

CANCER IMMUNOLOGY RESEARCH

TABLE OF CONTENTS

WHAT WE'RE READING

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

REVIEW

- 652** **Interactions between MDSCs and the Autonomic Nervous System: Opportunities and Challenges in Cancer Neuroscience**
Lin-Zhen Shu, Yi-Dan Ding, Jin-Yao Zhang,
Rui-Shan He, Li Xiao, Bing-Xing Pan, and Huan Deng

PRIORITY BRIEF

- 663** **The Exonuclease TREX1 Constitutes an Innate Immune Checkpoint Limiting cGAS/STING-Mediated Antitumor Immunity**
Junghyun Lim, Ryan Rodriguez, Katherine Williams,
John Silva, Alan G. Gutierrez, Paul Tyler,
Faezzah Baharom, Tao Sun, Eva Lin, Scott Martin,
Brandon D. Kayser, Robert J. Johnston, Ira Mellman,
Lélia Delamarre, Nathaniel R. West, Sören Müller,
Yan Qu, and Klaus Heger
Cancer cells are prone to cytosolic DNA accumulation. The authors demonstrate that the exonuclease TREX1, which degrades endogenous cytosolic DNA, is a key innate immune checkpoint limiting tumor immunogenicity and a potential target for cancer immunotherapy.

See related article, p. 673

RESEARCH ARTICLES

- 673** **Intratumoral TREX1 Induction Promotes Immune Evasion by Limiting Type I IFN**
Eléonore Toufektchan, Alexandra Dananberg,
Josefine Striepen, James H. Hickling, Abraham Shim,
Yanyang Chen, Ashley Nichols, Mercedes A. Duran Paez,
Lisa Mohr, Samuel F. Bakhoun, and John Maciejowski
It is unclear how chromosomally unstable cancer cells avoid immune responses from cGAS-STING detection of cytosolic DNA. The authors show that TREX1 nuclease upregulation guards against antitumor immune responses by degrading cytosolic DNA and limiting cGAS-STING-dependent interferon signaling.

See related article, p. 663

- 687** **Unleashing Natural IL18 Activity Using an Anti-IL18BP Blocker Induces Potent Immune Stimulation and Antitumor Effects**

Assaf Menachem, Zoya Alteber, Gady Cojocaru,
Tal Fridman Kfir, Dan Blat, Olga Leiderman,
Moran Galperin, Lital Sever, Nadav Cohen, Keren Cohen,
Roy Z. Granit, Sandra Vols, Masha Frenkel, Liron Soffer,
Karin Meyer, Keren Menachem, Hadas Galon Tilleman,
Dina Morein, Itamar Borukhov, Amir Toporik,
Michal Perpinial Shahor, Evgeny Tatirovsky,
Aviram Mizrachi, Adva Levy-Barda, Eran Sadot,
Yulia Strenov, Ram Eitan, Ariella Jakobson-Setton,
Natalia Yanichkin, Pierre Ferre, and Eran Ophir

Therapeutic usage of cytokines in patients is limited by toxicity. The authors report that blocking a cytokine binding protein, IL18BP, to enhance the cytokine's natural activity yields antitumor activity in preclinical models and shows promise for clinical translation.

- 704** **Randomized Phase II Study Evaluating the Addition of Pembrolizumab to Radium-223 in Metastatic Castration-resistant Prostate Cancer**

Atish D. Choudhury, Lucia Kwak, Alexander Cheung,
Kathryn M. Allaire, Jaqueline Marquez, David D. Yang,
Abhishek Tripathi, Jacqueline M. Kilar, Meredith Flynn,
Brianna Maynard, Rebecca Reichel, Amanda F. Pace,
Brandon K. Chen, Eliezer M. Van Allen, Kerry Kilbridge,
Xiao X. Wei, Bradley A. McGregor, Mark M. Pomerantz,
Rupal S. Bhatt, Christopher J. Sweeney, Glenn J. Bubley,
Heather A. Jacene, Mary-Ellen Taplin,
Franklin W. Huang, Lauren C. Harshman, and
Lawrence Fong

This first-in-human, randomized trial demonstrates that combining radium-223 with pembrolizumab does not significantly impact the tumor microenvironment in patients with metastatic castration-resistant prostate cancer. Data highlight that upregulation of immune checkpoint molecules could impede the combination's clinical efficacy.

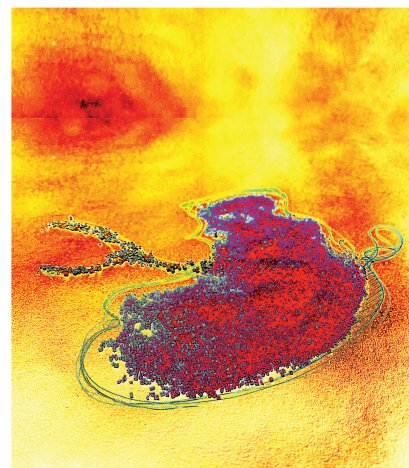
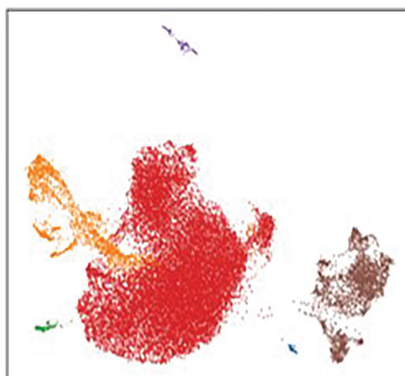
TABLE OF CONTENTS

- 719 Engineering CD3/CD137 Dual Specificity into a DLL3-Targeted T-Cell Engager Enhances T-Cell Infiltration and Efficacy against Small-Cell Lung Cancer**
 Hirofumi Mikami, Shu Feng, Yutaka Matsuda, Shinya Ishii, Sotaro Naoi, Yumiko Azuma, Hiroaki Nagano, Kentaro Asanuma, Yoko Kayukawa, Toshiaki Tsunenari, Shogo Kamikawaji, Ryutaro Iwabuchi, Junko Shinozuka, Masaki Yamazaki, Haruka Kuroi, Samantha Shu Wen Ho, Siok Wan Gan, Priyanka Chichili, Chai Ling Pang, Chiew Ying Yeo, Shun Shimizu, Naoka Hironiwa, Yasuko Kinoshita, Yuichiro Shimizu, Akihisa Sakamoto, Masaru Muraoka, Noriyuki Takahashi, Tatsuya Kawa, Hirotake Shiraiwa, Futa Mimoto, Kenji Kashima, Mika Kamata-Sakurai, Shumpei Ishikawa, Hiroyuki Aburatani, Takehisa Kitazawa, and Tomoyuki Igawa
 This study demonstrates that a CD3/CD137 dual-specific Fab, generated through mutagenesis of a conventional CD3 antibody, improves the efficacy of DLL3-targeted T-cell engagers, suggesting that engineering of the CD3 binding region can unlock the potential of T-cell engagers.
- 731 Preclinical Evaluation of Off-The-Shelf PD-L1⁺ Human Natural Killer Cells Secreting IL15 to Treat Non-Small Cell Lung Cancer**
 Ting Lu, Rui Ma, Anthony G. Mansour, Christian Bustillos, Zhiyao Li, Zhenlong Li, Shoubao Ma, Kun-Yu Teng, Hanyu Chen, Jianying Zhang, Miguel A. Villalona-Calero, Michael A. Caligiuri, and Jianhua Yu
 There is interest in harnessing NK cells to generate allogeneic cell therapies. The authors report IND-enabling studies testing the safety and efficacy of engineered PD-L1⁺ NK cells expressing soluble IL15, and supporting a clinical trial for NSCLC.
- 744 The ω -3 Polyunsaturated Fatty Acid Docosahexaenoic Acid Enhances NK-Cell Antitumor Effector Functions**
 Shuting Wu, Hongyan Peng, Songyang Li, Lanlan Huang, Xiangyu Wang, Yana Li, Yongjie Liu, Peiwen Xiong, Qinglan Yang, Kunpeng Tian, Weiru Wu, Rongxi Pu, Xiulan Lu, Zhenghui Xiao, Jian Yang, Zhaoyang Zhong, Yuan Gao, Yafei Deng, and Youcai Deng
 DHA has direct growth suppressing effects on tumour cells. The authors show it also has an immunomodulatory effect, limiting tumour growth by enhancing NK-cell IFN γ production and cytotoxicity, likely by upregulating mitochondrial activity via the PGC-1 α pathway.
- 759 The Neo-Open Reading Frame Peptides That Comprise the Tumor Framome Are a Rich Source of Neoantigens for Cancer Immunotherapy**
 Michael V. Martin, Salvador Aguilar-Rosas, Katka Franke, Mark Pieterse, Jamie van Langelaar, Renée Schreurs, Maarten F. Bijlsma, Marc G. Besselink, Jan Koster, Wim Timens, Mustafa Khasraw, David M. Ashley, Stephen T. Keir, Christian H. Ottensmeier, Emma V. King, Joanne Verheij, Cynthia Waasdorp, Peter J.M. Valk, Sem A.G. Engels, Ellen Oostenbach, Jip T. van Dinter, Damon A. Hofman, Juk Yee Mok, Wim J.E. van Esch, Hanneke Wilmink, Kim Monkhorst, Henk M.W. Verheul, Dennis Poel, T. Jeroen N. Hiltermann, Léon C.L.T. van Kempen, Harry J.M. Groen, Joachim G.J.V. Aerts, Sebastiaan van Heesch, Bob Löwenberg, Ronald Plasterk, and Wigard P. Kloosterman
 Identifying immunogenic cancer neoantigens for cancer vaccine design is challenging. The authors uncover NOPs as a widespread source of neoantigens derived from structural genomic variants and indels. The findings open new avenues towards personalized immunotherapies for cancer.
- 779 An IRF2-Expressing Oncolytic Virus Changes the Susceptibility of Tumor Cells to Antitumor T Cells and Promotes Tumor Clearance**
 Lulu Shao, Rashmi Srivastava, Greg M. Delgoffe, Stephen H. Thorne, and Saumendra N. Sarkar
 Tumor cell-intrinsic IRF1 was recently shown to promote tumor growth. The authors show that tumor cell-specific targeting of IRF1 through IRF2 expression can suppress tumor growth in a model of melanoma, suggesting a novel immunotherapeutic approach.

TABLE OF CONTENTS

ABOUT THE COVER

Recombinant cytokines show limited utility as a cancer treatment because the high doses needed for an antitumor effect cause severe systemic toxicities. After finding that IL18 is upregulated in the tumor microenvironment (TME) but is mostly inactive because it is bound to IL18 binding protein (IL18BP), Menachem and Alteber et al. generated an IL18BP-specific antibody that can displace IL18 from IL18:IL18BP complexes, activating CD8⁺ T cells and NK cells. A mouse surrogate for the human antibody inhibited tumor growth in several mouse models concomitant with TME immune activation. No effects were observed in the periphery, highlighting the potential of blocking IL18BP to therapeutically harness naturally occurring IL18 in the TME. Read more in this issue on page 687. Original image from Fig. 7A. Artwork by Lewis Long.



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