

WHAT WE'RE READING

- 1443** A Sampling of Highlights from the Literature

IN THE SPOTLIGHT

- 1444** Seeking Synergy of Checkpoint Blockade through TGF β 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 Eshet, 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
Immunotherapy-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 TGF β Inhibitor Sequencing in Melanoma
Fei Zhao, Kathy Evans, Christine Xiao, Nicholas DeVito, Balamayooran Theivanthiran, Alisha Holtzhausen, Peter J. Siska, Gerard C. Globe, and Brent A. Hanks
Melanoma-associated fibroblasts contributed to checkpoint blockade resistance via MMP-9-dependent PD-L1 cleavage and influenced the impact of TGF β 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. Astarita, Angelo L. Grauel, Shilpa Keerthivasan, Kenzie MacIsaac, Matthew C. Woodruff, Michael Wu, Lotte Spel, Stephen Santoro, Zohreh Amoozgar, Tyler Laszewski, Sara Cruz Migoni, Konstantin Knoblich, Anne L. Fletcher, Martin LaFleur, Kai W. Wucherpfennig, Ellen Pure, Glenn Dranoff, Michael C. Carroll, and Shannon J. Turley
Cancer-associated stromal cells restrain responses to immunotherapy and are associated with poor prognosis. Isolation 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 Massaccesi, Mirella Giovarelli, Roberta Galeazzi, Manuela Iezzi, Martina Tilio, Valentina Gambini, Junbiao Wang, Cristina Marchini, and Augusto Amici
Structural and immunogenic differences between HER2 and Δ 16HER2 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. Ghonime 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



Patrick H. Lizotte, Ruey-Long Hong, Troy A. Luster, Megan E. Cavanaugh, Luke J. Taus, Stephen Wang, Abha Dhaneshwar, Naomi Mayman, Aaron Yang, Meghana Kulkarni, Lauren Badalucco, Erica Fitzpatrick, Hsiang-Fong Kao, Mari Kuraguchi, Mark Bittinger, Paul T. Kirschmeier, Nathanael S. Gray, David A. Barbie, and Pasi A. Jänne
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**
Eleanor Clancy-Thompson, Christine A. Devlin, Paul M. Tyler, Mariah M. Servos, Lestat R. Ali, Katherine S. Ventre, M. Aladdin Bhuiyan, Patrick T. Bruck, Michael E. Birnbaum, and Stephanie K. Dougan
Influence of T-cell priming on effector antitumor responses was evaluated. Loss of secondary contacts between a peptide non-anchor residue and MHC skews effector functions to favor cytotoxicity over cytokine production in T cells specific for a melanoma self-antigen.

- 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 Muro, and Alfredo Minguela
Solid tumors modulate the expression of molecules induced by licensing interactions during NK-cell education and alter their function. Expression of these molecules can predict patient survival and have implications in the design of NK cell-based therapies.

- 1548** **PD-L1 Mediates Dysfunction in Activated PD-1⁺ NK Cells in Head and Neck Cancer Patients**
Fernando Concha-Benavente, Benjamin Kansy, Jessica Moskovitz, Jennifer Moy, Uma Chandran, and Robert L. Ferris
PD-1 expression and function were assessed in NK cells from patients with head and neck cancer. NK cell dysfunction was reversed by PD-1 blockade and improved responses to cetuximab therapy, thus, providing an approach to reverse tumor immune evasion.

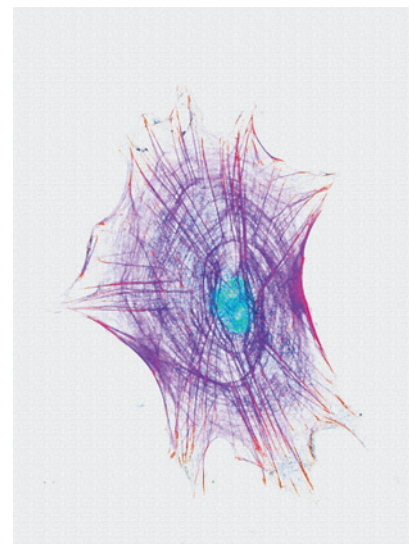
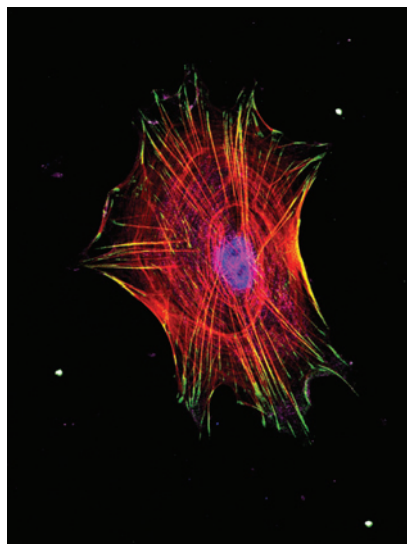
- 1561** **Entinostat Converts Immune-Resistant Breast and Pancreatic Cancers into Checkpoint-Responsive Tumors by Reprogramming Tumor-Infiltrating MDSCs**
Brian J. Christmas, Christine I. Rafie, Alexander C. Hopkins, Blake A. Scott, Hayley S. Ma, Kayla A. Cruz, Skylar Woolman, Todd D. Armstrong, Roisin M. Connolly, Nilo A. Azad, Elizabeth M. Jaffee, and Evanthia T. Roussos Torres
The HDAC inhibitor, entinostat, impairs myeloid immunosuppressive function, and in combination with immune checkpoint inhibitors, improves T-cell responses in models of breast and pancreatic cancers. These data provide rationale for combination therapy in patients to improve antitumor responses.

- 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
The Treg/Th17 ratio is altered in epithelial ovarian cancer. Exosomal miRNAs from tumor-associated macrophages contribute to this T-cell imbalance, which promotes an immune suppressive tumor microenvironment and favors progression and metastasis of epithelial ovarian cancer cells.

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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.



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