### 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
Anne Hansen Ree, Vigdis Nygaard, Hege G. Russnes, Daniel Heinrich, Vegard Nygaard, Christin Johansen, Inger Riise Bergheim, Eivind Hovig, Klaus Beiske, Anne-Niðé/C10r, Anne-Lise Børresen-Dale, Kjersti Flatmark, and Gunhild M. Mælandsmo

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
Quentin Haas, Kayluz Frias Boligan, Camilla Jandus, Christoph Schneider, Cedric Simillion, Michal A. Stanczak, Monika Haubitz, Seyed Morteza Seyed Jafari, Alfred Zippelius, Gabriela M. Baerlocher, Heinz Lübbi, Robert E. Hunger, Pedro Romero, Hans-Uwe Simon, and Stephan von Gunten

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** Tumor Microenvironment Characterization in Gastric Cancer Identifies Prognostic and Immunotherapeutically Relevant Gene Signatures
Dongqiang Zeng, Meiyi Li, Rui Zhou, Jingwen Zhang, Huiying 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.

**737** 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 Rossi, Luana Greco, Calogero Pitron, Emanuele Valtorta, Gianluca Mauri, Mauro Truini, Filippo Gustavo Dall’Olio, Giovanni Brandi, Andrea Santore-Bianchi, Luigi Ricciardiello, Valter Torri, Lorenza Rimassa, Salvatore Siena, Alberto Mantovani, Alberto Malesci, and Luigi Laghetti, on behalf of Alleanz 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.

**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 Dutti

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.
784 A Transcriptionally Distinct CXCL13⁺ CD103⁺ CD8⁺ T-cell Population Is Associated with B-cell Recruitment and Neoantigen Load in Human Cancer
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 Slieke, Carien L. Creutzberg, Arjan Kol, Annechien Plat, Mark Claire, David N. Church, Hans W. Nijman, and Marco de Bruyn

TGFβ stimulation of activated CD8⁺ T cells from cancer patients induces upregulation of CD103 and CXCL13, which is important for tertiary lymphoid structure formation. The data highlight a role for TGFβ in coordinating immune responses against tumors.

797 T Cells Specific for an Unconventional Natural Antigen Fail to Recognize Leukemic Cells
Margot J. Pont, Rimke Oostvogels, Cornelis A.M. van Bergen, Edith D. van der Meijden, Maria W. Honders, Sophie Bliss, Marlieke L.M. Jongema, Henk M. Lokhorst, J.H. Frederik Falkenburg, Tuna Mutis, Mariele Griffioen, and Robbert M. Spaapen

MHC-bound peptides derived from aberrant proteins may be an immunotherapeutic target on cancer cells. However, T cells recognizing such an antigen failed to react against leukemic cells. Thus, concern is warranted for immunotherapies targeting such antigens.

805 Multiple Immune-Suppressive Mechanisms in Fibrolamellar Carcinoma

The expression of immune checkpoint molecules PD-1, PD-L1, B7-H3, and IDO in fibrolamellar carcinoma (FLC) is related to CD8⁺ T-cell density. These checkpoints are clinically targetable with inhibitors. Thus, using immune checkpoint blockade may be efficacious in FLC.

813 The Pseudogene Olfr29-ps1 Promotes the Suppressive Function and Differentiation of Monocytic MDSCs
Wencong Shang, Yunhuan Gao, Zhenzhen Tang, Yuan Zhang, and Ronggan Yang

A conserved long noncoding RNA (lncRNA), pseudogene Olfr29-ps1, was identified and shown to be induced under inflammatory conditions and in melanomas. Olfr29-ps1 can regulate the immunosuppressive function and differentiation of monocytic MDSCs both in vitro and in vivo.

828 Suboptimal T-cell TherapyDRives a Tumor Cell Mutator Phenotype That Promotes Escape from First-Line Treatment
Laura Fegin, Amanda L. Huff, Timothy Kottke, Jill Thompson, Amy M. Molan, Christopher B. Driscoll, Matthew Schuelke, Kevin G. Shim, Phonphimon Wonghvida, Elizabeth J. Ilett, Karen Kahuza Smith, Reuben S. Harris, Matt Coffey, Jose S. Pulido, Hardev Pandha, Peter J. Selby, Kevin J. Harrington, Alan Melcher, and Richard G. Vile

Suboptimal antitumor immunotherapy increases genomic instability in tumor cells by inducing APOBEC3. Resulting mutations can promote tumor cell escape from co-applied therapies. Immunotherapies should be optimized early to prevent a direct enhancement of tumor cell escape.

841 Accumulation of Circulating CCR7⁺ Natural Killer Cells Marks Melanoma Evolution and Reveals a CCL19-Dependent Metastatic Pathway
Costanza Maria Cristiani, Alice Turdo, Valeria Ventura, Tiziana Apuzzo, Maiaelena Capone, Gabriele Madonna, Domenico Mallardo, Cinzia Carrozzi, Emilia Dora Giovannone, Antonio M. Grimaldi, Rossana Tallerico, Emanuela Marronato, Silvia Pesce, Genny Del Zotto, Valier Agosti, Francesco Saverio Costanzo, Elio Gulletta, Alessandro Moretta, Klas Karre, Paolo A. Ascierto, Nils Todaro, and Ennio Carbone

CCR7⁺ NK cells and CCL19 increased as melanoma progressed. Melanoma-derived cancer stem cells overexpressed CCR7 and were efficiently recognized and killed by NK cells. CCR7 may be a biomarker for metastatic melanoma.
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<sup>+</sup> T cells express Siglec-9. This subset of Siglec-9<sup>+</sup> T cells is highly cytotoxic and proliferative. However, engagement of siglec-9 inhibits the effector functions of the Siglec-9–expressing CD8<sup>+</sup> 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<sup>+</sup> T-cell activation to the tumor microenvironment. Read more in this issue on page 707. Original image from Fig. 2A. Artwork by Lewis Long.