WHAT WE'RE READING

CANCER IMMUNOLOGY AT THE CROSSROADS

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

RESEARCH ARTICLES

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 Aminmozaffari, 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

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

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 ADH1-mediated retinoic acid synthesis contributes to the accumulation of polymorphonuclear (PMN)-MDSs in colorectal cancer. The data highlight how restoring retinoic acid signaling could abrogate the generation of PMN-MDSs and improve antitumor responses.

A CRISPR Screen Reveals Resistance Mechanisms to CD3-Bispecific Antibody Therapy
Si-Qi Liu, Alyssa Grantham, Casey Landry, Brian Granda, Rajiv Chopra, Srinivas Chakravarty, 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 bispecific antibody antagonizes prosurvival CD40 signaling and promotes Vγ9Vδ2 T cell–Mediated Antitumor Responses in Human B-cell Malignancies
Iris de Weerdt, 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 Gruijl, Arnon P. Kater, and Hans J. van der Vliet

The generation of a CD40-specific Vγ9Vδ2 T-cell engager, which abrogates prosurvival CD40 signaling, is described. This bispecific antibody unleashes Vγ9Vδ2 T cell–mediated responses against both leukemia and multiple myeloma in vitro and in vivo.

CD28 Costimulatory Domain–Targeted Mutations Enhance Chimeric Antigen Receptor T-cell Function
Justin C. Boucher, Gongbo Li, Hiroshi Kotani, Maria L. Cabral, Dylan Morrissey, Sae Bom Lee, Kristen Spiterl, Nolan J. Beatty, Estelle V. Cervantes, Bishwas Shreshtha, Bin Yu, Aslamuzzaman Kazi, Xuefeng Wang, Said M. Sebti, and Marco L. Davila

CD28 mutations enhance CAR T-cell function by reducing expression of exhaustion-related genes. These data highlight considerations for CAR design that could improve antitumor responses.
The Cerebroventricular Environment Modifies CAR T Cells for Potent Activity against Both Central Nervous System and Systemic Lymphoma


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.

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


Acknowledgment to Reviewers

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.