WHAT WE’RE READING

1563  A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

1564  Metabolic Consequences of T-cell Costimulation in Anticancer Immunity
Alvaro Teijeira, Saray Garasa, Inaki Etxeberria, Maria Cato-Cañas, Ignacio Melero, and Greg M. Delgoffe

CANCER IMMUNOLOGY MINIATURES

1570  Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy
Aaron M. Goodman, Ethan S. Sokol, Garrett M. Frampton, Scott M. Lippman, and Razelle Kurzrock
Only a subset of cancer patients responds to immune checkpoint blockade, making predictive response biomarkers an important treatment tool. Analysis of Foundation Medicine data reveals tumor responsiveness to checkpoint blockade when they are microsatellite-stable, but multiply mutated.

1574  Immunopathologic Stratification of Colorectal Cancer for Checkpoint Blockade Immunotherapy
A composite score utilizing tumor PD-L1 expression and mucin content, the CPM score, was defined in patients with metastatic colorectal cancer. This score distinguished patients who achieved clinical benefit with anti–PD-1 from those who developed progressive disease.

PRIORITIZED BRIEF

1580  USP22 Deubiquitinates CD274 to Suppress Anticancer Immunity
Xing Huang, Qi Zhang, Yu Lou, Junli Wang, Xinyu Zhao, Lin Wang, Xiaozhen Zhang, Shanshan Li, Yulan Zhao, Qi Chen, Tingbo Liang, and Xueli Bai
CD274 (PD-L1) inhibits T-cell function and antitumor immune responses. Mouse models and human datasets show that CD274 expression is controlled by the deubiquitinase USP22, which limits immune-mediated tumor growth and responses to immune checkpoint blockade and chemotherapy.

RESEARCH ARTICLES

1591  Machine-Learning Prediction of Tumor Antigen Immunogenicity in the Selection of Therapeutic Epitopes
Christof C. Smith, Shengjie Chai, Amber R. Washington, Samuel J. Lee, Elisa Landoni, Kevin Field, Jason Garnes, Lisa M. Bisby, Sara R. Selinsky, Joel S. Parker, Barbara Savoldo, Jonathan S. Serody, and Benjamin G. Vincent
A machine-learning algorithm was developed for predicting immunogenic tumor-specific antigens (TSAs). This tool was demonstrated to: (i) predict therapeutically relevant TSAs, (ii) identify genomic signatures correlated with TSA immunogenicity, and (iii) identify out-of-frame TSAs that promote antitumor immunity.

1605  Immunosuppressive Immature Myeloid Cell Generation Is Controlled by Glutamine Metabolism in Human Cancer
Wen-Chao Wu, Hong-Wei Sun, Jing Chen, Han-Yue OuYang, Xing-Juan Yu, Hai-Tian Chen, Ze-Yu Shuang, Ming Shi, Zilian Wang, and Limin Zheng
The metabolism of immune cells in the tumor microenvironment is crucial to their function. The differentiation and immunosuppressive activity of immature myeloid cells in human tumor microenvironments is supported by glutamine-derived α-ketoglutarate and the glutamate–NMDA receptor axis.

1619  CD8+PD-1-ILT2+ T Cells Are an Intratumoral Cytotoxic Population Selectively Inhibited by the Immune-Checkpoint HLA-G
Clement Dumont, Alix Jacquier, Jerome Verine, Floriane Noel, Annabelle Goujon, Ching-Lien Wu, Tzu-Min Hung, François Desgrandchamps, Stephanie Culine, Edgardio D. Carosella, Nathalie Rouas-Freiss, and Joel LeMaoult
Transcriptomic and flow cytometric characterization of renal carcinoma identified intratumoral CD8+PD-1-ILT2+ T cells as a terminally differentiated, effector cell subset lacking PD-1 expression. Blocking interaction with the ILT2 ligand, HLA-G, has therapeutic potential to enhance checkpoint blockade efficacy.

1633  Enhanced SLAMF7 Homotypic Interactions by Elotuzumab Improves NK Cell Killing of Multiple Myeloma
Tatiana Pazina, Ashley M. James, Kimberly B. Colby, Yibin Yang, Andrew Gale, Amy Jhatakia, Alper Y. Kearney, Robert F. Graziano, Natalie A. Bezman, Michael D. Robbins, Adam D. Cohen, and Kerry S. Campbell
Elotuzumab is an effective immunotherapy that induces NK cell–mediated killing of multiple myeloma by CD16-dependent and –independent mechanisms. The CD16-independent mechanism involves the promotion of SLAMF7–SLAMF7 interactions.
### 1647  Mirc11 Disrupts Inflammatory but Not Cytotoxic Responses of NK Cells

The microRNA cluster Mirc11 regulates antitumor responses by targeting ubiquitin modifiers. Absence of Mirc11 led to deubiquitylation of scaffolding K63 and the addition of degradative K48 moieties on TRAF6, ultimately reducing NF-κB and AP1-mediated inflammatory cytokine production.

### 1663  CD47 Expression Defines Efficacy of Rituximab with CHOP in Non–Germinal Center B-cell (Non-GCB) Diffuse Large B-cell Lymphoma Patients (DLBCL), but Not in GCB DLBCL
Renée Bouwstra, Yuan He, Janneke de Boer, Hilde Kooistra, Ewa Cendrowicz, Rudolf S.N. Fehrmann, Emanuele Ammatuna, Christine zu Eulenburg, Marcel Nijland, Gerwin Huls, Edwin Bremer, and Tom van Moerern

High CD47 expression impacts survival of patients with non-germinal center, but not germinal center, diffuse large B-cell lymphoma treated with rituximab plus standard chemotherapy. Blocking CD47 in vitro enhanced phagocytosis of rituximab-mediated phagocytosis in only non-GCB cell lines.

### 1672  TAM Family Receptor Kinase Inhibition Reverses MDSC-Mediated Suppression and Augments Anti–PD-1 Therapy in Melanoma
Alisha Holtzhausen, William Harris, Eric Ubil, Debra M. Hunter, Ichen Zhao, Yuewei Zhang, Dehui Zhang, Qingyang Liu, Xiaodong Wang, Douglas K. Graham, Stephen C. Earp, and Tom van Oeijen

Myeloid-derived suppressor cells (MDSCs) promote melanoma tumor growth, making MDSCs potential therapeutic targets. Targeting receptor tyrosine kinases TYRO3, AXL, and MERTK (upregulated on MDSCs in melanoma models and patients) delays tumor growth and improves immune checkpoint blockade.

### 1687  Mediators of Inflammation-Driven Expansion, Trafficking, and Function of Tumor-Infiltrating MDSCs

Induction of MDSCs and their recruitment to the tumor microenvironment is the result of a coordinated response by tumor stromal components to IL1β and its downstream mediators. These data provide a deeper understanding of MDSC development and function.

### 1700  Blockade of TIGIT/CD155 Signaling Reverses T-cell Exhaustion and Enhances Antitumor Capability in Head and Neck Squamous Cell Carcinoma
Lei Wu, Liang Hao, Jian-Feng Liu, Lei Chen, Guang-Tao Yu, Lei-Lei Yang, Hao Wu, Lin-Lin Bu, Ashok B. Kulkarni, Wen-Feng Zhang, and Zhi-Jun Sun

Blockade of the TIGIT/CD155 checkpoint signaling pathway enhanced CD8+ T-cell effector function and antitumor responses in a transgenic HNSCC mouse model. PD-1/PD-L1 blockade increased TIGIT expression on Tregs, suggesting this combination for future studies to overcome immunosuppression.

### 1714  Irreversible Electroporation Combined with Checkpoint Blockade and TLR7 Stimulation Induces Antitumor Immunity in a Murine Pancreatic Cancer Model
Jayanth S. Shankara Narayanan, Partha Ray, Tomoko Hayashi, Thomas C. Whisenant, Diego Vicente, Dennis A. Carson, Aaron M. Miller, Stephen P. Schoenberger, and Rebekah R. White

Irreversible electroporation (IRE) is used for patients with locally advanced pancreatic cancer. IRE reduces local tumor burden and induces an “in situ vaccination” response against pancreatic cancer that could be combined with immunotherapy to treat distant metastatic disease.

### 1727  Human CD4+ T Cells Specific for Merkel Cell Polyomavirus Localize to Merkel Cell Carcinomas and Target a Required Oncogenic Domain
Natalie V. Longino, Junbao Yang, Jayaari G. Iyer, Dafina Ibrani, I-Ting Chow, Kerry J. Laing, Victoria L. Campbell, Kelly G. Paulson, Rima M. Kulikauskas, Candice D. Church, Eddie A. James, Paul Nghiem, William W. Kwok, and David M. Koelle

Tumor-specific CD4+ T-cell epitopes were identified and allowed detailed characterization of CD4+ T-cell responses in patients with Merkel cell carcinoma. The methods used in this study provide a foundation to investigate and develop CD4+ T-cell–based immunotherapies.
ABOUT THE COVER

Myeloid cells in the tumor microenvironment are often associated with poor patient survival and poor response to immune therapy. Wu and Sun et al. investigate the regulation of these cells and find that immature myeloid cells (IMCs) infiltrating several human tumors are highly immunosuppressive, correlating to their glycolytic and proliferative capacity. The generation of IMCs relies on glutamine metabolism, specifically glutamine-derived α-ketoglutarate and the glutamate–NMDA receptor axis. Blocking these pathways enhances the efficacy of anti–PD-L1 treatment in a mouse tumor model resistant to immune checkpoint blockade, suggesting that glutaminolysis of suppressive myeloid cells is a promising target to improve the outcome of immune therapy. Read more starting on page 1605. Original fluorescence micrograph of the myeloid cells at the invasive margin of tumor tissues provided by the Zheng laboratory. Artwork by Lewis Long.