# WHAT WE’RE READING

- **A Sampling of Highlights from the Literature**
- **Building on Success**
  Robert D. Schreiber and Philip D. Greenberg

# CANCER IMMUNOLOGY AT THE CROSSROADS

- **Insights into Tumor-Associated Tertiary Lymphoid Structures: Novel Targets for Antitumor Immunity and Cancer Immunotherapy**
  Anthony B. Rodriguez and Victor H. Engelhard

# CANCER IMMUNOLOGY MINIATURES

- **Tumor Mutation Burden and Structural Chromosomal Aberrations Are Not Associated with T-cell Density or Patient Survival in Acral, Mucosal, and Cutaneous Melanomas**
  Analysis shows that TMB does not correlate with tumor immune infiltrates, including tumor-resident CD8$^+$ T cells, in acral, mucosal, and cutaneous melanomas. The data indicate that TMB is not a significant driver of antitumor responses.

# PRIORITY BRIEF

- **A DNA-Launched Nanoparticle Vaccine Elicits CD8$^+$ T-cell Immunity to Promote In Vivo Tumor Control**
  Ziyang Xu, Neethu Chokkalingam, Edgar Tello-Ruiz, Megan C. Wise, Mamadou A. Bah, Susanne Walker, Nicholas J. Tursi, Paul D. Fisher, Katherine Schultheis, Kate E. Broderick, Laurent Humeau, Daniel W. Kulp, and David B. Weiner
  DNA nanoparticle vaccination plus electroporation robustly induces CD8$^+$ CTL responses that are able to control, or protect from, melanoma growth in mice. The data demonstrate the utility of this platform and offer a strategy to boost antitumor responses.

# RESEARCH ARTICLES

- **Melanoma Evolves Complete Immunotherapy Resistance through the Acquisition of a Hypermetabolic Phenotype**
  Under immune pressure from T-cell checkpoint blockade, melanoma evolves a hypermetabolic phenotype conferring complete immunotherapy resistance. Key genes driving enhanced glycolysis and oxidative phosphorylation confer resistance when transferred to the parental melanoma or to a pancreatic cancer.

- **Tumor-Derived IL33 Promotes Tissue-Resident CD8$^+$ T Cells and Is Required for Checkpoint Blockade Tumor Immunotherapy**
  Lujun Chen, Runzi Sun, Junchi Xu, Wensi Zhai, Dachuan Zhang, Min Yang, Cuilua Yue, Yichao Chen, Song Li, Heth Turnquist, Jingting Jiang, and Binfeng Lu
  Despite the clinical efficacy of immune checkpoint blockade (ICB), much of its impact on the tumor microenvironment is unclear. IL33 mediated ICB efficacy by inducing the accumulation of tumor-resident CD103$^+$ CD8$^+$ T cells and CD103$^+$ dendritic cells.

- **Tumor-Infiltrating Regulatory T-cell Accumulation in the Tumor Microenvironment Is Mediated by IL33/ST2 Signaling**
  Regulatory T cells (Tregs) suppress antitumor immunity, yet the mechanism for how they accumulate in tumors is unclear. IL33/ST2 signaling axis in Tregs is crucial for the accumulation of Tregs in the tumor microenvironment.
Glycans as Immune Checkpoints: Removal of Branched N-glycans Enhances Immune Recognition Preventing Cancer Progression

Mariana C. Silva, Ângela Fernandes, Maria Oliveira, Carlos Resende, Alexandra Correia, Julio C. de-Freitas-Junior, Aonghus Lavelle, Jéssica Andrade-da-Costa, Magdalena Leander, Helena Xavier-Ferreira, José Bessa, Carina Pereira, Rui M. Henrique, Fátima Carneiro, Mário Dinis-Ribeiro, Ricardo Marcos-Pinto, Margarida Lima, Bernd Lepenies, Harry Sokol, José C. Machado, Manuel Vilanova, and Salomé S. Pinho

Complex branched N-glycans are identified as glyco-immune checkpoints that are used by colorectal cancer cells to evade immune recognition. The data highlight how inhibiting this glycosylation could be a strategy to improve antitumor responses.

Blocking P2X7-Mediated Macrophage Polarization Overcomes Treatment Resistance in Lung Cancer

Juliang Qin, Xiaoyu Zhang, Binghe Tan, Su Zhang, Chengcong Yin, Qi Xue, Zhen Zhang, Hua Ren, Jinlian Chen, Mingyao Liu, Min Qian, and Bing Du

P2X7 is expressed in tumor-associated macrophages (TAM), yet its role in lung cancer progression is unknown. Blockade of P2X7 induces antitumor TAMs and rescues the efficacy of anti–PD-1 and chemotherapy against lung cancer.

Infiltration by IL22-Producing T Cells Promotes Neutrophil Recruitment and Predicts Favorable Clinical Outcome in Human Colorectal Cancer

Nadia Tosti, Eleonora Cremonesi, Valeria Governa, Camilla Basso, Venkatesh Kancherla, Mairere Coto-Llerena, Francesca Amicarella, Benjamin Weixler, Silvio Däster, Giuseppe Sconocchia, Pietro Edoardo Majno, Dimitri Christoforidis, Luigi Tornillo, Luigi Terracciano, Charlotte K.Y. Ng, Salvatore Piscuglia, Markus von Flée, Giulio Spagnoli, Serenella Eppenberger-Castori, Giandomenica Iezzi, and Raoul Andre Droeser

IL22-producing immune cells are involved in inflammatory gut diseases, yet their role in colorectal cancer (CRC) remains unclear. IL22-secreting T cells recruit neutrophils to CRC tumors, leading to enhanced patient survival.

ABOUT THE COVER

Although immune checkpoint blockade (ICB) has shown success in prolonging the survival of patients with cancer, the mechanisms behind this are not fully elucidated. Chen et al. find that tumor-derived IL33, whose expression increases after ICB treatment, and ST2 signaling in nontumor cells are key to inducing antitumor responses. IL33 increases functional CD103+CD8+ T cells and CD103+ dendritic cells (DC) in the tumor microenvironment (TME), and the CD103+ DCs are essential for the recruitment of tumor-infiltrating CD8+ T cells into the TME. By treating tumor-bearing mice with IL33 in combination with dual ICB, survival was extended, highlighting the important role of IL33 in mediating the efficacy of ICB. Read more in this issue on page 1381. Original image from Fig. 4F. Artwork by Lewis Long.