### WHAT WE'RE READING

**1443**  
A Sampling of Highlights from the Literature

### IN THE SPOTLIGHT

**1444**  
Seeking Synergy of Checkpoint Blockade through TGFβ Inhibition  
Ellen Puré  
See related article, p. 1459.

### CANCER IMMUNOLOGY AT THE CROSSROADS

**1445**  
The Balancing Act between Cancer Immunity and Autoimmunity in Response to Immunotherapy  
Arabella Young, Zoe Quandt, and Jeffrey A. Bluestone

### CANCER IMMUNOLOGY MINIATURE

**1453**  
Clinical Significance of Pancreatic Atrophy Induced by Immune-Checkpoint Inhibitors: A Case-Control Study  
Yael Esthet, Erez Nissim Baruch, Ronnie Shapira-Frommer, Yael Steinberg-Silman, Teodor Kuznetsov, Guy Ben-Betzalel, Sameh Daher, Iris Gluck, Nethanel Asher, Sara Apter, Jacob Schachter, Jair Bar, Ben Boursi, and Gal Markel  
Immune-checkpoint therapy-induced diarrhea is usually attributed to inflammatory colitis. However, late-onset diarrhea in patients treated with PD-1 inhibitors may be caused by pancreatic atrophy, leading to exocrine insufficiency. Although steroid-resistant, this condition may be treated with oral enzyme supplements.

### RESEARCH ARTICLES

**1459**  
Stromal Fibroblasts Mediate Anti–PD-1 Resistance via MMP-9 and Dictate TGFβ Inhibitor Sequencing in Melanoma  
Feri Zhao, Kathy Evans, Christine Xiao, Nicholas DeVito, Balamoyooran Theivagnithan, Alisha Holzhausen, Peter J. Siska, Gerard C. Blobe, and Brent A. Hanks  
Melanoma-associated fibroblasts contributed to checkpoint blockade resistance via MMP-9–dependent PD-L1 cleavage and influenced the impact of TGFβ inhibition on responses to anti–PD-1. These findings highlight the importance of understanding immunotherapy effects on the tumor microenvironment.  
See related Spotlight, p. 1444.

**1472**  
FAP Delineates Heterogeneous and Functionally Divergent Stromal Cells in Immune-Excluded Breast Tumors  
Viviana Cremasco, Jillian L. Astariat, Angelo L. Grauel, Shilpa Keerthivasan, Kenzhe Madsen, Matthew C. Woodruff, Michael Wu, Lotte Spel, Stephen Santoro, Zohreh Amoozgar, Tyler Laszewski, Sana Cruz-Migoni, Konstantin Knoblich, Anne L. Fletcher, Martin LaFleur, Kay W. Wucherpfennig, Ellen Puré, Glenn Dano, Michael C. Carroll, and Shannon J. Turley  
Cancer-associated stromal cells restrain responses to immunotherapy and are associated with poor prognosis. Identification of mesenchymal cells from fresh breast tumor samples revealed subsets with distinct phenotype and immunoregulatory potential. These observations may lead to better-designed immunotherapies.

**1486**  
Phage-Based Anti-HER2 Vaccination Can Circumvent Immune Tolerance against Breast Cancer  
Caterina Bartolacci, Cristina Andreani, Claudia Curcio, Sergio Occhipinti, Luca Massacesi, Mirella Giovarelli, Roberta Galeazzi, Manuela Iezzi, Martina Tilio, Valentina Gambini, Jinhao Wang, Cristina Marchini, and Augusto Amici  
Structural and immunogenic differences between HER2 and Δ16HER2 were determined, and DNA and phage-based vaccines were developed. This vaccine strategy led to breaking immune tolerance in a breast cancer model, allowing for improved antitumor responses.

**1499**  
Combination Therapy Using Ruxolitinib and Oncolytic HSV Renders Resistant MPNSTs Susceptible to Virotherapy  
Mohammed G. Ghoume and Kevin A. Cassady  
Treatment-resistant tumors were pretreated with an FDA-approved drug which rendered them responsive to virotherapy. Both viral replication and the immune-mediated antitumor response are integral to the efficacy of this combination therapy.

**1511**  
A High-Throughput Immune-Oncology Screen Identifies EGFR Inhibitors as Potent Enhancers of Antigen-Specific Cytotoxic T-Lymphocyte Tumor Cell Killing  
A screening tool capable of high-throughput identification of compounds and genes affecting antitumor responses is presented. Specific EGFR inhibitors were identified and validated as enhancing T cell–mediated killing of tumor cells, providing a proof-of-principle for this approach.
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1524 Altered Binding of Tumor Antigenic Peptides to MHC Class I Affects CD8+ T Cell–Effector Responses

1537 NK Cell Education in Tumor Immune Surveillance: DNAM-1/KIR Receptor Ratios as Predictive Biomarkers for Solid Tumor Outcome
Concepción F. Guillamón, María V. Martínez-Sánchez, Lourdes Gimeno, Anna Mrowiec, Jerónimo Martínez-García, Gerardo Server-Pastor, Jorge Martínez-Escribano, Amparo Torroba, Belén Ferri, Daniel Abellán, José A. Campillo, Isabel Legaz, María R. López-Álvarez, María Rosa Moya-Quiles, Manuel Muñoz, and Alfredo Minguela

1548 PD-L1 Mediates Dysfunction in Activated PD-1+ NK Cells in Head and Neck Cancer Patients
Fernando Concha-Benavente, Benjamin Kansy, Jessca Moskovitz, Jennifer Moy, Uma Chandran, and Robert L. Ferris

1561 Entinostat Converts Immune-Resistant Breast and Pancreatic Cancers into Checkpoint-Responsive Tumors by Reprogramming Tumor-Infiltrating MDSCs

1578 Exosomes Released from Tumor-Associated Macrophages Transfer miRNAs That Induce a Treg/Th17 Cell Imbalance in Epithelial Ovarian Cancer
Jieru Zhou, Xiaoduan Li, Xiaoli Wu, Ting Zhang, Qinyi Zhu, Xinjing Wang, Husheng Wang, Kai Wang, Yingying Lin, and Xipeng Wang

About the Cover
Poor clinical outcome in cancer patients is associated with the presence of cancer-associated fibroblasts (CAFs). However, fibroblasts are heterogeneous and can have different functions, and whether CAFs directly interact with and impact T cells in the tumor microenvironment remains to be determined. Cremasco and Astarita et al. show that two populations of FAP+ mesenchymal stromal cells exist in breast cancer tumors from humans and mice: those that express podoplanin (PDPN+ CAFs) and those that do not (cancer-associated pericytes; CAPs). Each population has a distinctive gene signature and localization within tumors, and FAP+ PDPN+ CAFs were shown to suppress T cells, whereas FAP+ PDPN- CAPs were not immunosuppressive. These data highlight how different FAP+ stromal cell populations can modulate the breast cancer tumor microenvironment. Read more in this issue on page 1472. Original image from Supplementary Fig. S1E. Artwork by Lewis Long.