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, 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. Finnin, Sunree Jalal, Pamela Krueger, Jason T. Giurleo, Dangshe Ma, Eric Smith, and Alison Crawford
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, Li Li, Dan Xiong, Xiaoxuan Huang, Zilong Xu, Zeng Yu, Yingbin Wang, Jun Zhang, Chenghao Huang, and Ninghao 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, Marliis Ott, Candice D. Church, Rima M. Kulikauskas, Dafina Ibrani, Jayasi G. Iyer, Olga K. Afanasiev, Arie 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 IL1α Antagonizes IL1β and Promotes Adaptive Immune Rejection of Malignant Tumors
Tian Tian, Serena Lofftus, Youdoung Pan, Claire A. Stingley, Sandra L. King, Jingxia Zhao, Timothy Y. Pan, Rebecca Lock, Jacob W. Marglous, Kevin Liu, Hans R. Wilmuth, Robert C. Fuhrbrigge, Karen Cichowski, and Thomas S. Kupper
Antibodies to IL1β can enhance antitumor immunity, but inhibiting IL1α reduces antitumor effects. Thus, antagonists that block the shared IL1RI do not improve antitumor immunity and are not equivalent to blocking IL1β alone.
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 vitro immune assays to identify cross-reactive TCRs.

Enhanced Immunogenicity of Mitochondrial-Localized Proteins in Cancer Cells
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.

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.

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.

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.