

WHAT WE'RE READING

- 881** A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

- 882** Treg Fragility: A Prerequisite for Effective Antitumor Immunity?
Abigail E. Overacre-Delgoffe and Dario A.A. Vignali

RESEARCH ARTICLES

- 888** The Mutation-Associated Neoantigen Functional Expansion of Specific T Cells (MANAFEST) Assay: A Sensitive Platform for Monitoring Antitumor Immunity



Ludmila Danilova, Valsamo Anagnostou, Justina X. Caushi, John-William Sidhom, Haidan Guo, Hok Yee Chan, Perna Suri, Ada Tam, Jijia Zhang, Margueritta El Asmar, Kristen A. Marrone, Jarushka Naidoo, Julie R. Brahmer, Patrick M. Forde, Alexander S. Baras, Leslie Cope, Victor E. Velculescu, Drew M. Pardoll, Franck Housseau, and Kellie N. Smith
The MANAFEST assay tracks the antitumor immune response in all biological compartments of patients receiving checkpoint blockade immunotherapy. It matches antigen specificity with T-cell clonotypic identity, which enables the monitoring of patients through prognostic and correlative analyses.

- 900** Primary T Cells from Cutaneous T-cell Lymphoma Skin Explants Display an Exhausted Immune Checkpoint Profile

Christiane Querfeld, Samantha Leung, Patricia L. Myskowski, Shane A. Curran, Debra A. Goldman, Glenn Heller, Xiwei Wu, Sung Hee Kil, Sneha Sharma, Kathleen J. Finn, Steven Horwitz, Alison Moskowitz, Babak Mehrara, Steven T. Rosen, Allan C. Halpern, and James W. Young
T cells are exhausted in lesions of cutaneous T-cell lymphoma. Genome-wide mRNA expression analysis and flow cytometry indicated that such T cells overexpress immune checkpoints, suggesting avenues for more effective therapies.

- 910** Exosomes Shuttle TREX1-Sensitive IFN-Stimulatory dsDNA from Irradiated Cancer Cells to DCs

Julie M. Diamond, Claire Vanpouille-Box, Sheila Spada, Nils-Petter Rudqvist, Jessica R. Chapman, Beatrix M. Ueberheide, Karsten A. Pilonis, Yasmeen Sarfraz, Silvia C. Formenti, and Sandra Demaria
Irradiated tumor-derived exosomes were shown to contain dsDNA that, when transported to DCs, induced upregulation of costimulatory molecules and IFN-I responses. In vivo, vaccination with the irradiated tumor-derived exosomes reduced tumor growth and induced potent CD8⁺ T-cell responses.

- 921** PD-L1 Binds to B7-1 Only *In Cis* on the Same Cell Surface



Apoorvi Chaudhri, Yanping Xiao, Alyssa N. Klee, Xiaoxu Wang, Baogong Zhu, and Gordon J. Freeman
PD-L1 and B7-1 only interact in cis on the same cell surface, but not in trans between two cells. Their coexpression is found, for example, on tumor-infiltrating myeloid cells. Cis B7-1 competes with trans PD-1 for binding to PD-L1.

- 930** Antitumor Activity of TLR7 Is Potentiated by CD200R Antibody Leading to Changes in the Tumor Microenvironment

Zofia Pilch, Katarzyna Tonecka, Agata Braniewska, Zuzanna Sas, Marcin Skorzynski, Louis Boon, Jakub Golab, Linde Meyaard, and Tomasz P. Rygiel
Treatments that alter the immune composition of the tumor microenvironment affect antitumor activity. Stimulating TLR7 in combination with an agonistic mAb to CD200R improved the antitumor effects of TLR7 signaling. Subsequent changes affected myeloid cell composition and activation.

- 941** Wnt3a/ β -Catenin Signaling Conditions Differentiation of Partially Exhausted T-effector Cells in Human Cancers

Valeria Schinzari, Eleonora Timperi, Giulia Pecora, Francesco Palmucci, Daniela Gallerano, Alessio Grimaldi, Daniela Angela Covino, Nicola Guglielmo, Fabio Melandro, Emy Manzi, Andrea Sagnotta, Francesco Lancellotti, Luca Sacco, Piero Chirletti, Gian Luca Grazi, Massimo Rossi, and Vincenzo Barnaba
The Wnt3a/ β -catenin pathway supports a protumor environment. Secreted Wnt3a was found to be overexpressed in human colorectal and hepatocellular carcinomas, interfere with naive and effector T-cell differentiation, and affect the function of infiltrating T cells.

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953 **Wnt3a Neutralization Enhances T-cell Responses through Indirect Mechanisms and Restrains Tumor Growth**

Ilenia Pacella, Ilenia Cammarata, Chiara Focaccetti, Stefano Miacci, Alessandro Gulino, Claudio Tripodo, Micol Ravà, Vincenzo Barnaba, and Silvia Piconese
The Wnt3a/ β -catenin pathways modulate antitumor T-cell responses. In a mouse tumor model, administration of an anti-Wnt3a neutralizing antibody-controlled tumor growth by reshaping signals in the tumor microenvironment.

965 **Enhanced Cancer Immunotherapy with Smad3-Silenced NK-92 Cells**

Qing-Ming Wang, Patrick Ming-Kuen Tang, Guang-Yu Lian, Chunjie Li, Jinhong Li, Xiao-Ru Huang, Ka-Fai To, and Hui-Yao Lan
Knockdown of Smad3 in the NK-92 cell line, currently in clinical trials, improved its anticancer effectiveness relative to the parental line in vitro and in mice bearing human tumors. This may represent a promising approach for cancer treatment.

978 **Experimental Lung Metastases in Mice Are More Effectively Inhibited by Blockade of IL23R than IL23**

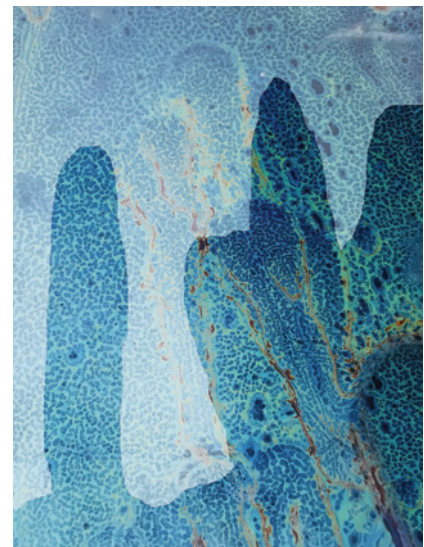
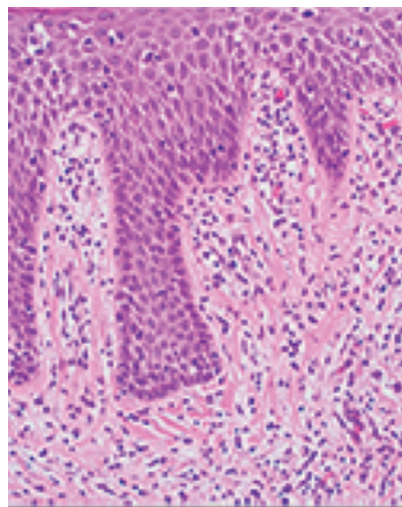
Juming Yan, Stacey Allen, Dipti Vijayan, Xian-Yang Li, Heidi Harjunpää, Kazuyoshi Takeda, Jing Liu, Daniel J. Cua, Mark J. Smyth, and Michele W.L. Teng
IL23 is an inflammatory cytokine with protumoral effects and is present in the serum of patients with some malignancies. In three different mouse tumor models, blocking IL23R was more effective at suppressing metastases than was neutralizing IL23.

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ABOUT THE COVER

Cutaneous T-cell lymphoma (CTCL) develops in chronic inflammatory conditions. However, how this inflammation affects T-cell antitumor functions remains unclear. Querfeld et al. show that in skin explants and skin biopsies from 86 patients with CTCL, mature PD-L1⁺ dendritic cells are detected and T cells are activated, but the T cells also express immune checkpoint molecules known to be markers of exhaustion. RNAseq at different disease stages demonstrated that expression of checkpoint molecules increased with progression, indicating that an exhausted T-cell phenotype is a hallmark in CTCL. Read more in this issue starting on page 900. Original image is an H&E stain of a patch/plaque lesion, from Fig. 4. Artwork by Lewis Long.



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