HIGHLIGHTS FROM THE LITERATURE

121 What We’re Reading

MEETING REPORT

122 Report on the NCI Microbial-Based Cancer Therapy Conference
Colleen S. Curran, Avraham Rasooly, Min He, Ben Prickril, Magdileena Thurin, and Elad Sharon

RESEARCH ARTICLES

127 Soluble SLAMF6 Receptor Induces Strong CD8⁺ T-cell Effector Function and Improves Anti-Melanoma Activity In Vivo
Galit Eisenberg, Roni Engelstein, Anat Geiger-Maor, Emma Hajaj, Sharon Merims, Shoshana Frankenburg, Ronny Uzana, Abraham Rutenberg, Arthur Machlenkin, Gabi Frei, Tamar Peretz, and Michal Lotem

Treatment of tumor-bearing mice with the ectodomain of SLAMF6, an immune receptor, improved tumor-infiltrating CD8⁺ lymphocyte persistence and function. Ectodomain-treated mice had enhanced tumor clearance, suggesting that converting the SLAMF6 interaction from inhibitory to stimulatory could be therapeutic.

139 Radiotherapy and CTLA-4 Blockade Shape the TCR Repertoire of Tumor-Infiltrating T Cells

Tumor-targeted radiotherapy can synergize with CTLA-4 blockade to induce T-cell-mediated rejection of tumors refractory to CTLA-4 blockade alone. The resultant T-cell repertoire has unique characteristics that suggest a diverse T-cell response is critical for tumor rejection.

151 ImmunoMap: A Bioinformatics Tool for T-cell Repertoire Analysis
John-William Sidhom, Catherine A. Bessell, Jonathan J. Havel, Alyssa Kosmides, Timothy A. Chan, and Jonathan P. Schneck

TCR sequencing provides insights into antigen-specific immune responses, but biologically meaningful conclusions are difficult to infer. ImmunoMap is a bioinformatics tool that reconciles TCR repertoire function and structure by quantifying the "relatedness" of the response by sequence homology.

163 TUSC2 Immunogene Therapy Synergizes with Anti–PD-1 through Enhanced Proliferation and Infiltration of Natural Killer Cells in Syngeneic Kras-Mutant Mouse Lung Cancer Models
Ismail M. Meraz, Mourad Majidi, Xiaobo Cao, Heather Lin, Lerong Li, Jing Wang, Vreera Baladandayuthapani, David Rice, Botis Sepesi, Lin Ji, and Jack A. Roth

 Provision of the TUSC2 gene via nanoparticles plus checkpoint inhibition enhanced the efficacy of antitumor responses in local and metastatic models of NSCLC. NK cells were required for this effect. Clinical trials of this combination may be warranted.

178 Peptide Blocking of PD-1/PD-L1 Interaction for Cancer Immunotherapy
Chunlin Li, Nengpan Zhang, Jundong Zhou, Chen Ding, Yaqing Jin, Xueyuan Cai, Kefeng Pu, and Yimin Zhu

A PD-L1–targeting peptide, TPP-1, was identified by bacterial surface display methods. TPP-1 was found to block PD-1/PD-L1 interactions, leading to T-cell reactivation, improved responses, and inhibition of tumor growth in a xenograft model.

189 Robust Antitumor Responses Result from Local Chemotherapy and CTLA-4 Blockade
Charlotte E. Ariyan, Mary Sue Brady, Robert H. Siegelbaum, Jian Hu, Danielle M. Bello, Jamie Rand, Charles Fisher, Robert A. Lefkowitz, Kathleen S. Panageas, Melissa Pulitzer, Marissa Vignali, Ryan Emerson, Christopher Tipton, Harlan Robins, Taha Merghoub, Jianda Yuan, Achim Jungbluth, Jorge Blando, Padmanee Sharma, Alexander Y. Rudensky, Jedd D. Wolchok, and James P. Allison

Immunotherapy success depends on inflamed tumor microenvironments. In tumor models, inflammation induced by chemotherapy, combined with CTLA-4 blockade, improved survival rates. In a clinical trial, patients with melanoma showed a durable response to such combined therapy.

201 Antigen-Specific Antitumor Responses Induced by OX40 Agonist Are Enhanced by the IDO Inhibitor Indoximod
Zazana Berrong, Mikayel Mkrtichyan, Shamim Ahmad, Mason Webb, Eslam Mohamed, Grigori Okoiev, Adelaida Matevosyan, Rajeev Shriram, Rasha Abu Eid, Scott Hammond, John E. Janik, and Samir N. Khleif

Tumors can suppress immune responses. Inhibition of immunosuppression with the IDO inhibitor indoximod improved response to an antitumor vaccine. Combined immunotherapy with anti-OX40 and indoximod led to both increased numbers and improved functionality of vaccine-induced effector T cells.
The Immune Checkpoint Modulator OX40 and Its Ligand OX40L in NK-Cell Immunosurveillance and Acute Myeloid Leukemia
Tina Nuebling, Carla Emilia Schumacher, Martin Hofmann, Ilona Hagelstein, Benjamin Joachim Schmiedel, Stefanie Maurer, Birgit Federmann, Kathrin Rothfelder, Malte Roerden, Daniela Dörfel, Pascal Schneider, Gundram Jung, and Helmut Rainer Salih

The TNFR-family member OX40 is expressed on AML cells, influencing various AML cellular functions as well as immunosurveillance by OX40L-expressing NK cells. These effects should be considered when developing OX40-targeted approaches for cancer immunotherapy.

T-cell Responses in the Microenvironment of Primary Renal Cell Carcinoma—Implications for Adoptive Cell Therapy
Rikke Andersen, Marie Christine Wulff Westergaard, Julie Westerlin Kjeldsen, Anja Müller, Natasa Wulff Pedersen, Sine Reker Hadrup, Özcan Met, Barbara Seliger, Bjarne Kromann-Andersen, Thomas Hasselager, Marco Donia, and Inge Marie Svane

TILs isolated from primary RCC specimens could recognize tumors. However, their immune responses were weaker than TILs from metastatic melanoma and displayed a mono-/oligofunctional pattern. The ability to select and expand polyfunctional T cells may improve cell therapy for RCC.

Exosomes Associated with Human Ovarian Tumors Harbor a Reversible Checkpoint of T-cell Responses

Exosomes derived from ovarian cancer tumors repress the function and proliferation of T cells in the tumor microenvironment. T cells can be reactivated after exosomes are removed, which may point to exosomes as a target for checkpoint modulation.

ABOUT THE COVER
Cytotoxic T cells rely on a complex system of checks and balances that modulates their activation, functional capabilities, and survival. One surface protein, SLAMF6, binds to itself in a homotypic fashion. Eisenberg and colleagues created a reagent from the ectodomain of SLAMF6 that interfered with this binding, resulting in increased activation of CD8⁺ T cells and stronger effector functions, even prolonging the survival of adoptively transferred CD8⁺ T cells, without the addition of IL2. This work provides evidence that when SLAMF6 is engaged via cell–cell contact it has an inhibitory effect on CD8⁺ T cells, which is relieved by the competitive binding of its soluble form. Read more in this issue, starting on page 127. The original confocal image is of human T cells activated with anti-CD3, with SLAMF6 (red) clustering at sites of cell–cell contact. Artwork by Lewis Long.