

# CANCER IMMUNOLOGY RESEARCH

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## CANCER IMMUNOLOGY AT THE CROSSROADS

- 7 **Determinants for Antitumor and Protumor Effects of Programmed Cell Death**  
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Katey S. Hunt and Elise Alspach

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- 26 **Combination of Anti-PD-1 and Electroacupuncture Induces a Potent Antitumor Immune Response in Microsatellite-Stable Colorectal Cancer**  
Yuan Wang, Fengyi Liu, Xiaoxue Du, Jiaqi Shi, Rui Yu, Shuang Li, Ruisi Na, Ying Zhao, Meng Zhou, Ying Guo, Liang Cheng, Guangyu Wang, and Tongsen Zheng  
EA is demonstrated to inhibit MSS colorectal cancer progression and enhance efficacy of anti-PD-1 by boosting antitumor responses. Combination EA and anti-PD-1 is highlighted as a feasible and safe treatment option for MSS colorectal cancer.
- 36 **Intracellular K<sup>+</sup> Limits T-cell Exhaustion and Preserves Antitumor Function**  
Camille Collier, Kelly Wucherer, Matthew McWhorter, Chelsea Jenkins, Alexandra Bartlett, Rahul Roychoudhuri, and Robert Eil  
Deletion of an ATPase in T cells promotes ROS accumulation, tonic signal transduction, and T-cell exhaustion due to decreased intracellular K<sup>+</sup>. Data provide a deeper understanding of T-cell ion transport and highlight how it can impact antitumor responses.  
See related Spotlight, p. 6

- 48 **Bexmarilimab Activates Human Tumor-Associated Macrophages to Support Adaptive Immune Responses in Interferon-Poor Immune Microenvironments**

Jenna H. Rannikko, Petri Bono, Johanna Hynninen, and Maija Hollmén

Interferons are essential components of the immune response against tumors. The authors identify a possible approach to induce interferons in the tumor microenvironment and promote the effectiveness of other immune therapies relying on preexisting interferon signaling.

## RESEARCH ARTICLES

- 60 **T cell-Dependent Bispecific Therapy Enhances Innate Immune Activation and Antibody-Mediated Killing**  
Rickvinder Besla, Elicia Penuel, Geoff Del Rosario, Ely Cosino, Szymon Myrta, Mike Dillon, Greg A. Lazar, Dorothee Nickles, Christoph Spiess, Shang-Fan Yu, and Andrew G. Polson

This work provides evidence for combining antibody therapies that involve cell types from both the adaptive and innate arms of the immune system. The data could inform future treatment practices and expand regimens of antibody-based immunotherapies for cancer.

- 72 **The Tautomerase Activity of Tumor Exosomal MIF Promotes Pancreatic Cancer Progression by Modulating MDSC Differentiation**

Xuebing Jia, Jianbei Xi, Binle Tian, Yuanyuan Zhang, Zhilong Wang, Fan Wang, Zheng Li, Jiang Long, Jianfei Wang, Guo-Huang Fan, and Qi Li

The authors show that inhibition of MIF tautomerase activity blocks exosomal MIF-induced MDSC differentiation and suppresses pancreatic cancer growth in mice, suggesting translational potential for this approach.

- 91 **Notch Signaling Regulates Immunosuppressive Tumor-Associated Macrophage Function in Pancreatic Cancer**

Wei Yan, Rosa E. Menjivar, Monica E. Bonilla, Nina G. Steele, Samantha B. Kemp, Wenting Du, Katelyn L. Donahue, Kristee L. Brown, Eileen S. Carpenter, Faith R. Avritt, Valerie M. Irizarry-Negron, Sion Yang, William R. Burns, Yaqing Zhang, Marina Pasca di Magliano, and Filip Bednar

Active Notch signaling in pancreatic TAMs is demonstrated to regulate their immunosuppressive phenotype. Notch signaling inhibition sensitizes pancreatic tumors to immune checkpoint blockade by reshaping the tumor microenvironment, highlighting targeting Notch signaling as a potential pancreatic cancer immunotherapy.

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**107 Tyrosine Kinase Inhibition Activates Intratumoral  $\gamma\delta$  T Cells in Gastrointestinal Stromal Tumor**

Mark S. Etherington, Andrew N. Hanna, Benjamin D. Medina, Mengyuan Liu, Andrew D. Tieniber, Hyunjee V. Kwak, Katherine J. Tardy, Lillian Levin, Kevin J. Do, Ferdinando Rossi, Shan Zeng, and Ronald P. DeMatteo  
Infiltrating IL17A<sup>+</sup>  $\gamma\delta$  T cells are demonstrated to have antitumoral activity in GIST and can be further activated by tumor oncogene inhibition. The data highlight the potential of this rare, but potent, cell type as an immunotherapeutic target.

**120 Spatial Distribution of Immune Cells Drives Resistance to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer**

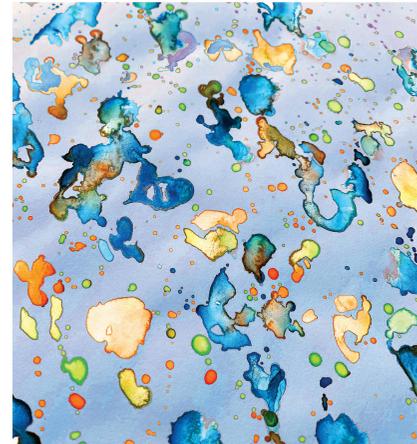
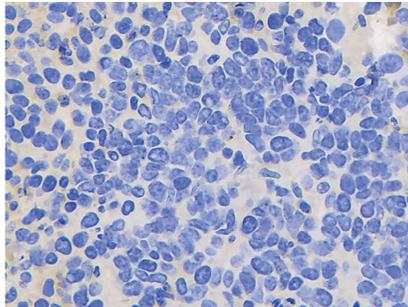
Benedetta Donati, Francesca Reggiani, Federica Torricelli, Giacomo Santandrea, Teresa Rossi, Alessandra Bisagni, Elisa Gasparini, Antonino Neri, Laura Cortesi, Guglielmo Ferrari, Giancarlo Bisagni, Moira Ragazzi, and Alessia Ciarrocchi

The authors use a morphology-guided transcriptomic approach to resolve the spatial complexity of TNBC samples to analyze response to NAC, finding information on the multidimensionality of TNBC that may allow prediction of tumor behavior and NAC response.

**135 Acknowledgment to Reviewers**

## ABOUT THE COVER

Efficacy of immune checkpoint blockade in microsatellite-stable (MSS) colorectal cancer is limited, and strategies to improve responses are needed. Wang, Liu, Du, and Shi et al. demonstrate the utility and safety of adding electroacupuncture (EA) to anti-PD1 for treating MSS colorectal cancer. The effects of EA are intensity-specific, whereby a moderate EA intensity results in the most effective treatment effects. The combination treatment has enhanced effects over monotherapies in multiple tumor models due to activation of STING signaling and increased antitumor responses. These results indicate that the EA needle can “STING” the MSS colorectal tumors through immune boosting and highlight combining EA and anti-PD1 as a feasible and safe potential treatment for MSS colorectal cancer. Read more in this issue on page 26. Original image from Fig. 1H. Artwork by Lewis Long.



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