

CANCER IMMUNOLOGY RESEARCH

TABLE OF CONTENTS

WHAT WE'RE READING

- 1463** **A Sampling of Highlights from the Literature**

IN THE SPOTLIGHT

- 1464** **TGF β : Protecting PD-1 from mRNA Decay**
Stephanie K. Dougan
See related article, p. 1470

CANCER IMMUNOLOGY AT THE CROSSROADS

- 1465** **Personal Neoantigen Cancer Vaccines: A Road Not Fully Paved**
Edward F. Fritsch, Ute E. Burkhardt, Nir Hacohen, and Catherine J. Wu

RESEARCH ARTICLES

- 1470** **Tumor Cell-Derived TGF β 1 Attenuates Antitumor Immune Activity of T Cells via Regulation of PD-1 mRNA**
A C Pengfei Wu, Bo Geng, Qun Chen, Enyang Zhao, Jiang Liu, Chen Sun, Caijun Zha, Yong Shao, Bosen You, Wenfu Zhang, Lulu Li, Xiangqi Meng, Jinqian Cai, and Xuedong Li

TGF β 1 is shown to regulate PD-1 expression, thereby modulating CD8⁺ T-cell responses in clear-cell renal cell carcinoma (ccRCC). By targeting this regulatory mechanism, antitumor responses are boosted. The data highlight an immune evasion strategy used by ccRCC.

See related Spotlight, p. 1464

- 1485** **Treatment of Multiple Myeloma Using Chimeric Antigen Receptor T Cells with Dual Specificity**
Anat Globerson Levin, Moran Rawet Slobodkin, Tova Waks, Galit Horn, Lihi Ninio-Many, Naamit Deshet Unger, Yaara Ohayon, Shimrit Suliman, Yael Cohen, Boris Tartakovsky, Ella Naparstek, Irit Avivi, and Zelig Eshhar

CAR T cells mostly induce nondurable and nonspecific responses in multiple myeloma (MM). The creation of a dual CAR with split configuration targeting two MM-associated antigens has better specificity and superior antitumor activity than single target CAR T cells.

- 1496** **Long-term Sculpting of the B-cell Repertoire following Cancer Immunotherapy in Patients Treated with Sipuleucel-T**

A C Li Zhang, Harini Kandadi, Hai Yang, Jason Cham, Tao He, David Y. Oh, Nadeem A. Sheikh, and Lawrence Fong

Sipuleucel-T, an autologous cell-based immunotherapy, improves survival in castration-resistant prostate cancer patients, yet how this therapy induces antitumor B-cell immunity remains unclear. Sipuleucel-T induces long-term immune memory and lasting changes to the B-cell repertoire.

- 1508** **Prognostic Integrated Image-Based Immune and Molecular Profiling in Early-Stage Endometrial Cancer**

A C Nanda Horeweg, Marco de Bruyn, Remi A. Nout, Ellen Stelloo, Katarzyna Kedziersza, Alicia León-Castillo, Annechien Plat, Kirsten D. Mertz, Michelle Osse, Ina M. Jürgenliemk-Schulz, Ludy C.H.W. Lutgens, Jan J. Jobsen, Elzbieta M. van der Steen-Banasik, Vincent T. Smit, Carien L. Creutzberg, Tjalling Bosse, Hans W. Nijman, Viktor H. Koelzer, and David N. Church

Risk stratification in endometrial cancer (EC) incorporates molecular factors but not tumor-infiltrating lymphocytes. In this study, machine learning-based quantification of intraepithelial CD8⁺ T cells improves EC risk stratification beyond molecular factors.

- 1520** **Immune Remodeling of the Extracellular Matrix Drives Loss of Cancer Stem Cells and Tumor Rejection**

A C Ana Pires, Alexander Greenshields-Watson, Emma Jones, Kathryn Smart, Sarah N. Lauder, Michelle Somerville, Stefan Milutinovic, Howard Kendrick, James P. Hindley, Rhiannon French, Matthew J. Smalley, William J. Watkins, Robert Andrews, Andrew Godkin, and Awen Gallimore

Antitumor immune responses shape the tumor microenvironment (TME). There is an inverse relationship between the extracellular matrix (ECM) and T-cell infiltration, whereby effective antitumor T-cell responses reduce ECM and cancer stem cells in the TME.

TABLE OF CONTENTS

1532 **Idelalisib Rescues Natural Killer Cells from Monocyte-Induced Immunosuppression by Inhibiting NOX2-Derived Reactive Oxygen Species**

Ali A. Akhiani, Alexander Hallner, Roberta Kiffin, Ebru Aydin, Olle Werlenius, Johan Aurelius, Anna Martner, Fredrik B. Thorén, and Kristoffer Hellstrand

Idelalisib, a PI3K δ inhibitor, inhibits antibody-induced formation of ROS in human monocytes by preventing Akt-dependent phosphorylation of NOX2. By rescuing NK cells from immunosuppressive ROS, idelalisib promotes NK cell-mediated antibody-dependent cellular cytotoxicity against malignant B cells.

1542 **Pharmacologic Inhibition of FGFR Modulates the Metastatic Immune Microenvironment and Promotes Response to Immune Checkpoint Blockade**

Saeed S. Akhand, Zian Liu, Stephen C. Purdy, Ammara Abdullah, Hang Lin, Gregory M. Cresswell, Timothy L. Ratliff, and Michael Wendt

Immune checkpoint blockade (ICB) is limited in its effectiveness as a treatment for metastatic breast cancer. Sequential dosing of an FGFR inhibitor followed by ICB limits metastatic tumor growth and increases overall survival as compared to either monotherapy.

1554 **Dysregulated NF- κ B-Dependent ICOSL Expression in Human Dendritic Cell Vaccines Impairs T-cell Responses in Patients with Melanoma**

Deena M. Maurer, Juraj Adamik, Patricia M. Santos, Jian Shi, Michael R. Shurin, John M. Kirkwood, Walter J. Storkus, and Lisa H. Butterfield

Key molecules and pathways induced by DC-based vaccines to elicit effective antitumor responses are unknown. ICOSL is differentially regulated in melanoma patients, in part, due to NF- κ B dysregulation, which correlates with responses and clinical outcomes of vaccinated patients.

1568 **An Antibody Targeting ICOS Increases Intratumoral Cytotoxic to Regulatory T-cell Ratio and Induces Tumor Regression**

A C

Richard C.A. Sainson, Anil K. Thotakura, Miha Kosmac, Gwenoline Borhis, Nahida Parveen, Rachael Kimber, Joana Carvalho, Simon J. Henderson, Kerstin L. Pryke, Tracey Okell, Siobhan O'Leary, Stuart Ball, Cassie Van Krinks, Lauriane Gamand, Emma Taggart, Eleanor J. Pring, Hanif Ali, Hannah Craig, Vivian W.Y. Wong, Qi Liang, Robert J. Rowlands, Morgane Lecointre, Jamie Campbell, Ian Kirby, David Melvin, Volker Germaschewski, Elisabeth Oelmann, Sonia Quaratino, and Matthew McCourt

T-regulatory cells (Treg) can inhibit the efficacy of immune checkpoint blockade in cancer. Depleting Tregs with an ICOS-specific antibody increases the function of T effector cells, delays tumor growth, and improves immune checkpoint blockade efficacy.

CORRECTION

1583 **Correction: Targeting the YB-1/PD-L1 Axis to Enhance Chemotherapy and Antitumor Immunity**

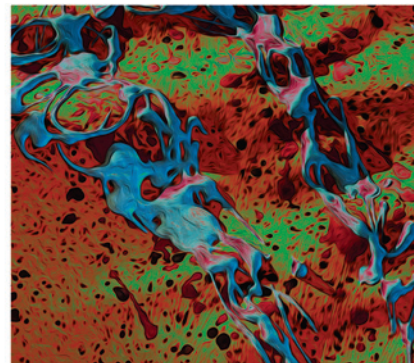
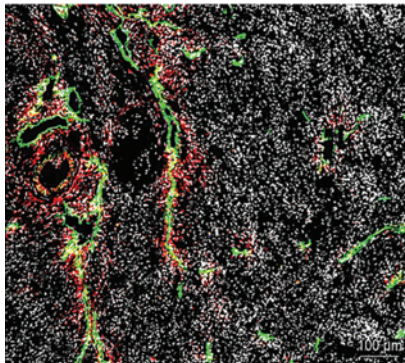
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TABLE OF CONTENTS

ABOUT THE COVER

Immune-suppressive mechanisms in the tumor microenvironment (TME) are still being defined. By comparing tumors that respond to regulatory T-cell depletion with those that do not, Pires and colleagues find that responding tumors are T-cell enriched and exhibit loss of extracellular matrix (ECM) components. These ECM changes in responding tumors correlate with increased T-cell infiltration and the formation of new lymphatic and vasculature networks. Non-responding tumors have a significant enrichment of stem cell-like gene signatures compared with responding tumors. The data highlight a role of adaptive immunity in reshaping the TME by altering the ECM and further driving antitumor responses. Read more in this issue on page 1520. Original image from Fig. 5D. Artwork by Lewis Long.



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