WHAT WE'RE READING
695 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS
696 The Highs and Lows of Immune-Checkpoint Blockade in Lymphoma
Stephen M. Ansell

CANCER IMMUNOLOGY MINIATURE
701 Responsiveness to PD-1 Blockade in End-Stage Colon Cancer with Gene Locus 9p24.1 Copy-Number Gain
Most patients with metastasis of large bowel cancer do not benefit from immune therapy. This case study shows that a rare gene mutation, termed 9p24.1 copy-number gain, in this otherwise incurable tumor provoked a response to immune therapy.

RESEARCH ARTICLES
707 Siglec-9 Regulates an Effector Memory CD8⁺ T-cell Subset That Congregates in the Melanoma Tumor Microenvironment
The lectin Siglec-9 can regulate TCR signaling and effector function of human cytotoxic CD8⁺ T cells. Siglec-9 expression defines a subset of effector memory CD8⁺ T cells that is prevalent in melanoma tissues.

719 Performance Evaluation of MHC Class-I Binding Prediction Tools Based on an Experimentally Validated MHC–Peptide Binding Data Set
Maria Bonsack, Stephanie Hoppe, Jan Winter, Diana Tichy, Christine Zeller, Marius D. Küpper, Eva C. Schitter, Renata Blatnik, and Angelika B. Riemer
Evaluation of MHC class-I binding predictors based on experimentally validated binders revealed that individual thresholds are needed for different HLA types and peptide lengths to optimize sensitivity and increase the number of epitopes as potential targets for immunotherapy.

737 Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and Immunotherapeutically Relevant Gene Signatures
Dongqiang Zeng, Meiyi Li, Rui Zhou, Jingwen Zhang, Huiyin Sun, Min Shi, Jianping Bin, Yulin Liao, Jinjun Rao, and Wangjun Liao
Gastric cancer TME infiltration patterns were determined and systematically correlated with TME cell phenotypes, genomic traits, and patient clinicopathological features to establish the "TMEscore." This score was a prognostic and predictive factor for immune checkpoint blockade response.

751 Combined Low Densities of FoxP3⁺ and CD3⁺ Tumor-Infiltrating Lymphocytes Identify Stage II Colorectal Cancer at High Risk of Progression
Tommaso Cavalleri, Paolo Bianchi, Gianluca Basso, Giuseppe Celesti, Fabio Grizzi, Paola Bossi, Luana Greco, Calogero Pitroni, Emanuele Valtorta, Gianluca Mauri, Mauro Trunin, Filippo Gustavo Dall’Olio, Giovanni Brandi, Andrea Sartore-Bianchi, Luigi Ricciardiello, Valter Torri, Lorenza Rimassa, Salvatore Siena, Alberto Mantovani, Alberto Maltesci, and Luigi Laghi, on behalf of Alleanza contro il Cancro (ACC) Colorectal Cancer Working Group
For nonmetastatic colorectal cancer, FoxP3⁺ and CD3⁺ T-cell densities have prognostic value up to stage III is reached. Loss of prognostic value at that point indicates that various T-cell subsets are differentially influential as the cancer progresses.

759 IL15 Enhances CAR-T Cell Antitumor Activity by Reducing mTORC1 Activity and Preserving Their Stem Cell Memory Phenotype
IL15 promotes metabolically fit CAR-T cells with a less-differentiated stem cell memory phenotype. Addition of IL15 is a clinically translatable method for improving the antitumor function of ex vivo expanded CAR-T cells, which could improve outcomes for patients.

773 Cancer Immunotherapy with T Cells Carrying Bispecific Receptors That Mimic Antibodies
Sarah Ahn, Jingjing Li, Chuang Sun, Keliang Gao, Koichi Hirabayashi, Hongxia Li, Barbara Savoldo, Rihe Liu, and Gianpietro Dotto
CAR T-cell antitumor therapy fails when the tumor loses expression of the chosen epitope. Receptors that mimic antibodies and that recognize two epitopes may reduce the chances for tumor cells to escape immune surveillance.
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<td>Hagma H. Workel, Joyce M. Lubbers, Roland Arnold, Thalina M. Prins, Pieter van der Vlies, Kim de Lange, Tjalling Bosse, Inge C. van Gool, Florine A. Eggink, Maartje C.A. Wouters, Fenne L. Komdeur, Elisabeth C. van der Spilker, Carien L. Creutzberg, Hans W. Nijman, and Marco de Bruyn</td>
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ABOUT THE COVER

Altered tumor glycosylation is now appreciated to have an immunosuppressive role, whereby immune responses can be downregulated via activity of Siglecs, cell surface proteins that bind sialic acid–containing glycans. Although Siglecs are expressed on some immune cells, T cells rarely express them. Haas et al. report that in melanoma, the majority of tumor-infiltrating, but not circulating, CD8+ T cells express Siglec-9. This subset of Siglec-9+ T cells is highly cytotoxic and proliferative. However, engagement of siglec-9 inhibits the effector functions of the Siglec-9–expressing CD8+ T cells, due to dephosphorylation of the TCR pathway molecules by the SHP-1 phosphatase, which dampens TCR signaling. The majority of primary and metastatic melanoma cells express Siglec-9 ligands. Thus, Siglec-9 receptor-ligand interactions are a glycosylation-dependent inhibitory circuit that suppresses immune responses in the tumor microenvironment. These data suggest that blocking this interaction may enhance antitumor responses, while also confining CD8+ T-cell activation to the tumor microenvironment. Read more in this issue on page 707. Original image from Fig. 2A. Artwork by Lewis Long.