

## HIGHLIGHTS FROM THE LITERATURE

## 831 What We're Reading

## PRIORITY BRIEFS

832 Photodynamic-Immune Checkpoint Therapy Eradicates Local and Distant Tumors by CD8<sup>+</sup> T Cells

Jan Willem Kleinovink, Marieke F. Fransens, Clemens W. Löwik, and Ferry Ossendorp  
*Local tumor destruction by photodynamic therapy induces potent antitumor T-cell responses, which can be enhanced by systemic CTLA-4 blockade to eliminate local and distant tumors in mice. This provides an alternative approach to treating advanced multifocal cancer.*

## 839 Extracellular S100A9 Protein in Bone Marrow Supports Multiple Myeloma Survival by Stimulating Angiogenesis and Cytokine Secretion

Kim De Veirman, Nathan De Beule, Ken Maes, Eline Menu, Elke De Bruyne, Hendrik De Raeve, Karel Fostier, Jérôme Moreaux, Alboukadel Kassambara, Dirk Hose, Roy Heusschen, Helena Eriksson, Karin Vanderkerken, and Els Van Valckenborgh  
*In mouse multiple myeloma, treatment with the small molecule ABR-238901 interfered with calcium-binding protein S100A9, affected cytokine secretion and angiogenesis, and reduced tumor load. Results improved further when ABR-238901 was delivered in combination with the proteasome inhibitor bortezomib.*

## RESEARCH ARTICLES

## 847 Customized Viral Immunotherapy for HPV-Associated Cancer

Matthew J. Atherton, Kyle B. Stephenson, Jonathan Pol, Fuan Wang, Charles Lefebvre, David F. Stojdl, Jake K. Nikota, Anna Dvorkin-Gheva, Andrew Nguyen, Lan Chen, Stephanie Johnson-Obaseki, Patrick J. Villeneuve, Jean-Simon Diallo, Jim Dimitroulakos, Yonghong Wan, and Brian D. Lichtig  
*Oncolytic Maraba virus can selectively infect HPV<sup>+</sup> human cancers as well as generate substantial antitumor immunity. This resulted in complete destruction of advanced HPV<sup>+</sup> tumors in mice, providing a promising immunological approach to combat HPV-associated cancer.*

## 860 CD28 and 41BB Costimulation Enhances the Effector Function of CD19-Specific Engager T Cells

Mireya Paulina Velasquez, Arpad Szoor, Abishek Vaidya, Aarohi Thakkar, Phuong Nguyen, Meng-Fen Wu, Hao Liu, and Stephen Gottschalk

*T cells expressing a bispecific linker coupling tumor-expressed CD19 to CD3 were more effective when also expressing CD80 and 41BBL costimulatory molecules. Such T cells had increased IFN $\gamma$  and IL2 production and enhanced antitumor activity in mouse models.*

## 871 Neoadjuvant Interferons: Critical for Effective PD-1–Based Immunotherapy in TNBC

Natasha K. Brockwell, Katie L. Owen, Damien Zanker, Alex Spurling, Jai Rautela, Hendrika M. Duivenvoorden, Nikola Baschuk, Franco Caramia, Sherene Loi, Phillip K. Darcy, Elgene Lim, and Belinda S. Parker  
*Combination therapy exploiting the interplay between type I IFN signaling and the PD-1/PD-L1 axis induced a tumor-specific cytotoxic response in mouse models of triple-negative breast cancer, extending survival specifically in the neoadjuvant setting.*

## 885 Tumor-Associated Macrophages Promote Epigenetic Silencing of Gelsolin through DNA Methyltransferase 1 in Gastric Cancer Cells

Hao-Chen Wang, Chin-Wang Chen, Chia-Lung Yang, I-Min Tsai, Ya-Chin Hou, Chang-Jung Chen, and Yan-Shen Shan  
*Dysregulation of DNA methylation can promote tumor progression. In gastric cancer cells, M2 macrophages enhanced expression of DNMT1, which aberrantly methylated the promoter of the tumor suppressor gelsolin, reducing its expression. Interference with methylation could reduce tumor growth.*

898 Antigen-Presenting Intratumoral B Cells Affect CD4<sup>+</sup> TIL Phenotypes in Non–Small Cell Lung Cancer Patients

Tullia C. Bruno, Peggy J. Ebner, Brandon L. Moore, Olivia G. Squalls, Katherine A. Waugh, Evgeniy B. Eruslanov, Sunil Singhal, John D. Mitchell, Wilbur A. Franklin, Daniel T. Merrick, Martin D. McCarter, Brent E. Palmer, Jeffrey A. Kern, and Jill E. Slansky  
*B cells in non–small cell lung cancer tumors can present antigen. Activated or exhausted B cells were associated with effector or regulatory CD4<sup>+</sup> T cells, respectively, which may make intratumoral B cells a viable target for immunotherapy.*

# Table of Contents

- 908**    **The Antitumor Effects of Vaccine-Activated CD8<sup>+</sup> T Cells Associate with Weak TCR Signaling and Induction of Stem-Like Memory T Cells**  
Sha Wu, Wei Zhu, Yibing Peng, Lan Wang, Yuan Hong, Lei Huang, Dayong Dong, Junping Xie, Todd Merchen, Edward Kruse, Zong Sheng Guo, David Bartlett, Ning Fu, and Yukai He  
*Vaccine-activated CD8<sup>+</sup> T cells that had weaker TCR signaling had stronger antitumor effects. Weak activation halted differentiation at the stem-like memory T-cell stage, generating more Tscm cells, and protected T effectors from antigen-induced exhaustion and apoptosis.*

- 920**    **The Inhibitory Signaling Receptor Protocadherin-18 Regulates Tumor-Infiltrating CD8<sup>+</sup> T-cell Function**  
Alan B. Frey  
*Protocadherin-18 is expressed on memory T cells. It behaved like an inhibitory signaling receptor, interfering with the response of T cells to cancer, and its blockade in vitro or in vivo enhances the T-cell effector phase.*

- 929**    **IL15 Infusion of Cancer Patients Expands the Subpopulation of Cytotoxic CD56<sup>bright</sup> NK Cells and Increases NK-Cell Cytokine Release Capabilities**  
Sigrid Dubois, Kevin C. Conlon, Jürgen R. Müller, Jennifer Hsu-Albert, Nancy Beltran, Bonita R. Bryant, and Thomas A. Waldmann  
*Infusions of the cytokine IL15 in cancer patients altered NK cell populations, favoring CD56<sup>bright</sup> NK cells and improving cytotoxic activities toward target cells. IL15 infusions may be particularly useful with tumor-targeted antibodies in the treatment of cancer.*

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## ABOUT THE COVER

Human papilloma virus (HPV) is associated with several malignancies, especially cervical and head and neck cancers. Vaccines are being used to treat various cancers, but with limited success. Atherton et al. demonstrate a promising approach that may provide more consistent antitumor responses. They infected mice with the oncolytic Maraba virus, which selectively infects and lyses tumor cells, while also acting as a vaccine, based on attenuated HPV E6 and E7 transforming proteins. Antigen-specific CD8<sup>+</sup> T cells were activated, HPV<sup>+</sup> tumors eradicated, and memory induced. This one-two punch strategy may overcome the immunosuppression of advanced disease. Read more in this issue starting on page 847. The micrograph is a hematoxylin-eosin stain of a TC1 tumor harvested from a vaccine-treated mouse. Artwork by Lewis Long.

