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## 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  
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.  
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## Research Articles

1243  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.  
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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

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

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An IL6–Adenosine Positive Feedback Loop between CD73+γδTregs 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+γδTregs are found to be the predominant regulatory cells in human breast cancer. A positive feedback loop between CD73+γδTregs and cancer-associated fibroblasts promotes tumor progression and could be a potential target of immunotherapy.
Cross-dressing of CD8α⁺ Dendritic Cells with Antigens from Live Mouse Tumor Cells Is a Major Mechanism of Cross-priming
Alok Das Mohapatra, Isaac Tirrell, Alexandre P. Bénèchet, Shashmita Pattanayak, 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 CD8α⁺ dendritic cells, inducing robust cross-priming and antitumor immunity by cross-dressing.

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, Jaffar 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.

CD39 Identifies the CD4⁺ Tumor-Specific T-cell Population in Human Cancer
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.

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 Kang, Nathan P. Croft, Chen Li, Rochelle Ayala, Jonathan S. Cebron, 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.

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.