

## CANCER IMMUNOLOGY RESEARCH

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- 1229 **A Sampling of Highlights from the Literature**

## CANCER IMMUNOLOGY AT THE CROSSROADS

- 1230 **Understanding and Overcoming the Inflammatory Toxicities of Immunotherapy**  
Michael Dougan

## CANCER IMMUNOLOGY MINIATURES

- 1236 **Association of Probiotic *Clostridium butyricum* Therapy with Survival and Response to Immune Checkpoint Blockade in Patients with Lung Cancer**

**AC** Yusuke Tomita, Tokunori Ikeda, Shinya Sakata, Koichi Saruwatari, Ryo Sato, Shinji Iyama, Takayuki Jodai, Kimitaka Akaike, Shiho Ishizuka, Sho Saeki, and Takuro Sakagami

The gut microbiome associates with the efficacy of immune checkpoint blockade (ICB). The probiotic *Clostridium butyricum* MIYAIRI 588 strain improves the efficacy of ICB in lung cancer patients.

See related articles, p. 1243 and p. 1251

## RESEARCH ARTICLES

- 1243 **The Gut Microbiome Associates with Immune Checkpoint Inhibition Outcomes in Patients with Advanced Non-Small Cell Lung Cancer**

Taiki Hakozaki, Corentin Richard, Arielle Elkrief, Yukio Hosomi, Myriam Benlaïfaoui, Iris Mimpfen, Safae Terrisse, Lisa Derosa, Laurence Zitvogel, Bertrand Routy, and Yusuke Okuma

The gut microbiome influences the efficacy of immune checkpoint inhibition (ICI). In non-small cell lung carcinoma patients, antibiotics have a negative impact on ICI efficacy, correlating to enrichment of *Ruminococcaceae* UCG 13 and *Agathobacter* in the gut.

See related articles, p. 1236 and p. 1251

- 1251 **The Gut Microbiome Is Associated with Clinical Response to Anti-PD-1/PD-L1 Immunotherapy in Gastrointestinal Cancer**

Zhi Peng, Siyuan Cheng, Yan Kou, Ziqi Wang, Rong Jin, Han Hu, Xiaotian Zhang, Ji-fang Gong, Jian Li, Ming Lu, Xicheng Wang, Jun Zhou, ZhiHao Lu, Quan Zhang, David T.W. Tzeng, Dongtao Bi, Yan Tan, and Lin Shen

This analysis of the gut microbiome of patients with gastrointestinal cancer receiving anti-PD-1/PD-L1 shows that responders and nonresponders exhibit differential microbial genera. This suggests that the composition of the microbiome could serve as a biomarker of response.

See related articles, p. 1236 and p. 1243

- 1262 **Hyperglycemia Enhances Cancer Immune Evasion by Inducing Alternative Macrophage Polarization through Increased O-GlcNAcylation**

Natália Rodrigues Mantuano, Michal A. Stanczak, Isadora de Araújo Oliveira, Nicole Kirchhammer, Alessandra A. Filardy, Gianni Monaco, Ronan Christian Santos, Agatha Carlos Fonseca, Miguel Fontes, César de Souza Bastos Jr, Wagner B. Dias, Alfred Zippelius, Adriane R. Todeschini, and Heinz Läubli

Hyperglycemia increases O-GlcNAc in tumor-associated macrophages, shifting them to a protumor phenotype (M2-like) and contributing to cancer progression. Inhibition of O-GlcNAcylation reprograms intratumoral macrophages to an antitumoral phenotype, slowing tumor growth.

- 1273 **An IL6-Adenosine Positive Feedback Loop between CD73<sup>+</sup>  $\gamma\delta$ Tregs and CAFs Promotes Tumor Progression in Human Breast Cancer**

Guoming Hu, Pu Cheng, Jun Pan, Shimin Wang, Qiannan Ding, Zhou Jiang, Lu Cheng, Xuan Shao, Liming Huang, and Jian Huang

CD73<sup>+</sup> $\gamma\delta$ Tregs are found to be the predominant regulatory cells in human breast cancer. A positive feedback loop between CD73<sup>+</sup> $\gamma\delta$ Tregs and cancer-associated fibroblasts promotes tumor progression and could be a potential target of immunotherapy.

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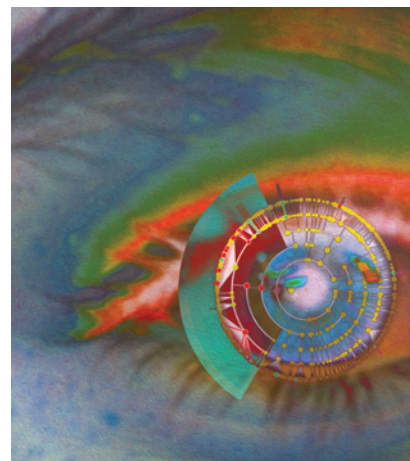
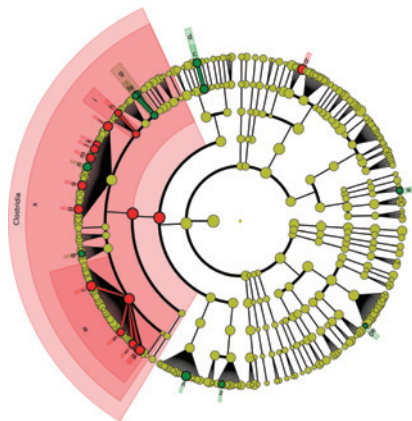
- 1287** **Cross-dressing of CD8 $\alpha^+$  Dendritic Cells with Antigens from Live Mouse Tumor Cells Is a Major Mechanism of Cross-priming**  
Alok Das Mohapatra, Isaac Tirrell, Alexandre P. Bén chet, Shashmita Pattnayak, Kamal M. Khanna, and Pramod K. Srivastava  
Understanding of uptake and presentation of antigens from live tumor cells is important for tumor immunity. Live tumor cells are an abundant source of antigen for CD8 $\alpha^+$  dendritic cells, inducing robust cross-priming and antitumor immunity by cross-dressing.
- 1300** **Bispecific Targeting of PD-1 and PD-L1 Enhances T-cell Activation and Antitumor Immunity**  
Helen Kotanides, Yiwen Li, Maria Malabunga, Carmine Carpenito, Scott W. Eastman, Yang Shen, George Wang, Ivan Inigo, David Surguladze, Anthony L. Pennello, Krishnadatt Persaud, Sagit Hindi, Michael Topper, Xinlei Chen, Yiwei Zhang, Danielle K. Bulaon, Tim Bailey, Yanbin Lao, Bing Han, Stacy Torgerson, Darin Chin, Andreas Sonyi, Jaafar N. Haidar, Ruslan D. Novosiadly, Christopher M. Moxham, Gregory D. Plowman, Dale L. Ludwig, and Michael Kalos  
Many patients do not respond to immune checkpoint blocking antibodies, thus new approaches are needed. A bispecific antibody targeting both PD-1 and PD-L1 has better antitumor efficacy than the single antibody or combination antibody treatments.
- 1311** **CD39 Identifies the CD4 $^+$  Tumor-Specific T-cell Population in Human Cancer**  
Kim E. Kortekaas, Saskia J. Santegoets, Gregor Sturm, Ilna Ehsan, Sylvia L. van Egmond, Francesca Finotello, Zlatko Trajanoski, Marij J.P. Welters, Mariette I.E. van Poelgeest, and Sjoerd H. van der Burg  
Immunotherapy of cancer is based on the activation of tumor-reactive CD4 $^+$  and CD8 $^+$  T cells. The authors show that the expression of CD39 can be used to identify, isolate, and expand tumor-reactive T-cell populations in cancers.
- 1322** **Spliced Peptides and Cytokine-Driven Changes in the Immunopeptidome of Melanoma**  
Pouya Faridi, Katherine Woods, Simone Ostrouska, Cyril Deceneux, Ritchlynn Aranha, Divya Duscharla, Stephen Q. Wong, Weisan Chen, Sri H. Ramarathinam, Terry C.C. Lim Kam Sian, Nathan P. Croft, Chen Li, Rochelle Ayala, Jonathan S. Cebon, Anthony W. Purcell, Ralf B. Schittenhelm, and Andreas Behren  
Spliced peptide antigens are shown to be abundant in the immunopeptidome of melanoma, can change with cytokine exposure, and are targets of T cells. The data identify these posttranslationally spliced peptides as potential targets in cancer immunotherapy.

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## ABOUT THE COVER

The gut microbiome contributes to antitumor immune responses and the efficacy of immune checkpoint inhibition (ICI) in cancer patients. Here, the Okuma, Routy, and Zitvogel labs study how previous antibiotic treatment impacts ICI efficacy in 70 non-small cell lung cancer (NSCLC) patients. Performing 16S rRNA V3-V4 sequencing of fecal samples, they found that NSCLC patients with pre-ICI antibiotic treatment had less bacterial alpha-diversity, but enrichment of *Ruminococcaceae* UCG 13 and *Agathobacter*, in the gut. These alterations correlate to dampened ICI efficacy. Thus, antibiotic treatment negatively impacts ICI efficacy in NSCLC patients. To read more, Hakozaki et al. begins on page 1243. Taxonomic cladogram of the gut microbiota of patients treated with or without antibiotics from the Okuma laboratory. Artwork by Lewis Long.



# Cancer Immunology Research

**8 (10)**

*Cancer Immunol Res* 2020;8:1229-1334.

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