

CANCER IMMUNOLOGY RESEARCH

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- 2 **Lighting a Fire: Can We Harness Pyroptosis to Ignite Antitumor Immunity?**
Zhibin Zhang, Ying Zhang, and Judy Lieberman

RESEARCH ARTICLES

- 8 **The Prognostic Role of Macrophage Polarization in the Colorectal Cancer Microenvironment**

Juha P. Väyrynen, Koichiro Haruki, Mai Chan Lau, Sara A. Väyrynen, Rong Zhong, Andressa Dias Costa, Jennifer Borowsky, Melissa Zhao, Kenji Fujiyoshi, Kota Arima, Tyler S. Twombly, Junko Kishikawa, Simeng Gu, Saina Aminmzaffari, Shanshan Shi, Yoshifumi Baba, Naohiko Akimoto, Tomotaka Ugai, Annacarolina Da Silva, Jennifer L. Guerriero, Mingyang Song, Kana Wu, Andrew T. Chan, Reiko Nishihara, Charles S. Fuchs, Jeffrey A. Meyerhardt, Marios Giannakis, Shuji Ogino, and Jonathan A. Nowak
Macrophage polarization state, rather than overall density, in the colorectal cancer microenvironment is associated with cancer-specific survival independent of potential confounding factors, with M1-like and M2-like macrophage phenotypes exhibiting distinct prognostic roles.

- 20 **Retinoic Acid Synthesis Deficiency Fosters the Generation of Polymorphonuclear Myeloid-Derived Suppressor Cells in Colorectal Cancer**

Hong-Wei Sun, Jing Chen, Wen-Chao Wu, Yan-Yan Yang, Yi-Tuo Xu, Xing-Juan Yu, Hai-Tian Chen, Zilian Wang, Xiao-Jun Wu, and Limin Zheng
A defect in ADHI-mediated retinoic acid synthesis contributes to the accumulation of polymorphonuclear (PMN)-MDSCs in colorectal cancer. The data highlight how restoring retinoic acid signaling could abrogate the generation of PMN-MDSCs and improve antitumor responses.

- 34 **A CRISPR Screen Reveals Resistance Mechanisms to CD3-Bispecific Antibody Therapy**

A C Si-Qi Liu, Alyssa Grantham, Casey Landry, Brian Granda, Rajiv Chopra, Srinivas Chakravarthy, Sabine Deutsch, Markus Vogel, Katie Russo, Katherine Seiss, William R. Tschantz, Tomas Rejtar, David A. Ruddy, Tiancen Hu, Kimberly Aardalen, Joel P. Wagner, Glenn Dranoff, and Joseph A. D'Alessio

A genome-wide CRISPR screen was developed to understand cancer cell-derived resistance mechanisms to CD3-bispecific antibodies. The screen identifies IFN γ signaling being pivotal for responsiveness to CD3 bispecifics, and deficiency in core fucosylation as causing resistance to the therapeutic flotetuzumab.

- 50 **A Bispecific Antibody Antagonizes Prosurvival CD40 Signaling and Promotes V γ 9V δ 2 T cell-Mediated Antitumor Responses in Human B-cell Malignancies**

Iris de Weerd, Roeland Lameris, George L. Scheffer, Jana Vree, Renate de Boer, Anita G. Stam, Rieneke van de Ven, Mark-David Levin, Steven T. Pals, Rob C. Roovers, Paul W.H.I. Parren, Tanja D. de Gruij, Arnon P. Kater, and Hans J. van der Vliet

The generation of a CD40-specific V γ 9V δ 2 T-cell engager, which abrogates prosurvival CD40 signaling, is described. This bispecific antibody unleashes V γ 9V δ 2 T cell-mediated responses against both leukemia and multiple myeloma *in vitro* and *in vivo*.

- 62 **CD28 Costimulatory Domain-Targeted Mutations Enhance Chimeric Antigen Receptor T-cell Function**

A C Justin C. Boucher, Gongbo Li, Hiroshi Kotani, Maria L. Cabral, Dylan Morrissey, Sae Bom Lee, Kristen Spitler, Nolan J. Beatty, Estelle V. Cervantes, Bishwas Shrestha, Bin Yu, Aslamuzzaman Kazi, Xuefeng Wang, Said M. Sebti, and Marco L. Davila

CD28 mutations enhance CAR T-cell function by reducing expression of transcription factors such as NFAT and NUR77, which in turn reduce expression of exhaustion-related genes. These data highlight considerations for CAR design that could improve antitumor responses.

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75 The Cerebroventricular Environment Modifies CAR T Cells for Potent Activity against Both Central Nervous System and Systemic Lymphoma

AC Xiuli Wang, Christian Huynh, Ryan Urak, Lihong Weng, Miriam Walter, Laura Lim, Vibhuti Vyas, Wen-Chung Chang, Brenda Aguilar, Alfonso Brito, Aniee Sarkissian, N. Achini Bandara, Lu Yang, Jinhui Wang, Xiwei Wu, Jianying Zhang, Saul J. Priceman, Hong Qin, Larry W. Kwak, Lihua E. Budde, Sandra H. Thomas, Mary C. Clark, Leslie Popplewell, Tanya Siddiqi, Christine E. Brown, and Stephen J. Forman

In the clinic, CD19-CAR T cells are administered IV and are not used specifically to treat CNS lymphoma. The authors show a single ICV infusion of CD19-CAR T cells completely eradicates both CNS and systemic lymphoma in mice.

89 Activin A Promotes Regulatory T-cell-Mediated Immunosuppression in Irradiated Breast Cancer

Mara De Martino, Camille Daviaud, Julie M. Diamond, Jeffrey Kraynak, Amandine Alard, Silvia C. Formenti, Lance D. Miller, Sandra Demaria, and Claire Vanpouille-Box

Activin A and TGF β can shape the breast cancer tumor microenvironment after radiotherapy. Dual blockade of activin A and TGF β reverses radiotherapy-induced Treg increases and boosts antitumor responses, highlighting potential targetable factors for breast cancer treatment.

103 Improved T-cell Receptor Diversity Estimates Associate with Survival and Response to Anti-PD-1 Therapy

Dante S. Bortone, Mark G. Woodcock, Joel S. Parker, and Benjamin G. Vincent

Inaccurate TCR diversity estimates from RNA sequencing data have made the relationship between diversity and immunotherapy responses unclear. Improved estimation of diversity uncovers the association between diversity and responses of melanoma patients treated with PD-1 inhibition.

113 Sialylation of CD55 by ST3GAL1 Facilitates Immune Evasion in Cancer

Wen-Der Lin, Tan-Chi Fan, Jung-Tung Hung, Hui-Ling Yeo, Sheng-Hung Wang, Chu-Wei Kuo, Kay-Hooi Khoo, Li-Mei Pai, John Yu, and Alice L. Yu

Silencing of the ST3GAL1 glycosyltransferase in breast cancer cells reduces O-sialylation of CD55, enhancing C3 deposition and susceptibility to complement- and antibody-dependent cytotoxicity. These findings suggest ST3GAL1 inhibition could be a strategy to block breast cancer immune evasion.

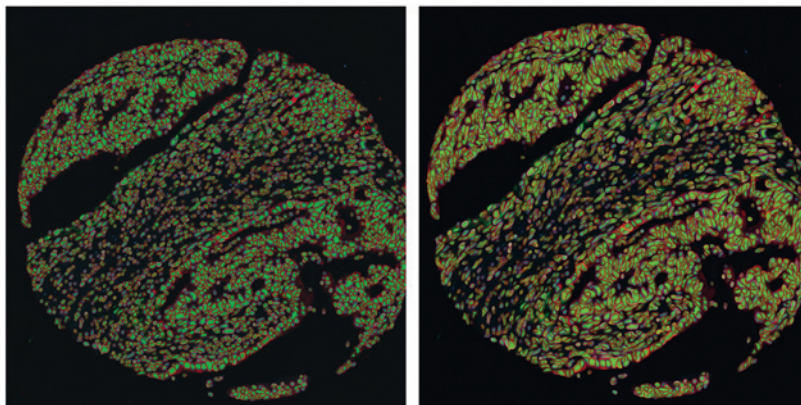
123 Acknowledgment to Reviewers

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ABOUT THE COVER

The prognostic value of tumor-associated macrophages (TAM) remains to be fully elucidated. By combining multiplex immunofluorescence with digital analysis and machine learning, Väyrynen et al. show that TAM subsets have distinct prognostic roles in patients with colorectal cancer. Total intraepithelial and stromal TAM densities are not prognostic. Rather, TAM polarization is key, with M2-like TAMs correlating with worse cancer-specific survival. Interestingly, a survival benefit is not seen when assessing M1-like TAMs in the tumor stromal region, although high M1:M2 density ratio is associated with better survival. The study highlights the importance of utilizing multiplex analysis to more accurately determine the prognostic value of immune-cell subsets, as total population assessment or single-marker analysis may mask underlying associations. Read more in this issue on page 8. Original image from Supplementary Fig. S3B. Artwork by Lewis Long.



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