## What We’re Reading

995  A Sampling of Highlights from the Literature

## In the Spotlight

996  Fighting Liver Metastasis by Activating MAIT Cells
Oliver Lantz
See related article, p. 1024

## Commentary


## Priority Brief

999  CRASH-IT Switch Enables Reversible and Dose-Dependent Control of TCR and CAR T-cell Function
Ali Can Sahillioglu, Mireille Toebes, Georgi Apriamashvili, Raquel Gomez, and Ton N. Schumacher
The authors report a modular T-cell control system, CRASH-IT, that allows the function of T cells activated by their TCR or genetically introduced TCRs or CARs to be adjusted in a reversible manner over a wide dynamic range.

## Research Articles

1008  Overproduction of Gastrointestinal 5-HT Promotes Colitis-Associated Colorectal Cancer Progression via Enhancing NLRP3 Inflammasome Activation
Tao Li, Bin Fu, Xin Zhang, Yunjiang Zhou, Mengdi Yang, Mengran Cao, Yaxin Chen, Yingying Tan, and Rong Hu
A 5-HT-NLRP3 positive feedback loop is demonstrated to maintain persistent inflammation in the colon, resulting in promotion of CRC development and progression. The data highlight the potential to target this feedback loop as a CRC therapeutic strategy.

1024  Activating Mucosal-Associated Invariant T Cells Induces a Broad Antitumor Response
Benjamin Ruf, Vanessa V. Catania, Simon Wabitsch, Chi Ma, Laurence P. Diggs, Qianfei Zhang, Bernd Heinrich, Varun Subramanyam, Linda L. Cui, Marie Pouzolles, Christine N. Evans, Raj Chari, Shunsuke Sakai, Sangmi Oh, Clifton E. Barry III, Daniel L. Barber, and Tim F. Greten
In vitro evidence suggests mucosal-associated invariant T (MAIT) cells can have antitumor function. This study shows MAIT cells stimulated in vivo using 5-OP-RU and CpG orchestrate potent antitumor responses, suggesting these cells as potential targets for cancer immunotherapy.

1035  Development of a Clinically Relevant Reporter for Chimeric Antigen Receptor T-cell Expansion, Trafficking, and Toxicity
Currently, a robust imaging platform to monitor CART cells is lacking. Imaging using 18F-TFB-PET is demonstrated to be an efficient, noninvasive technique to monitor CART-cell expansion and trafficking in vivo in multiple tumor models.

1047  Rationally Designed Transgene-Encoded Cell-Surface Polypeptide Tag for Multiplexed Programming of CAR T-cell Synthetic Outputs
Adam J. Johnson, Jia Wei, James M. Rosser, Annette Künkele, Cindy A. Chang, Aquene N. Reid, and Michael C. Jensen
The authors describe a cell-surface tag system that allows the generation of CAR T cells that recognize more than one target or carry the complex synthetic biology payloads needed to overcome current challenges to advancing CAR T-cell therapy.
CD19/CD22 Dual-Targeted CAR T-cell Therapy for Relapsed/Refractory Aggressive B-cell Lymphoma: A Safety and Efficacy Study

Guoqing Wei, Yanlei Zhang, Houli Zhao, Yiyun Wang, Yandan Liu, Bin Liang, Xiujuan Wang, Huijun Xu, Jiazhen Cui, Wenjun Wu, Kui Zhao, Arnon Nagler, Alex H. Chang, Yongxian Hu, and He Huang

This clinical trial shows CD19/CD22 dual-targeted CAR T cells yield potent and durable responses for patients with B-cell lymphoma without severe cytokine release syndrome, suggesting a way to overcome the antigen-negative relapse seen with monospecific CAR T cells.

A Fusion Protein Complex that Combines IL-12, IL-15, and IL-18 Signaling to Induce Memory-Like NK Cells for Cancer Immunotherapy


A scalable platform, with GMP application, that can be used to generate a multitude of different heteromeric proteins is presented. The platform’s use to generate memory-like NK cells for immunotherapy is demonstrated and provides insights into their biology.

TIGIT-Fc Promotes Antitumor Immunity

Xian Shen, Wenyan Fu, Yongpeng Wei, Junle Zhu, Yue Yu, Changhui Lei, Jian Zhao, and Shi Hu

A TIGIT-Fc fusion protein is demonstrated to modulate NK-cell and T-cell antitumor responses. Treatment leads to generation of immune memory and enhances efficacy of immune checkpoint blockade, highlighting its promise as a cancer immunotherapy.

CD86+ Antigen-Presenting B Cells Are Increased in Cancer, Localize in Tertiary Lymphoid Structures, and Induce Specific T-cell Responses

Kerstin Wennhold, Martin Thelen, Jonas Lehmann, Simon Schran, Ella Preugsatz, Maria García-Marquez, Axel Lechner, Alexander Shimabukuro-Vornhagen, Meryem S. Ercanoglu, Florian Klein, Fabinshy Thangarajah, Sebastian Eitd, Heike Løser, Christiane Bruns, Alexander Quaas, Michael von Bergwelt-Baldin, and Hans A. Schlößer

B cells are shown to be present in multiple cancer types and could be potential immunotherapeutic targets. These cells localize to tertiary lymphoid structures in the tumor microenvironment and through antigen presentation induce antigen-specific T-cell responses.

ABOUT THE COVER

The neurotransmitter 5-hydroxytryptamine (5-HT) promotes gastrointestinal inflammation, a process that can facilitate development of colitis-associated cancer. Li and Fu et al. find that the rate-limiting enzyme in 5-HT synthesis is upregulated in tumor tissues of mouse models, as well as patients with colorectal cancer. Tumor cell–derived 5-HT leads to inflammasome activation in macrophages via HTR3A (5-hydroxytryptamine receptor 3A), an ion channel receptor, and the resulting calcium influx. Interestingly, inflammasome-mediated IL1β release from macrophages then further promotes tumor cell 5-HT production, demonstrating a positive feedback loop that has potential to be therapeutically targeted. Read more in this issue on page 1008. Original image from Fig. 7I. Artwork by Lewis Long.
Cancer Immunology Research

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