

CANCER IMMUNOLOGY RESEARCH

TABLE OF CONTENTS

WHAT WE'RE READING

- 1109 **A Sampling of Highlights from the Literature**

IN THE SPOTLIGHT

- 1110 **Putting On the Gas and Taking Off the Brakes: A Novel Combinatorial Strategy to Enhance Tumor-Infiltrating Lymphocytes**
Martin Felices and Jeffrey S. Miller
See related article, p. 1141

RESEARCH ARTICLES

- 1111 ***A. muciniphila* Suppresses Colorectal Tumorigenesis by Inducing TLR2/NLRP3-Mediated M1-Like TAMs**
Lina Fan, Chaochao Xu, Qiwei Ge, Yifeng Lin, Chi Chun Wong, Yadong Qi, Bin Ye, Qingwu Lian, Wei Zhuo, Jianmin Si, Shujie Chen, and Liangjing Wang
The authors show that *A. muciniphila* can induce M1-like macrophages through a TLR2/NF- κ B/NLRP3 pathway to suppress colorectal cancer progression, suggesting a new potential therapeutic strategy for colorectal cancer prevention and treatment.
- 1125 **The Ratio of Exhausted to Resident Infiltrating Lymphocytes Is Prognostic for Colorectal Cancer Patient Outcome**
Momeneh Foroutan, Ramyar Molania, Aline Pfeifferle, Corina Behrenbruch, Sebastian Scheer, Axel Kallies, Terence P. Speed, Joseph Cursons, and Nicholas D. Huntington
The authors identify tumor mutations and tumor microenvironmental factors that drive residency programs in infiltrating lymphocytes, impairing their antitumor function and patient outcomes. Understanding how tumor lymphocyte residency is regulated might offer new approaches for therapeutic intervention.

- 1141 **An Engineered IL15 Cytokine Mutein Fused to an Anti-PD1 Improves Intratumoral T-cell Function and Antitumor Immunity**

Yuanming Xu, Lucia Campos Carrascosa, Yik Andy Yeung, Matthew Ling-Hon Chu, Wenjing Yang, Ivana Djuretic, Danielle C. Pappas, John Zeytounian, Zhouhong Ge, Valeska de Ruiter, Gabriel R. Starbeck-Miller, James Patterson, Diamanda Rigas, Shih-Hsun Chen, Eugenia Kraynov, Patrick P. Boor, Lisanne Noordam, Michael Doukas, Dave Tsao, Jan N. Ijzermans, Jie Guo, Dirk J. Grünhagen, Joris Erdmann, Joanne Verheij, Martin E. van Royen, Pascal G. Doornebosch, Renny Feldman, Terrence Park, Salah Mahmoudi, Magdalena Dorywalska, Irene Ni, Sherman M. Chin, Tina Mistry, Lidia Mosyak, Laura Lin, Keith A. Ching, Kevin C. Lindquist, Changhua Ji, Luz Marina Londono, Bing Kuang, Robert Rickert, Jaap Kwekkeboom, Dave Sprengers, Tzu-Hsuan Huang, and Javier Chaparro-Riggers

To overcome challenges associated with cytokine-based immunotherapies, the authors engineered a fusion protein of a single, potency-reduced, IL15 mutein and a PD1-specific antibody. The agent preferentially activates intratumoral CD8⁺ T cells and demonstrates potent preclinical antitumor efficacy.

See related Spotlight, p. 1110

- 1158 **Bispecific CAR T Cells against EpCAM and Inducible ICAM-1 Overcome Antigen Heterogeneity and Generate Superior Antitumor Responses**

Yanping Yang, Jaclyn E. McCloskey, Huan Yang, Janusz Puc, Yago Alcaina, Yogindra Vedvyas, Angel A. Gomez Gallegos, Elizabeth Ortiz-Sánchez, Elisa de Stanchina, Irene M. Min, Eric von Hofe, and Moonsoo M. Jin

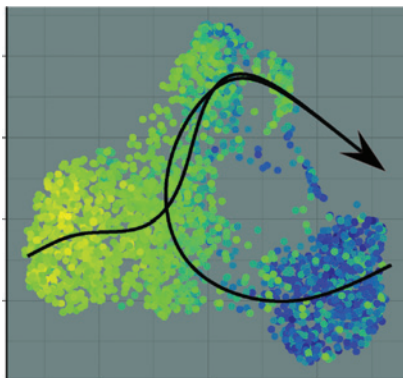
Generation of EpCAM/ICAM-1 dual CAR T cells improves the efficacy of single-targeting EpCAM CAR T cells in multiple tumor models. The data highlight a broadly applicable strategy to boost the activity of single antigen-specific CAR T-cell therapy.

TABLE OF CONTENTS

- 1175** **IPSC-Derived Neoantigen-Specific CTL Therapy for Ewing Sarcoma**
Midori Ishii, Jun Ando, Satoshi Yamazaki, Tokuko Toyota, Kazuo Ohara, Yoshiki Furukawa, Yoshiyuki Suehara, Mahito Nakanishi, Kazutaka Nakashima, Koichi Ohshima, Hiromitsu Nakauchi, and Miki Ando
Functionally rejuvenated iPSC-derived CTLs targeting the EWS/FLI1 fusion gene product are efficacious against Ewing sarcoma. These cells have a stem cell memory phenotype and potent antitumor effects, permitting potential use in therapy.
- 1187** **Context-Dependent Immunomodulatory Effects of MEK Inhibition Are Enhanced with T-cell Agonist Therapy**
Lauren Dennison, Amanda Ruggieri, Aditya Mohan, James Leatherman, Kayla Cruz, Skylar Woolman, Nilofer Azad, Gregory B. Lesinski, Elizabeth M. Jaffee, and Mark Yarchoan
The authors distinguish tumor-mediated and tumor-independent mechanisms of MEK inhibitor immunomodulation. Pharmacologic MEK inhibition enhances tumor immunogenicity but impairs T-cell activation. Antitumor activity with pharmacologic MEK inhibition is enhanced by combination with T-cell agonist therapy.
- 1202** **TMB and Inflammatory Gene Expression Associated with Clinical Outcomes following Immunotherapy in Advanced Melanoma**
F. Stephen Hodi, Jedd D. Wolchok, Dirk Schadendorf, James Larkin, Georgina V. Long, Xiaozhong Qian, Abdel Saci, Tina C. Young, Sujaya Srinivasan, Han Chang, Hao Tang, Megan Wind-Rotolo, Jasmine I. Rizzo, Donald G. Jackson, and Paolo A. Ascierto
This exploratory analysis investigating biomarkers of response to nivolumab and ipilimumab in melanoma patients demonstrates that combined assessment of tumor mutational burden, an inflammatory gene signature, and BRAF mutation status has the potential to predict response to immunotherapy.
- 1214** **Combining an Alarmin HMG1 Peptide with PD-L1 Blockade Results in Robust Antitumor Effects with a Concomitant Increase of Stem-Like/Progenitor Exhausted CD8⁺ T Cells**
Chang-Yu Chen, Satoshi Ueha, Yoshiro Ishiwata, Shigeyuki Shichino, Shoji Yokochi, De Yang, Joost J. Oppenheim, Haru Ogiwara, Shungo Deshimaru, Yuzuka Kanno, Hiroyasu Aoki, Tatsuro Ogawa, Shiro Shibayama, and Kouji Matsushima
An alarmin HMG1 peptide combined with PD-L1 blockade improves antitumor responses in multiple murine tumor models. This combination alters specific CD8⁺ T-cell subsets in the tumor microenvironment and confers protection from subsequent tumor challenges.
- 1229** **Hijacking TYRO3 from Tumor Cells via Trogocytosis Enhances NK-cell Effector Functions and Proliferation**
Ting Lu, Rui Ma, Zhenlong Li, Anthony G. Mansour, Kun-Yu Teng, Li Chen, Jianying Zhang, Tasha Barr, Michael A. Caligiuri, and Jianhua Yu
The authors show TYRO3 is transferred to natural killer (NK) cells via trogocytosis from feeder cells, improving NK-cell proliferation *ex vivo*. This provides a potential novel strategy to manufacture NK cells for adoptive-cell transfer cancer immunotherapy.

ABOUT THE COVER

The identity and frequency of immune cells in the tumor microenvironment impact outcomes for patients with colorectal cancer. Using single-cell RNA sequencing data, Foroutan et al. identify signatures of residency and exhaustion for tumor-infiltrating CD8⁺, CD4⁺, and natural killer (NK) cells. Different signature combinations associated with distinct patient outcomes; for example, signatures of high NK-cell exhaustion and low NK-cell residency were associated with improved survival. The data provide new insight into the characteristics of tumor-infiltrating lymphocytes and suggest that preventing tumor residency by NK cells may enhance antitumor immunity and patient outcomes. Read more in this issue on page 1125. Artwork by Momeneh Foroutan inspired by several figures in the article, including the CD8 residency panel of Fig. 1B, shown here.



doi: 10.1158/2326-6066.CIR-9-10-CVR

Cancer Immunology Research

9 (10)

Cancer Immunol Res 2021;9:1109-1241.

Updated version Access the most recent version of this article at:
<http://cancerimmunolres.aacrjournals.org/content/9/10>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerimmunolres.aacrjournals.org/content/9/10>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.