

HIGHLIGHTS FROM THE LITERATURE

- 617 What We're Reading

RESEARCH ARTICLES

- 618 **SLC45A2: A Melanoma Antigen with High Tumor Selectivity and Reduced Potential for Autoimmune Toxicity**



Jungsun Park, Amjad H. Talukder, Seon A. Lim, Kwanghee Kim, Ke Pan, Brenda Melendez, Sherille D. Bradley, Kyle R. Jackson, Jahan S. Khalili, Junmei Wang, Caitlin Creasy, Bih-Fang Pan, Scott E. Woodman, Chantale Bernatchez, David Hawke, Patrick Hwu, Kyung-Mi Lee, Jason Roszik, Gregory Lizée, and Cassian Yee

T cell–based immunotherapy against melanoma-associated antigens can result in on-target/off-tumor cytotoxicity. SLC45A2, a protein overexpressed in melanoma compared with normal melanocytes, was identified as a T-cell target that may be less prone to inducing autoimmune side effects.

- 630 **Vaccination with High-Affinity Epitopes Impairs Antitumor Efficacy by Increasing PD-1 Expression on CD8⁺ T Cells**

Christopher D. Zahm, Viswa T. Colluru, and Douglas G. McNeel

T cells activated by high-affinity epitopes are not guaranteed strong antitumor activity. High-affinity epitopes prolonged APC: T-cell contact time and led to elevated, persistent PD-1 expression and decreased antitumor efficacy in the absence of PD-1 blockade.

- 642 **CD4⁺ T Cell and NK Cell Interplay Key to Regression of MHC Class I^{low} Tumors upon TLR7/8 Agonist Therapy**

Elien M. Doorduyn, Marjolein Sluijter, Daniela C. Salvatori, Serenella Silvestri, Saskia Maas, Ramon Arens, Ferry Ossendorp, Sjoerd H. van der Burg, and Thorbald van Hall

Current immunotherapy targets CD8⁺ T cells. For tumors that have escaped the immune system, activating NK cells with TLR7/8 agonists generated tumor-specific CD4⁺ T cells that successfully eliminated tumors in a mouse model, providing additional therapeutic opportunities.

- 654 **Ex Vivo Expanded Adaptive NK Cells Effectively Kill Primary Acute Lymphoblastic Leukemia Cells**

Lisa L. Liu, Vivien Béziat, Vincent Y.S. Oei, Aline Pfefferle, Marie Schaffer, Sören Lehmann, Eva Hellström-Lindberg, Stefan Söderhäll, Mats Heyman, Dan Grandér, and Karl-Johan Malmberg

Insights into the functional diversification of human NK cells promise improved NK cell therapy. A robust platform was developed to selectively expand adaptive NK cells that have unique specificity and enhanced cytotoxic potential against primary acute lymphoblastic leukemia.

- 666 **Modulation of Endoplasmic Reticulum Stress Controls CD4⁺ T-cell Activation and Antitumor Function**

Jessica E. Thaxton, Caroline Wallace, Brian Riesenberg, Yongliang Zhang, Chrystal M. Paulos, Craig C. Beeson, Bei Liu, and Zihai Li

T cells rapidly proliferate when activated. This initiates an endoplasmic reticulum stress response with increased chaperone activity and Ca²⁺ release. Modulation of ER stress alters CD4⁺ T-cell metabolism, activation, and ability to control tumors in vivo.

- 676 **Intratumoral STING Activation with T-cell Checkpoint Modulation Generates Systemic Antitumor Immunity**

Casey R. Ager, Matthew J. Reilly, Courtney Nicholas, Todd Bartkowiak, Ashvin R. Jaiswal, and Michael A. Curran
Intratumoral administration of myeloid agonists combined with a cocktail of T-cell checkpoint–modulating antibodies elicited systemic antitumor immunity against bilateral TRAMP-C2 prostate tumors. Limited agonist dosing coupled with intratumoral antibody injection reduced toxicity but preserved abscopal immunity.

- 685 **Combining Local Immunotoxins Targeting Mesothelin with CTLA-4 Blockade Synergistically Eradicates Murine Cancer by Promoting Anticancer Immunity**

Yasmin Leshem, James O'Brien, Xiufen Liu, Tapan K. Bera, Masaki Terabe, Jay A. Berzofsky, Birgit Bossenmaier, Gerhard Niederfellner, Chin-Hsien Tai, Yoram Reiter, and Ira Pastan

Patients with mesothelioma showed delayed responses to immunotoxin SS1P, suggesting the development of anticancer immunity. A mouse model was developed in which tumor regressions were greatly enhanced by checkpoint blockade when immunotoxins were directly injected into tumors.

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695 **Constitutive IDO1 Expression in Human Tumors Is Driven by Cyclooxygenase-2 and Mediates Intrinsic Immune Resistance**

Marc Hennequart, Luc Pilotte, Stefania Cane, Delia Hoffmann, Vincent Stroobant, Etienne De Plaen, and Benoît J. Van den Eynde

Certain tumors resistant to immunotherapy express indoleamine 2,3-dioxygenase 1 (IDO1), due to oncogenic PI3K and MAPK signaling triggering autocrine prostaglandin secretion. Treatment with a COX-2 inhibitor reduced IDO1 expression and improved efficacy of immunotherapy.

CANCER IMMUNOLOGY MINIATURE

710 **Monocyte-Derived Dendritic Cells with Silenced PD-1 Ligands and Transpresenting Interleukin-15 Stimulate Strong Tumor-Reactive T-cell Expansion**

Johan M.J. Van den Bergh, Evelien L.J.M. Smits, Zwi N. Berneman, Tim J.A. Hutten, Hans De Reu, Viggo F.I. Van Tendeloo, Harry Dolstra, Eva Lion, and Willemijn Hobo

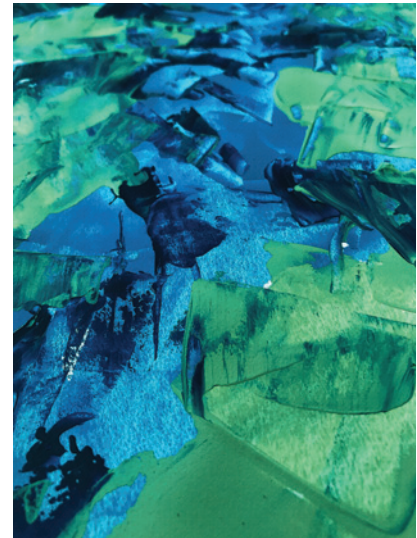
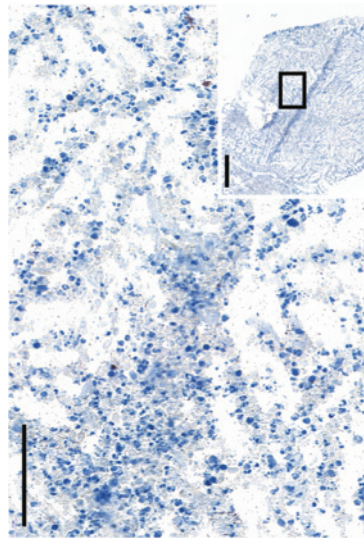
A modified DC vaccine that comprised DCs expressing IL15 and a subunit of the IL15 receptor in combination with silenced PD-1 ligand expression resulted in superior activation of antigen-specific T cells compared with either of these modifications alone.

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ABOUT THE COVER

Tumors are masters of hiding in plain sight and secrete molecules into their surroundings that cloak their presence from the immune system. These dampen immunity, but the route through which they operate may be circuitous. One such enzyme is COX-2, which is expressed by many tumors. Hennequart et al. found that COX-2 activity produces prostaglandin E₂, which, when bound to its receptor on tumor cells, initiates a series of signaling cascades involving PKC and PI3K that ultimately turn on the *IDO1* gene. IDO1 (indoleamine 2,3-dioxygenase 1) is a known suppressor of T cells in its vicinity, converting a necessary amino acid, tryptophan, into kynurenine, a substance that can induce T-cell suicide and enhance generation of regulatory T cells. The COX-2 inhibitor celecoxib was able to block the IDO1-dependent immunosuppression of human tumors in a mouse model with human lymphocytes, restoring tumor rejection. Read more in this issue of *Cancer Immunology Research* starting on page 695. The micrograph is from Fig. 7D. Artwork by Lewis Long.



Cancer Immunology Research

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