WHAT WE'RE READING

1563 A Sampling of Highlights from the Literature

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 Garner, Lisa M. Bidh, Sara R. Selinski, Joel S. Parker, Barbara Savoldo, Jonathan S. Serody, and Benjamin G. Vincent
A machine-learning algorithm was developed for predicting immunogenic tumor-specific antigens (TSA). This tool was demonstrated to: (i) predict therapeutically relevant TSA, (ii) identify genomic signatures correlated with TSA immunogenicity, and (iii) identify out-of-frame TSA 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 alpha-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, Francois Desgranchamps, Stephanie Culine, Edgardo D. Carosella, Nathalie Rouas-Freiss, and Joel LeMaoult
Transcriptomic and flow cytometric characterization of renal carcinoma identified intratumoral CD8⁺ 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 API-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 Moerkeren

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 Lbil, Debra M. Hunter, Ichen Zhao, Yuewei Zhang, Dehui Zhang, Qingyang Liu, Xiaodong Wang, Douglas K. Graham, Stephen P. Schoenberger, and Rebekah R. White

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.

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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.