# WHAT WE’RE READING

599  A Sampling of Highlights from the Literature

## IN THE SPOTLIGHT

600  A γδ T-cell Imprint in a Rare Skin Tumor
Natalia Jaeger and Marco Colonna
See related article, p. 612

601  Repertoire Remodeling through CD4⁺ T-cell Depletion
Winnie Yao and Ansuman T. Satpathy
See related article, p. 624

## PRIORITY BRIEF

602  Robust Antitumor Immunity in a Patient with Metastatic Colorectal Cancer Treated with Cytotoxic Regimens
Venkatesh Rajamanickam, Carmen Ballesteros-Merino, Kimberly Samson, David Ross, Brady Bernard, Bernard A. Fox, Eric Tran, Pippa Newell, and Thomas Duhun

Metastatic colorectal cancers usually have low immune infiltration and poor prognosis. This report of a patient with a strong tumor antigen–specific CD8⁺ T-cell response following cytotoxic regimens suggests these treatments have potential to prime the immune system.

## RESEARCH ARTICLES

612  γδ T Cells in Merkel Cell Carcinomas Have a Proinflammatory Profile Prognostic of Patient Survival

The data show many Merkel cell carcinomas have prominent γδ T-cell infiltrates. These unconventional T cells recognize MHC-like ligands and have a proinflammatory gene-expression profile that is associated with improved patient survival, suggesting potential prognostic and therapeutic utility.

See related Spotlight, p. 600

624  Transient Depletion of CD4⁺ Cells Induces Remodeling of the TCR Repertoire in Gastrointestinal Cancer

Analysis of the blood-tumor overlapping TCR repertoire reveals that transient depletion of CD4⁺ cells causes beneficial remodeling of the TCR repertoire and contributes to the expansion of CD8⁺ tumor-reactive clones in patients with cancer.

See related Spotlight, p. 601

637  Alternative Splicing of the Inhibitory Immune Checkpoint Receptor SLAMF6 Generates a Dominant Positive Form, Boosting T-cell Effector Functions
Emma Hajaj, Elad Zisman, Shai Traban, Sharon Merims, Jonathan Cohen, Shiri Klein, Shoshana Frankenburg, Moshe Sade-Feldman, Yuval Tabach, Keren Yizhak, Ami Navon, Polina Stepsensky, Nir Hacohen, Tamar Peretz, André Veillette, Rotem Karni, Galit Eisenberg, and Michal Lotem

Alternative splicing of SLAMF6 generates two isoforms with opposing effects on T-cell activation; immune checkpoint blockade enriches for the shorter agonistic isoform in T cells, and switching SLAMF6 splicing using antisense oligonucleotides leads to improved antitumor T-cell responses.

651  Chronic Adrenergic Stress Contributes to Metabolic Dysfunction and an Exhausted Phenotype in T Cells in the Tumor Microenvironment
Guanxi Qiao, Minhui Chen, Hemn Mohammompour, Cameron R. MacDonald, Mark J. Buscek, Bonnie L. Hylander, Joseph J. Barb, and Elizabeth A. Repasky

T-cell exhaustion impacts immunotherapy efficacy. How T-cell exhaustion is regulated remains incompletely understood. Here, the sympathetic stress response is shown to regulate the development of T-cell exhaustion by modulating CD8⁺ T-cell metabolism and function in the TME.
Chemotherapy Induces Tumor-Associated Macrophages that Aid Adaptive Immune Responses in Ovarian Cancer
Owen Heath, Chiara Berlato, Eleni Maniati, Anissa Lakhani, Colin Pegrum, Panoraia Kotantaki, Samar Elorbany, Steffen Böhm, Simon T. Barry, Alessandro Annibaldi, Desmond P. Barton, and Frances R. Balkwill
Neoadjuvant chemotherapy is shown to reduce the density of tumor-associated macrophages (TAM). In addition, chemotherapy reduces M2-related markers and increases proinflammatory signaling in TAMs, including inflammasome activation, thus highlighting an opportunity to improve antitumor responses.

Pro- and Antitumorigenic Capacity of Immunoproteasomes in Shaping the Tumor Microenvironment
Data demonstrate that the immunoproteasome is essential for shaping the tumor microenvironment. Opposing pro- and antitumor functions of the immunoproteasome are identified, highlighting the importance of understanding its role in different cancer types.

Virus-Like Particle–Drug Conjugates Induce Protective, Long-lasting Adaptive Antitumor Immunity in the Absence of Specifically Targeted Tumor Antigens
Rhonda C. Kines, Cynthia D. Thompson, Sean Spring, Zhenyu Li, Elisabet de los Pinos, Stephen Monks, and John T. Schiller
AU-011 is composed of an HPV VLP conjugated to photoactivatable IRDye-700DX. Their broad, tumor-tropic nature combined with light-induced cytotoxic activity induces tumor immunogenic cell death, boosts antitumor immunity, and elicits long-term antitumor immunity.

Targeting Triple-Negative Breast Cancer with Combination Therapy of EGFR CAR T Cells and CDK7 Inhibition
CAR T-cell resistance can occur due to multiple factors. EGFR CAR T-cell treatment induces expression of an immunosuppressive gene set. Interruption of transcriptional activity using a “unite-and-conquer” strategy sensitizes refractory TNBC to treatment and reduced tumor growth.

About the Cover
The effects of neoadjuvant chemotherapy (NACT) on innate antitumor immunity are not fully understood. Heath et al. find that NACT promotes tumor-associated macrophages (TAM) to acquire an antitumor phenotype in high-grade serous ovarian cancer (HGSOC). Although TAM density is reduced with NACT, the treatment also decreases expression of M2-related markers while increasing proinflammatory pathways, including the inflammasome. These TAMs are found to be important for disease-free and overall survival in orthotopic HGSOC models. The data highlight the potential of targeting tumor-promoting TAMs whilst augmenting the activity of antitumor TAMs to boost therapeutic responses in the context of NACT. Read more in this issue on page 665. Original image from Fig. 1C. Artwork by Lewis Long.