

## CANCER IMMUNOLOGY RESEARCH

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## WHAT WE'RE READING

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

## PRIORITY BRIEFS

- 844 **Tumor Fusion Burden as a Hallmark of Immune Infiltration in Prostate Cancer**  
Marie-Claire Wagle, Joseph Castillo, Shrividhya Srinivasan, Thomas Holcomb, Kobe C. Yuen, Edward E. Kadel, Sanjeev Mariathasan, Daniel L. Halligan, Adrian R. Carr, Max Bylesjo, Paul R. McAdam, Sarah Lynagh, Koen M. Marien, Mark Kockx, Yannick Waumans, Shih-Min A. Huang, Mark R. Lackner, and Zineb Mounir  
Despite the link of tumor mutational burden with response to immunotherapy, it is not universal across tumor types. In prostate cancer, the burden of tumor gene fusions positively correlates with antitumor immunity, inversely correlating with tumor mutational burden.

- 851 **Demographic Factors Associated with Toxicity in Patients Treated with Anti-Programmed Cell Death-1 Therapy**  
Kaustav P. Shah, Haocan Song, Fei Ye, Javid J. Moslehi, Justin M. Balko, Joe-Elie Salem, and Douglas B. Johnson  
Immune-related adverse events (irAEs), and the resulting length of hospitalization and mortality rate, are age specific in patients with melanoma treated with immunotherapy. These differences could be due to specific irAEs that occur in different age groups.

## RESEARCH ARTICLES

- 856 **Vaccination against Nonmutated Neoantigens Induced in Recurrent and Future Tumors**  
Greta Garrido, Brett Schrand, Agata Levay, Ailem Rabasa, Anthony Ferrantella, Diane M. Da Silva, Francesca D'Eramo, Koen A. Marijt, Zhuoran Zhang, Deukwoo Kwon, Marcin Kortylewski, W. Martin Kast, Vikas Dudeja, Thorbald van Hall, and Eli Gilboa  
A vaccination approach is presented. This strategy overcomes the main limitation of focusing on tumor mutation-derived neoantigens by vaccinating against neoantigens that are experimentally induced in tumor cells.

- 869 **Dual Relief of T-lymphocyte Proliferation and Effector Function Underlies Response to PD-1 Blockade in Epithelial Malignancies**

Camille-Charlotte Balança, Clara-Maria Scarlata, Marie Michelas, Christel Devaud, Victor Sarradin, Camille Franchet, Carlos Martinez Gomez, Carlos Gomez-Roca, Marie Tosolini, Diana Heaugwane, Françoise Lauzéral-Vizcaino, Lucile Mir-Mesnier, Virginie Féliu, Carine Valle, Frédéric Pont, Gwénaél Ferron, Laurence Gladieff, Stéphanie Motton, Yann Tanguy Le Gac, Agnès Dupret-Bories, Jérôme Sarini, Benjamin Vairel, Claire Illac, Aurore Siegfried-Vergnon, Eliane Mery, Jean-Jacques Fournié, Sébastien Vergez, Jean-Pierre Delord, Philippe Rochaix, Alejandra Martinez, and Maha Ayyoub

Tumor-infiltrating CD8<sup>+</sup> T cells from patients with three cancer types exhibit a memory phenotype, a sequential pattern of immune checkpoint expression with additional CD39 expression, and CD28 loss. These cells' effector potential can be unleashed with anti-PD-1.

- 883 **SHP-2 and PD-L1 Inhibition Combined with Radiotherapy Enhances Systemic Antitumor Effects in an Anti-PD-1-Resistant Model of Non-Small Cell Lung Cancer**

Dawei Chen, Hampartsoum B. Barsoumian, Liangpeng Yang, Ahmed I. Younes, Vivek Verma, Yun Hu, Hari Menon, Mark Wasley, Fatemeh Masropour, Sara Mosaffa, Tugce Ozgen, Katherine Klein, Maria Angelica Cortez, and James W. Welsh

A triple-therapy combination leads to repolarization of M2 tumor-associated macrophages (TAMs) to M1 TAMs. As a result, this combination therapy elicits robust antitumor responses against primary NSCLC tumors and can also boost antitumor abscopal responses.

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- 895**     **Characterization of BAY 1905254, an Immune Checkpoint Inhibitor Targeting the Immunoglobulin-Like Domain Containing Receptor 2 (ILDR2)**  
**AC**     Julia Huetter, Uwe Gritzan, Ilona Gutcher, Wolf-Dietrich Doecke, Merlin V. Luetke-Eversloh, Sven Golfier, Helge G. Roider, Anna-Lena Frisk, John Hunter, Andrew Pow, Andrew Drake, Zurit Levine, Ofer Levy, Meir Azulay, Inbal Barbiro, Gady Cojocar, Ilan Vaknin, Bertolt Kreft, and Lars Roese  
ILDR2 is an immune checkpoint expressed by certain stromal lymph node cells called fibroblastic reticular cells. ILDR2 negatively interferes with T-cell activity, and its inhibition by the antibody BAY 1905254 is beneficial in preclinical models.
- 912**     **CD226<sup>hi</sup>CD8<sup>+</sup> T Cells Are a Prerequisite for Anti-TIGIT Immunotherapy**  
Hyung-seung Jin, Minkyung Ko, Da-som Choi, June Hyuck Kim, Dong-hee Lee, Seong-Ho Kang, Inki Kim, Hee Jin Lee, Eun Kyung Choi, Kyu-pyo Kim, Changhoon Yoo, and Yoon Park  
A subset of CD8<sup>+</sup> T cells highly express CD226. The efficacy of anti-TIGIT therapy is more profound on high CD226 expressors rather than low. TIGIT blockade activity depends on CD226 phosphorylation, which predicts the outcome of anti-TIGIT therapy.
- 926**     **Genetic Ablation of HLA Class I, Class II, and the T-cell Receptor Enables Allogeneic T Cells to Be Used for Adoptive T-cell Therapy**  
Yuki Kagoya, Tingxi Guo, Brian Yeung, Kayoko Saso, Mark Anczurowski, Chung-Hsi Wang, Kenji Murata, Kenji Sugata, Hiroshi Saijo, Yukiko Matsunaga, Yota Ohashi, Marcus O. Butler, and Naoto Hirano  
Antitumor T-cell grafts with HLA class I, HLA class II, and TCR molecules concurrently ablated evade allogeneic T-cell responses. These cells can be used as a universal T-cell source for adoptive cancer immunotherapy.
- 937**     **Long Noncoding RNAs Control the Modulation of Immune Checkpoint Molecules in Cancer**  
Shouping Xu, Qin Wang, Yujuan Kang, Jiena Liu, Yanling Yin, Lei Liu, Hao Wu, Siwei Li, Shiyao Sui, Meiyong Shen, Wei Zheng, and Da Pang  
Long noncoding RNAs (lncRNAs) could potentially regulate immune checkpoint molecules. The lncRNAs HCP5 and MIAT are upregulated when prognosis is poor. They drive PD-L1 expression and inhibit the efficacy of immune checkpoint blockade.
- 952**     **Verteporfin Inhibits PD-L1 through Autophagy and the STAT1-IRF1-TRIM28 Signaling Axis, Exerting Antitumor Efficacy**  
**AC**     Jiyong Liang, Lulu Wang, Chao Wang, Jianfeng Shen, Bojin Su, Anantha L. Marisetty, Dexing Fang, Cynthia Kassab, Kang Jin Jeong, Wei Zhao, Yiling Lu, Abhinav K. Jain, Zhicheng Zhou, Han Liang, Shao-Cong Sun, Changming Lu, Zhi-Xiang Xu, Qinghua Yu, Shan Shao, XiaoHua Chen, Meng Gao, Francois X. Claret, Zhiyong Ding, Jian Chen, Pingsheng Chen, Michelle C. Barton, Guang Peng, Gordon B. Mills, and Amy B. Heimmerger  
Antibody blockade of PD-L1 is associated with toxicities, thus new targeting strategies are needed. Verteporfin suppresses PD-L1 expression via Golgi-related autophagy and disruption of STAT1-IRF1-TRIM28 signaling.
- 966**     **Transfer of MicroRNA via Macrophage-Derived Extracellular Vesicles Promotes Proneural-to-Mesenchymal Transition in Glioma Stem Cells**  
Zongpu Zhang, Jianye Xu, Zihang Chen, Huizhi Wang, Hao Xue, Chunlei Yang, Qindong Guo, Yanhua Qi, Xiaofan Guo, Mingyu Qian, Shaobo Wang, Wei Qiu, Xiao Gao, Rongrong Zhao, Xing Guo, and Gang Li  
The progression of glioblastoma is marked by a proneural-to-mesenchymal transition (PMT) and is associated with radiation resistance. PMT is triggered by the release of microRNA-filled small extracellular vesicles from tumor-associated macrophages that target CHD7 in glioma stem cells.

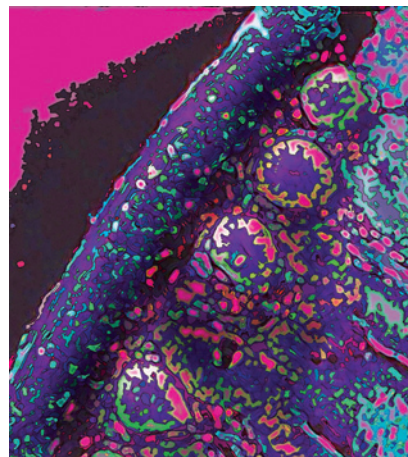
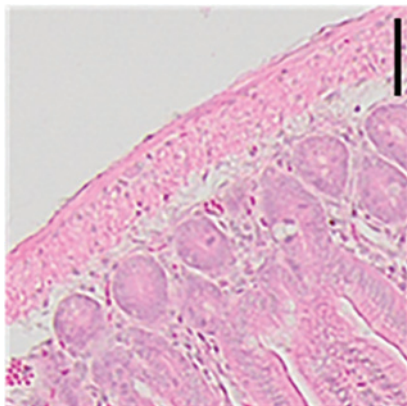
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## ABOUT THE COVER

Determining which tumor neoantigens to target with cancer vaccines is challenging and has been limited to mutation-derived, mostly nonclonal, antigens expressed in the patients' tumors. Garrido and Schrand et al. develop a vaccination method that induces expression of clonal neoantigens via targeted delivery of an siRNA that downregulates the TAP (transporter associated with antigen processing) protein in either DCs or tumor cells in mice. TAP-low DCs can prime polyclonal CD8<sup>+</sup> T-cell responses against neoantigens induced in TAP-low tumor cells. Targeting the induced antigens is more efficacious than vaccination against mutation-derived tumor antigens and protects mice from TAP siRNA-treated concurrent or relapsing tumors without toxicity. The data highlight how this method could have broad applicability as a vaccine strategy for cancer patients. Read more in this issue on page 856. Original image from Supplementary Fig. S5B. Artwork by Lewis Long.



# Cancer Immunology Research

**8 (7)**

*Cancer Immunol Res* 2020;8:843-981.

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