

CANCER IMMUNOLOGY RESEARCH

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WHAT WE'RE READING

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

CANCER IMMUNOLOGY MINIATURES

- 580 **Previous Infection Positively Correlates to the Tumor Incidence Rate of Patients with Cancer**

Shinako Inaida and Shigeo Matsuno

Determining links to tumor formation is critical for combating cancer. A 7-year study of over 50,000 patients indicates that certain previous infections are linked to the formation of various cancers.

PRIORITY BRIEF

- 587 **Remodeling Translation Primes CD8⁺ T-cell Antitumor Immunity**

Katie E. Hurst, Kiley A. Lawrence, Rob A. Robino, Lauren E. Ball, Dongjun Chung, and Jessica E. Thaxton

Altering protein translation in T cells can affect their antitumor function. IL15-conditioned T cells have diminished protein translation *in vitro* but reinvigorate translation in tumors, a property that is attributed to T cells that produce superior tumor control.

RESEARCH ARTICLES

- 596 **A PSMA-Targeting CD3 Bispecific Antibody Induces Antitumor Responses that Are Enhanced by 4-1BB Costimulation**

Danica Chiu, Richard Tavaré, Lauric Haber, Olulanu H. Aina, Kristin Vazzana, Priyanka Ram, Makenzie Danton, Jennifer Finney, Sumreen Jalal, Pamela Krueger, Jason T. Giurleo, Dangshe Ma, Eric Smith, Gavin Thurston, Jessica R. Kirshner, and Alison Crawford

A CD3 bispecific antibody that targets a prostate tumor antigen elicits effective antitumor responses against smaller, but not larger, solid tumors. Addition of 4-1BB controls tumors through enhanced T-cell responses, T-cell memory formation, and response persistence.

- 609 **Single-Cell Immune Competency Signatures Associate with Survival in Phase II GVAX and CRS-207 Randomized Studies in Patients with Metastatic Pancreatic Cancer**

Nitya Nair, Shih-Yu Chen, Ed Lemmens, Serena Chang, Dung T. Le, Elizabeth M. Jaffee, Aimee Murphy, Chan Whiting, Thomas Müller, and Dirk G. Brockstedt

Circulating immune subsets that associate with survival in pancreatic cancer patients treated with GVAX pancreas and/or CRS-207 immunotherapy are identified. These immune subsets can potentially be used as biomarkers to stratify patients most likely to respond to treatment.

- 618 **Deciphering the Immunomodulatory Capacity of Oncolytic Vaccinia Virus to Enhance the Immune Response to Breast Cancer**

Brittany A. Umer, Ryan S. Noyce, Brian C. Franczak, Mira M. Shenouda, Rees G. Kelly, Nicole A. Favis, Megan Desaulniers, Troy A. Baldwin, Mary M. Hitt, and David H. Evans

Genomic alterations of oncolytic viruses can improve their antitumor efficacy. Various genomic alterations of VACV are tested "head-to-head" in order to determine their impact on antitumor efficacy and immunity in murine tumor models.

- 632 **Intratumoral Delivery of a PD-1-Blocking scFv Encoded in Oncolytic HSV-1 Promotes Antitumor Immunity and Synergizes with TIGIT Blockade**

Chaolong Lin, Wenfeng Ren, Yong Luo, Shaopeng Li, Yating Chang, Lu Li, Dan Xiong, Xiaoxuan Huang, Zilong Xu, Zeng Yu, Yingbin Wang, Jun Zhang, Chenghao Huang, and Ningshao Xia

Oncolytic virus activity is often limited by an immunosuppressive tumor microenvironment. The antitumor efficacy of oncolytic herpes simplex virus is improved by delivering a single-chain variable fragment specific for PD-1. Pairing this with TIGIT blockade enhances antitumor responses.

- 648 **Prevalent and Diverse Intratumoral Oncoprotein-Specific CD8⁺ T Cells within Polyomavirus-Driven Merkel Cell Carcinomas**

Lichen Jing, Mariliis Ott, Candice D. Church, Rima M. Kulikauskas, Dafina Ibrani, Jayasri G. Iyer, Olga K. Afanasiev, Aric Colunga, Maclean M. Cook, Hong Xie, Alexander L. Greninger, Kelly G. Paulson, Aude G. Chapuis, Shailender Bhatia, Paul Nghiem, and David M. Koelle

Merkel cell carcinoma is frequently associated with Merkel cell polyomavirus infection. Most patients' tumors contain virus-specific CD8⁺ T cells restricted by specific HLAs, highlighting the potential of using vaccination as part of immunotherapy strategies for this cancer.

- 660 **IL1 α Antagonizes IL1 β and Promotes Adaptive Immune Rejection of Malignant Tumors**

Tian Tian, Serena Lofftus, Youdong Pan, Claire A. Stingley, Sandra L. King, Jingxia Zhao, Timothy Y. Pan, Rebecca Lock, Jacob W. Marglous, Kevin Liu, Hans R. Widlund, Robert C. Fuhlbrigge, Karen Cichowski, and Thomas S. Kupper

Antibodies to IL1 β can enhance antitumor immunity, but inhibiting IL1 α reduces antitumor effects. Thus, antagonists that block the shared IL1R1 do not improve antitumor immunity and are not equivalent to blocking IL1 β alone.

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672 Identification of the Targets of T-cell Receptor Therapeutic Agents and Cells by Use of a High-Throughput Genetic Platform

Ron S. Gejman, Heather F. Jones, Martin G. Klatt, Aaron Y. Chang, Claire Y. Oh, Smita S. Chandran, Tatiana Korontsvit, Viktoriya Zakahleva, Tao Dao, Christopher A. Klebanoff, and David A. Scheinberg

The cross-reactivity of TCR-based therapies can lead to serious adverse events. PresentER is a high-throughput method for producing MHC-I peptide minigenes that can be used in *in vitro* immune assays to identify cross-reactive TCRs.

685 Enhanced Immunogenicity of Mitochondrial-Localized Proteins in Cancer Cells

AC Gennaro Prota, Uzi Gileadi, Margarida Rei, Ana Victoria Lechuga-Vieco, Ji-Li Chen, Silvia Galiani, Melissa Bedard, Vivian Wing Chong Lau, Lorenzo F. Fanchi, Mara Artibani, Zhiyuan Hu, Siamon Gordon, Jan Rehwinkel, Jose A. Enríquez, Ahmed A. Ahmed, Ton N. Schumacher, and Vincenzo Cerundolo

Compared to cytosolic antigens, mitochondrial tumor antigens prime a stronger antitumor immune response, instigated by enhanced cross-presentation and involvement of the STING pathway. Thus, cellular location of tumor antigens is relevant to improved cancer vaccine development.

698 GITR Agonism Triggers Antitumor Immune Responses through IL21-Expressing Follicular Helper T Cells

Choong-Hyun Koh, Il-Kyu Kim, Kwang-Soo Shin, Insu Jeon, Boyeong Song, Jeong-Mi Lee, Eun-Ah Bae, Hyungseok Seo, Tae-Seung Kang, Byung-Seok Kim, Yeonseok Chung, and Chang-Yuil Kang

Agonistic antibodies to GITR have antitumor effects. IL4-exposed CD4⁺ T cells activate c-Maf to generate IL21-expressing Tfh cells, which is required for antitumor activity and may be a surrogate marker for the effectiveness of GITR agonistic antibodies.

710 RIPK3 Orchestrates Fatty Acid Metabolism in Tumor-Associated Macrophages and Hepatocarcinogenesis

Lei Wu, Xiao Zhang, Lu Zheng, Huakan Zhao, Guifang Yan, Qi Zhang, Yu Zhou, Juan Lei, Jiangang Zhang, Jingchun Wang, Rong Xin, Lu Jiang, Jin Peng, Qian Chen, Sin Man Lam, Guanghou Shui, Hongming Miao, and Yongsheng Li

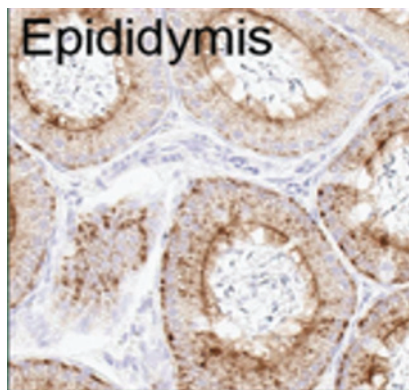
The immune-suppressive effects of tumor-associated macrophages (TAM) are partially controlled by metabolic reprogramming. RIPK3 shifts TAMs to an antitumor phenotype in hepatocellular carcinoma by modulating fatty acid metabolism, thus decreasing tumorigenesis.

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ABOUT THE COVER

Evidence for bispecific antibody efficacy against solid tumors is limited, and additional approaches may be required in the clinic to achieve the success seen with hematologic tumors. Chiu et al. address this by designing a CD3 bispecific antibody that also targets a major prostate cancer tumor antigen, prostate-specific membrane antigen (PSMA). Preclinical models show positive responses to bispecific antibody treatment that is dependent on tumor size, with smaller tumors being more sensitive than larger tumors. However, by combining the bispecific antibody with 4-1BB costimulation, larger tumors are more readily reduced due to boosted, durable T-cell responses and the generation of immune memory. The data highlight that tumor size matters and that 4-1BB costimulation can be used to increase the potency of bispecific antibody treatment in solid tumors. Read more in this issue on page 596. Original image from Supplementary Fig. S5A. Artwork by Lewis Long.



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