# Cancer Immunology Research

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### In the Spotlight

- 1464 TGFβ: 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 TGFβ1 Attenuates Antitumor Immune Activity of T Cells via Regulation of PD-1 mRNA
  - Pengfei Wu, Bo Geng, Qun Chen, Enyang Zhao, Jiang Liu, Chen Sun, Caijun Zha, Yong Shao, Bosen You, Wenfu Zhang, Lulu Li, Xiangqi Meng, Jinquan Cai, and Xuedong Li
  - TGFβ1 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
  - 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
  - Nanda Horeweg, Marco de Bruyn, Remi A. Nout, Ellen Stellino, Katarzyna Kedzierska, Alicia León-Castillo, Annehien Plat, Kirsten D. Mertz, Michelle Osse, Ina M. Jürgens-Lienk-Schulz, Lady C.H.W. Lutgens, Jan J. Jørgensen, Elektra M. van der Steen-Banasík, 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
  - 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.
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 PI3Kδ 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.

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.

Dysregulated NF-κB-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-κB dysregulation, which correlates with responses and clinical outcomes of vaccinated patients.

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

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