

WHAT WE'RE READING

- 989 A Sampling of Highlights from the Literature


CANCER IMMUNOLOGY AT THE CROSSROADS

- 990 T Cell–Inflamed versus Non-T Cell–Inflamed Tumors: A Conceptual Framework for Cancer Immunotherapy Drug Development and Combination Therapy Selection
Jonathan A. Trujillo, Randy F. Sweis, Riyue Bao, and Jason J. Luke

CANCER IMMUNOLOGY MINIATURES

- 1001 Response to Immune Checkpoint Inhibition in Two Patients with Alveolar Soft-Part Sarcoma
Jeremy Lewin, Scott Davidson, Nathaniel D. Anderson, Beatrice Y. Lau, Jacalyn Kelly, Uri Tabori, Samer Salah, Marcus O. Butler, Kyaw L. Aung, Adam Shlien, Brendan C. Dickson, and Albiruni R. Abdul Razak
Two patients with ASPS responded to immune checkpoint inhibition. Genomic analysis of a larger group of patients demonstrated molecular mismatch repair deficiency signatures in 71% of patients. Immune checkpoint blockade may be a useful therapy for ASPS.
- 1008 Siglec-6 on Chronic Lymphocytic Leukemia Cells Is a Target for Post-Allogeneic Hematopoietic Stem Cell Transplantation Antibodies
Jing Chang, Haiyong Peng, Brian C. Shaffer, Sivasubramanian Baskar, Ina C. Wecken, Matthew G. Cyr, Gustavo J. Martinez, Jo Soden, Jim Freeth, Adrian Wiestner, and Christoph Rader
Mining the antibody repertoire of patients responding well to allogeneic hematopoietic stem cell transplantation (alloHST) can unveil targets with therapeutic potential. Through the use of phage display, Siglec-6 was identified as a major antigenic target of such antibodies.

RESEARCH ARTICLES

- 1014 IL35 Hinders Endogenous Antitumor T-cell Immunity and Responsiveness to Immunotherapy in Pancreatic Cancer
 Bhalchandra Mirlekar, Daniel Michaud, Ryan Searcy, Kevin Greene, and Yuliya Pylayeva-Gupta
IL35 was identified as a major regulator of T cell–mediated antitumor responses in pancreatic ductal adenocarcinoma. IL35 deficiency in vivo allowed for increased effector T-cell infiltration into tumors and improved the efficacy of anti–PD-1 therapy.
- 1025 Enhancement of Peptide Vaccine Immunogenicity by Increasing Lymphatic Drainage and Boosting Serum Stability
Kelly D. Moynihan, Rebecca L. Holden, Naveen K. Mehta, Chensu Wang, Mark R. Karver, Jens Dinter, Simon Liang, Wuhbet Abraham, Mariane B. Melo, Angela Q. Zhang, Na Li, Sylvie Le Gall, Bradley L. Pentelute, and Darrell J. Irvine
Augmented antitumor vaccines were synthesized by conjugating albumin-binding moieties to peptide antigens. This platform improved vaccine stability and lymphatic distribution, leading to augmented and extended antigen presentation in lymph nodes and enhanced CD8⁺ T-cell priming.
- 1039 Improved Risk-Adjusted Survival for Melanoma Brain Metastases in the Era of Checkpoint Blockade Immunotherapies: Results from a National Cohort
J. Bryan Iorgulescu, Maya Harary, Cheryl K. Zogg, Keith L. Ligon, David A. Reardon, F. Stephen Hodi, Ayal A. Aizer, and Timothy R. Smith
Melanoma patients presenting with brain metastases have been mostly excluded from treatment trials. A large-scale analysis of these patients from a national cohort revealed that after immune checkpoint blockade, median and 4-year overall survival were significantly improved.
- 1046 Circulating Tumor Microparticles Promote Lung Metastasis by Reprogramming Inflammatory and Mechanical Niches via a Macrophage-Dependent Pathway
Huafeng Zhang, Yuandong Yu, Li Zhou, Jingwei Ma, Ke Tang, Pingwei Xu, Tiantian Ji, Xiaoyu Liang, Jiadi Lv, Wenqian Dong, Tianzhen Zhang, Degao Chen, Jing Xie, Yuying Liu, and Bo Huang
Lung macrophages are induced by tumor-derived microparticles to drive development of metastasis via mediators that promote immune, inflammatory, and mechanical reprogramming of the microenvironment. Elucidation of this pathway has implications for therapeutic prevention or treatment of lung metastasis.



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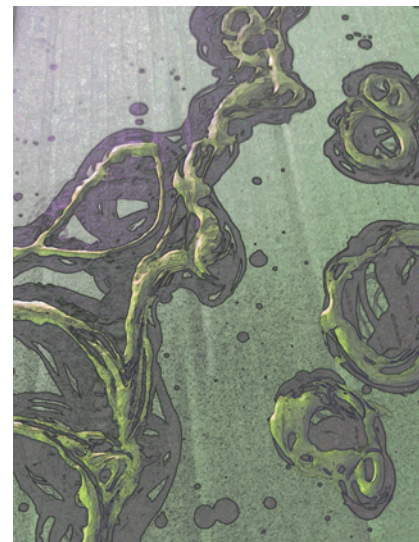
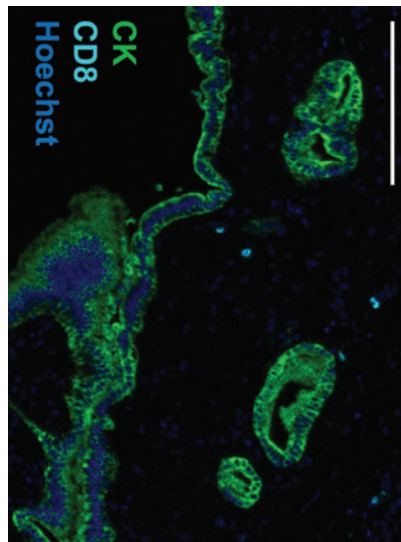
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- 1057** **Mechanisms by Which Dendritic Cells Present Tumor Microparticle Antigens to CD8⁺ T Cells**
Jingwei Ma, Keke Wei, Huafeng Zhang, Ke Tang, Fei Li, Tianzhen Zhang, Junwei Liu, Pingwei Xu, Yuandong Yu, Weiwei Sun, LiYan Zhu, Jie Chen, Li Zhou, Xiaoyu Liang, Jiadi Lv, Roland Fiskesund, Yuying Liu, and Bo Huang
Tumor-derived microparticles activate a lysosomal pathway enabling dendritic cell upregulation of costimulatory molecules and presentation of tumor antigens to CD8⁺ T cells. Elucidation of this molecular pathway has clinical implications for the development of improved cancer vaccines.
- 1069** **Dual PD-1 and CTLA-4 Checkpoint Blockade Promotes Antitumor Immune Responses through CD4⁺Foxp3⁻ Cell-Mediated Modulation of CD103⁺ Dendritic Cells**
 Paul A. Beavis, Melissa A. Henderson, Lauren Giuffrida, Alexander J. Davenport, Emma V. Petley, Imran G. House, Junyun Lai, Kevin Sek, Nicole Milenkovski, Liza B. John, Sherly Mardiana, Clare Y. Slaney, Joseph A. Trapani, Sherene Loi, Michael H. Kershaw, Nicole M. Haynes, and Phillip K. Darcy
It is unclear how combined PD-1/CTLA-4 checkpoint blockade works. CD4⁺ T_H1 cells are directly activated by the blockade and cause the numbers and functionality of CD103⁺ dendritic cells to increase, providing a mechanistic underpinning to the therapy's efficacy.
- 1082** **RORγt-Expressing Tregs Drive the Growth of Colitis-Associated Colorectal Cancer by Controlling IL6 in Dendritic Cells**
Angelamaria Rizzo, Martina Di Giovangiulio, Carmine Stolfi, Eleonora Franzè, Hans-Joerg Fehling, Rita Carsetti, Ezio Giorda, Alfredo Colantoni, Angela Orteni, Massimo Rugge, Claudia Mescoli, Giovanni Monteleone, and Massimo C. Fantini
Tumor-infiltrating RORγt⁺FoxP3⁺ Tregs were found to be a stable population in cancer-associated colitis. In a murine model, this population accumulates in chronically inflamed colons and sustains dysplastic cell STAT3 activation and proliferation, while preventing FoxO3-mediated suppression of IL6.
- 1093** **Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC**
Fernando C. Santini, Hira Rizvi, Andrew J. Plodkowski, Andy Ni, Mario E. Lacouture, Maya Gambarin-Gelwan, Olivia Wilkins, Elizabeth Panora, Darragh F. Halpenny, Niamh M. Long, Mark G. Kris, Charles M. Rudin, Jamie E. Chaft, and Matthew D. Hellmann
Treatment interruption due to irAEs in NSCLC patients treated with anti-PD-L1 was retrospectively assessed. Data suggest that treatment discontinuation should be considered for patients requiring hospitalization for irAEs and those with objective responses prior to irAE onset.
- 1100** **Reducing Ex Vivo Culture Improves the Antileukemic Activity of Chimeric Antigen Receptor (CAR) T Cells**
Saba Ghassemi, Selene Nunez-Cruz, Roddy S. O'Connor, Joseph A. Fraietta, Prachi R. Patel, John Scholler, David M. Barrett, Stefan M. Lundh, Megan M. Davis, Felipe Bedoya, Changfeng Zhang, John Leferovich, Simon F. Lacey, Bruce L. Levine, Stephan A. Grupp, Carl H. June, J. Joseph Melenhorst, and Michael C. Milone
The efficacy of CAR T-cell therapy depends on the engraftment and persistence of T cells following adoptive transfer. Limiting ex vivo culture time of CD19-specific CAR T cells during manufacturing yielded improved persistence and effector function in vivo.
- 1110** **Cytomegalovirus Serostatus Affects Autoreactive NK Cells and Outcomes of IL2-Based Immunotherapy in Acute Myeloid Leukemia**
Elin Bernson, Alexander Hallner, Frida E. Sander, Malin Nicklasson, Malin S. Nilsson, Karin Christenson, Ebru Aydin, Jan-Åke Liljeqvist, Mats Brune, Robin Foà, Johan Aurelius, Anna Martner, Kristoffer Hellstrand, and Fredrik B. Thorén
AML patients who are seropositive for CMV had poorer leukemia-free and overall survival after IL2-based immunotherapy. This negative impact may relate to CMV-driven NK-cell differentiation that leads to depletion of the pool of unlicensed, anti-leukemic NK cells.

ABOUT THE COVER

Although immunotherapy has shown success in treating a variety of cancers, patients with pancreatic ductal adenocarcinoma (PDA) remain unresponsive to treatment, and the lack of efficient antitumor responses is not yet well understood. Mirlekar et al. establish IL35 as a driver of PDA tumor growth via suppression of T cell-mediated responses. Comparison of mice with and without this cytokine show that IL35's absence significantly reduces pancreatic tumor growth, increases tumor infiltration by CD8⁺ T cells, and improves anti-PD-1 efficacy. Thus, IL35 is a cytokine that may be targeted to improve antitumor responses in PDA, including responses to PD-1 blockade. Read more in this issue starting on page 1014. Original immunofluorescence image of human PDA from Supplementary Fig. S4C. Artwork by Lewis Long.



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