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Chun Chou and Ming O. Li

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### 378 Identification of Tumoricidal TCRs from Tumor-Infiltrating Lymphocytes by Single-Cell Analysis

Kiyomi Shitaka, Hiroshi Hamana, Hiroyuki Kishi, Yoshihiro Hayakawa, Eiji Kobayashi, Kenta Sukegawa, Xiuhong Piao, Fulian Lyu, Takuya Nagata, Daisuke Sugiyama, Hiroyoshi Nishikawa, Atsushi Tanemura, Ichiro Katayama, Mutsunori Murahashi, Yasushi Takamatsu, Kenzaburo Tani, Tatsuhiko Ozawa, and Atsushi Muraguchi

*Tumoricidal T-cell receptors (TCRs) are key components of some immunotherapies. TCR analysis of single T cells isolated from tumor-infiltrating lymphocytes identified TCRs with killing activity in vivo and in vitro, without prior knowledge of their peptide-MHC specificity.*

### 389 Targeting Cytokine Therapy to the Pancreatic Tumor Microenvironment Using PD-L1-Specific VHHS

Michael Dougan, Jessica R. Ingram, Hee-Jin Jeong, Munir M. Mosaheb, Patrick T. Bruck, Lestat Ali, Novalia Pishesha, Olga Blomberg, Paul M. Tyler, Mariah M. Servos, Mohammad Rashidian, Quang-De Nguyen, Ulrich H. von Andrian, Hidde L. Ploegh, and Stephanie K. Dougan

*Although cytokines modulate immune responses, systemic administration necessitates high doses. With the use of cytokines fused to "VHHS" specific for PD-L1, systemic delivery of low doses led to intratumoral localization, allowing for therapeutic effects in pancreatic cancer models.*

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### Durable Clinical Benefit in Metastatic Renal Cell Carcinoma Patients Who Discontinue PD-1/PD-L1 Therapy for Immune-Related Adverse Events

Dylan J. Martini, Lana Hamieh, Rana R. McKay, Lauren C. Harshman, Raphael Brandao, Craig K. Norton, John A. Steinharter, Katherine M. Krajewski, Xin Gao, Fabio A. Schutz, Bradley McGregor, Dominick Bossé, Aly-Khan A. Lalani, Guillermo De Velasco, M. Dror Michaelson, David F. McDermott, and Toni K. Choueiri

*mRCC patients who had a clinical response to PD-1/PD-L1 blockade and discontinued treatment due to irAE continued to derive prolonged clinical benefit after treatment was stopped. Current clinical trials are exploring customized approaches to application of PD-1/PD-L1 blockade.*

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### Interleukin 33 Signaling Restrains Sporadic Colon Cancer in an Interferon- $\gamma$ -Dependent Manner

Moritz F. Eissmann, Christine Dijkstra, Merridee A. Wouters, David Baloyan, Dmitri Mouradov, Paul M. Nguyen, Mercedes Davalos-Salas, Tracy L. Putoczki, Oliver M. Sieber, John M. Mariadason, Matthias Ernst, and Frederick Masson

*Progression of human colorectal cancer coincides with a downregulated IFN $\gamma$  gene signature. IL-33 signaling induced this IFN $\gamma$ -signature in mesenchymal cells of the mouse colon and suppressed tumor formation. Therapeutically, IL-33 administration restricted colon cancer growth in mice.*

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### TNF $\alpha$ and Radioresistant Stromal Cells Are Essential for Therapeutic Efficacy of Cyclic Dinucleotide STING Agonists in Nonimmunogenic Tumors

Brian J. Francica, Ali Ghasemzadeh, Anthony L. Desbien, Debebe Theodros, Kelsey E. Sivick, Gabrielle L. Reiner, Laura Hix Glickman, Ariel E. Marciscano, Andrew B. Sharabi, Meredith L. Leong, Sarah M. McWhirter, Thomas W. Dubensky Jr, Drew M. Pardoll, and Charles G. Drake

*Stromal and immune cells are required for effective responses to intratumoral cyclic dinucleotide therapy. Responses leading to productive innate and adaptive antitumor responses are demonstrated and highlight the cooperation between the tumor stroma and immune compartments during immunotherapy.*



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- 434** Macrophages and CD8<sup>+</sup> T Cells Mediate the Antitumor Efficacy of Combined CD40 Ligation and Imatinib Therapy in Gastrointestinal Stromal Tumors  
Jennifer Q. Zhang, Shan Zeng, Gerardo A. Vitiello, Adrian M. Seifert, Benjamin D. Medina, Michael J. Beckman, Jennifer K. Loo, Juan Santamaría-Barria, Joanna H. Maltbaek, Nesteene J. Param, John A. Moral, Julia N. Zhao, Vinod Balachandran, Ferdinand Rossi, Cristina R. Antonescu, and Ronald P. DeMatteo  
*The kinase inhibitor imatinib is used to treat gastrointestinal stromal tumors. Combined with agonistic anti-CD40, macrophages and CD8<sup>+</sup> T cells improved the antitumor effects of imatinib alone, supporting the combination's use in patients with these tumors.*
- 448** Low-Density Lipoprotein Uptake Inhibits the Activation and Antitumor Functions of Human Vγ9Vδ2 T Cells  
**AC** Neidy V. Rodrigues, Daniel V. Correia, Sofia Mensurado, Sandra Nóbrega-Pereira, Ana deBarros, Fernanda Kyle-Cezar, Andrew Tutt, Adrian C. Hayday, Haakan Norell, Bruno Silva-Santos, and Sérgio Dias  
*Certain cancer immunotherapies use transferred γδ T cells. LDL-cholesterol inhibited activation and antitumor function of human γδ T cells in models of breast cancer. Management of LDL-cholesterol levels may improve results from immunotherapies based on γδ T cells.*
- 458** NK Cell-Specific CDK8 Deletion Enhances Antitumor Responses  
**AC** Agnieszka Witalisz-Siepracka, Dagmar Gotthardt, Michaela Prchal-Murphy, Zrinka Didara, Ingeborg Menzl, Daniela Prinz, Leo Edlinger, Eva Maria Putz, and Veronika Sexl  
*Mice with an NK cell-specific knockout of CDK8 were used to show that loss of CDK8 enhances NK-cell cytotoxicity and tumor surveillance in vivo. Thus, CDK8 is a promising target for immunotherapy against cancer.*
- 467** Intrinsic Functional Potential of NK-Cell Subsets Constrains Retargeting Driven by Chimeric Antigen Receptors  
**AC** Vincent Yi Sheng Oei, Marta Siernicka, Agnieszka Graczyk-Jarzynka, Hanna Julie Hoel, Weiwen Yang, Daniel Palacios, Hilde Almåsbak, Małgorzata Bajor, Dennis Clement, Ludwig Brandt, Björn Önfelt, Jodie Goodridge, Magdalena Winiarska, Radosław Zagózdzon, Johanna Olweus, Jon-Amund Kyte, and Karl-Johan Malmberg  
*Natural killer cells can carry chimeric antigen receptors (CARs). CARs were expressed in NK cells by transient transfection of mRNA. Functional responses of CAR-expressing NK cells depended on their diversification as well as donor and recipient HLA genotypes.*
- 481** Quantitative Analysis of Immune Infiltrates in Primary Melanoma  
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*Quantitative multiplex immunofluorescence and quantitative spatial analysis were used to evaluate the tumor microenvironment and allowed for the identification of a biomarker that correlated with survival in melanoma—the cytotoxic T lymphocyte-to-macrophage ratio.*

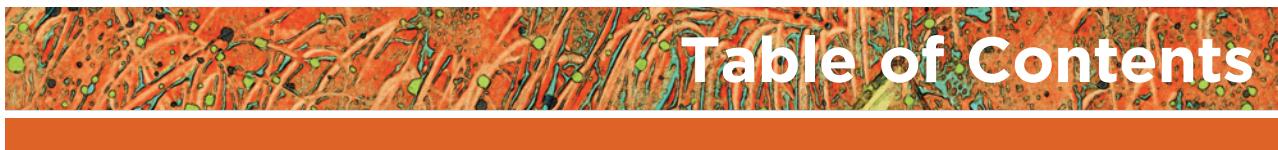
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## CORRECTION

- 498** Correction: Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients

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## ABOUT THE COVER

Interleukin 33 (IL33) is an unusual cytokine with many purported functions in tumorigenesis. IL33 expression is associated with poor prognosis in multiple solid tumors and is also released during inflammatory colitis. Because many different types of immune cells express the receptor for IL33, its effects on immune functions are broad. It can promote Th2, Th1, and cytotoxic responses. However, IL33 also appears to play a role during homeostatic renewal of the epithelial lining of the gut. Therefore, Eissmann et al. examined the role of IL33 during the initiation of sporadic colorectal cancers, which accounts for the majority of the disease occurrences in humans. Through the use of a sporadic colon cancer model in mice that lacked the receptor for IL33, they determined that IL33 signaling can protect against tumor initiation. The authors found that IL33 signaling in mice increased IFN $\gamma$  production and decreased the number of Tregs in the colon, which correlates with findings in human patients with colon cancer. Read more starting on page 409 of this issue. Micrograph of infiltrating macrophages in a colon tumor of receptor-ablated mice from Supplementary Fig. S5. Artwork by Lewis Long.

