

CANCER IMMUNOLOGY RESEARCH

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RESEARCH ARTICLES

- 558** **Phosphoantigen-Stimulated $\gamma\delta$ T Cells Suppress Natural Killer-Cell Responses to Missing-Self**
Katherine Walwyn-Brown, Jason Pugh,
Alexander T.H. Cocker, Niassan Beyzaie,
Bernhard B. Singer, Daniel Olive, Lisbeth A. Guethlein,
Peter Parham, and Zakia Djaoud
Phosphoantigen-stimulated $\gamma\delta$ T cells are shown to function as brakes of natural killer-cell responses to HLA class I-deficient cells. This role of $\gamma\delta$ T cells does not affect antigen-specific cytotoxic T-cell responses.
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- 571** **IDO Vaccine Ablates Immune-Suppressive Myeloid Populations and Enhances Antitumor Effects Independent of Tumor Cell IDO Status**
Rahul Nandre, Vivek Verma, Pankaj Gaur,
Veerupaxagouda Patil, Xingdong Yang, Zainab Ramlaoui,
Nour Shobaki, Mads Hald Andersen,
Ayako Wakatsuki Pedersen, Mai-Britt Zocca,
Mikayel Mkrtichyan, Seema Gupta, and Samir N. Khleif
An IDO-specific peptide vaccine is demonstrated to target IDO⁺ cells, enhancing vaccine-induced immune responses against non-IDO tumor antigens. These effects reduce tumor growth and inhibit immune-suppressive myeloid populations in multiple tumor models.

- 581** **Discovery of a Conditionally Activated IL-2 that Promotes Antitumor Immunity and Induces Tumor Regression**
Christopher J. Nirschl, Heather R. Brodtkin,
Daniel J. Hicklin, Nesreen Ismail, Kristin Morris,
Cynthia Seidel-Dugan, Philipp Steiner, Zoe Steuert,
Jenna M. Sullivan, Ethika Tyagi, William M. Winston,
and Andres Salmeron
WTX 124 is an inducible IL-2 prodrug that is selectively activated in the tumor microenvironment. Administration of WTX-124 generates potent antitumor immunity by activating tumor-infiltrating lymphocytes while preventing the toxicity associated with systemic, high dose IL-2 treatment.

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- 597** **BHLHE40 Regulates the T-Cell Effector Function Required for Tumor Microenvironment Remodeling and Immune Checkpoint Therapy Efficacy**
Avery J. Salmon, Alexander S. Shavkunov, Qi Miao,
Nicholas N. Jarjour, Sunita Keshari, Ekaterina Esaulova,
Charmelle D. Williams, Jeffrey P. Ward,
Anna M. Highsmith, Josué E. Pineda, Reshma Taneja,
Ken Chen, Brian T. Edelson, and Matthew M. Gubin
The authors show that tumor-specific T cells upregulate and require the transcriptional regulator BHLHE40 for tumor microenvironment remodeling and effective immune checkpoint therapy. BHLHE40 is a potential biomarker for immune checkpoint therapy efficacy and possible therapeutic target.

- 612** **Targeting the PSGL-1 Immune Checkpoint Promotes Immunity to PD-1-Resistant Melanoma**
Julia M. DeRogatis, Karla M. Viramontes,
Emily N. Neubert, Monique L. Henriquez,
Christian F. Guerrero-Juarez, and Roberto Tinoco
Therapeutic PSGL-1 antibody targeting increases infiltration, activation, and function of CD4⁺ and CD8⁺ T cells in melanoma tumors, leading to improved tumor control and altered tumor immune landscape that includes decreased Tregs and increased antigen-specific T cells.

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626 **A Multispecific Anti-CD40 DARPIn Construct Induces Tumor-Selective CD40 Activation and Tumor Regression**

Nicolò Rigamonti, Niina Veitonmäki, Clara Domke, Sophie Barsin, Sarah Jetzer, Omar Abdelmotalieb, Ralph Bessey, Tamara Lekishvili, Francesca Malvezzi, Mariam Gachechiladze, Martin Behe, Victor Levitsky, and Pamela A. Trail

The authors report an immunomodulator, anti-FAPxCD40, based on a non-antibody scaffold that agonizes CD40 selectively in the tumor microenvironment, leading to tumor rejection without systemic toxicity. This new molecule may improve therapeutic windows and clinical activity.

641 **Circulating Tregs Accumulate in Omental Tumors and Acquire Adipose-Resident Features**

Mingyong Liu, Dmytro Starenki, Christopher D. Scharer, Aaron Silva-Sanchez, Patrick A. Molina, Jennifer S. Pollock, Sara J. Cooper, Rebecca C. Arend, Alexander F. Rosenberg, Troy D. Randall, and Selene Meza-Perez

Immunosuppressive adipose-associated Tregs in omental metastases are derived from circulating Tregs, rather than locally expanded Tregs, and rapidly acquire characteristics of adipose-resident cells. Preventing this accumulation may improve antitumor immune responses in the omentum.

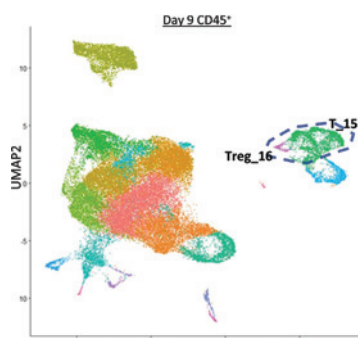
656 **Entinostat Decreases Immune Suppression to Promote Antitumor Responses in a HER2⁺ Breast Tumor Microenvironment**

Dimitrios N. Sidiropoulos, Christine I. Rafie, Julie K. Jang, Sofi Castanon, Aaron G. Baugh, Edgar Gonzalez, Brian J. Christmas, Valerie H. Narumi, Emily F. Davis-Marcisak, Gaurav Sharma, Emma Bigelow, Ajay Vaghasia, Anuj Gupta, Alyza Skaist, Michael Considine, Sarah J. Wheelan, Sathish Kumar Ganesan, Min Yu, Srinivasan Yegnasubramanian, Vered Stearns, Roisin M. Connolly, Daria A. Gaykalova, Luciane T. Kagohara, Elizabeth M. Jaffee, Elana J. Fertig, and Evanthis T. Roussos Torres

Epigenetic modulation using entinostat is demonstrated to sensitize HER2⁺ breast tumors to immune checkpoint inhibition. Entinostat promotes antitumor myeloid cell signatures, reduces MDSC suppression, and boosts T-cell infiltration and cytotoxicity in the tumor microenvironment.

ABOUT THE COVER

Successful responses to immune checkpoint blockade depend on T-cell mediated antitumor immunity. Salmon and Shavkunov et al. find that T-cell expression of the transcriptional regulator BHLHE40 is required for effective immune checkpoint blockade in tumor-bearing mice. Single-cell RNA sequencing of intratumoral immune cells revealed that in the absence of BHLHE40, the tumor immune microenvironment is dysregulated, including showing a defective IFN γ response. The data provide new insight into the molecular features of T cells that mediate effective antitumor immunity following immune checkpoint blockade and suggest that BHLHE40 could be a potential biomarker for response to such treatments. Read more in this issue on page 597. Original image from Fig. 4A. Artwork by Lewis Long.



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