. Gygi, Roel G.W. Verhaak, Vassiliki A. Boussiotis, and Al Charest

Glioblastoma is frequently refractory to radiation, chemotherapy, and immunotherapy. The authors show in genetic mouse models that the mutational profile of glioblastoma influences the tumor immune microenvironment and offers a pharmacological means to sensitize glioblastoma to checkpoint immunotherapy.

- 646** **SWI/SNF Complex Genomic Alterations as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors in Multiple Cancers**

Di Wang, Jianchao Wang, Dongmei Zhou, Zhixian Wu, Wei Liu, Yanping Chen, Gang Chen, and Jing Zhang

By analyzing all 31 SWI/SNF complex genes, the authors show SWI/SNF complex alterations are associated with improved clinical outcomes following immune checkpoint inhibitor (ICI) therapy across cancer types, suggesting that such alterations could serve as a prognostic biomarker for ICI therapy.

- 657** **HDAC3 Inhibition Promotes Antitumor Immunity by Enhancing CXCL10-Mediated Chemotaxis and Recruiting of Immune Cells**

Lili Li, Shumin Hao, Meiling Gao, Junxiao Liu, Xin Xu, Jianfei Huang, Genhong Cheng, and Heng Yang

Histone deacetylase 3 (HDAC3) is shown to regulate expression of genes encoding chemokines CXCL9/10/11, as well as impact antitumor immune-cell recruitment in the tumor microenvironment. The data highlight how targeting HDAC3 could boost antitumor immune responses.

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674 Reverse Translation Identifies the Synergistic Role of Immune Checkpoint Blockade and IL15 to Enhance Immunotherapy of Ovarian Cancer

Martin Felices, Erin Wesley, Laura E. Bendzick, Behiye Kodali, Rachel Hopps, Bartosz Grzywacz, Peter Hinderlie, Jeffrey S. Miller, and Melissa A. Geller

The authors show in ovarian cancer that IL15 induces a negative feedback loop driven by upregulation of the PD-1/PD-L1 checkpoint axis partly through NK cell-produced IFN γ . Addition of immune checkpoint blockade synergizes with IL15, improving cytokine-driven immunotherapy.

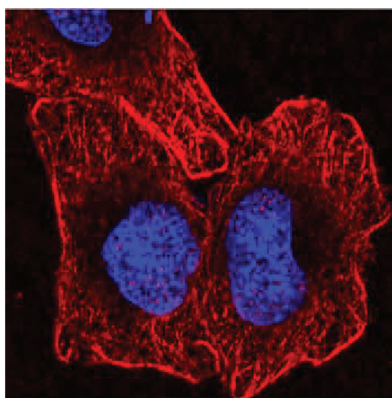
687 Hedgehog Signaling Regulates Treg to Th17 Conversion Through Metabolic Rewiring in Breast Cancer

Dominique C. Hinshaw, Gloria A. Benavides, Brandon J. Metge, Courtney A. Swain, Sarah C. Kammerud, Heba A. Alsheikh, Amr Elhamamsy, Dongquan Chen, Victor Darley-Usmar, Jeffrey C. Rathmell, Robert S. Welner, Rajeev S. Samant, and Lalita A. Shevde

Hedgehog signaling metabolically programs and supports differentiation and activity of regulatory T cells (Treg). Inhibiting Hedgehog shifts Tregs into inflammatory Th17 cells and creates an immune-reactive tumor microenvironment, paving the way for novel combinatorial approaches to treat triple-negative breast cancer.

ABOUT THE COVER

Activation of stimulator of IFN genes (STING) by cyclic GMP–AMP (cGAMP) can lead to antitumor immune responses in preclinical models. Using a cell-based phenotypic screen, Han, Hu, Hu et al. identify the microtubule destabilizer podofilox as an enhancer of cGAMP–STING signaling. Podofilox mediates this effect by altering STING trafficking, which promotes STING oligimerization and delays STING degradation. Adding podofilox to cGAMP enhances antitumor immune responses in tumor organoids and a preclinical model in a STING-dependent manner, suggesting a new approach to therapeutic targeting of the STING pathway. Read more in this issue on page 583. Original image from Fig. 2H. Artwork by Lewis Long.



doi: 10.1158/2326-6066.CIR-11-5-CVR