

## WHAT WE'RE READING

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## MASTERS OF IMMUNOLOGY

- 2 About the Master
- 3 Myeloid-Derived Suppressor Cells  
Dmitry I. Gabrilovich

## PRIORITY BRIEF

- 9 Efficacy of PD-1 Blockade Is Potentiated by Metformin-Induced Reduction of Tumor Hypoxia  
Nicole E. Scharping, Ashley V. Menk, Ryan D. Whetstone, Xue Zeng, and Greg M. Delgoffe  
*Low oxygen levels in tumors can act as a barrier to effective antitumor immunity. Mitigation of tumor hypoxia using a commonly prescribed type II diabetes drug, metformin, resulted in significant synergy with PD-1 blockade immunotherapy.*

## RESEARCH ARTICLES

- 17 Angiopoietin-2 as a Biomarker and Target for Immune Checkpoint Therapy  
Xinqi Wu, Anita Giobbie-Hurder, Xiaoyun Liao, Courtney Connelly, Erin M. Connolly, Jingjing Li, Michael P. Manos, Donald Lawrence, David McDermott, Mariano Severgnini, Jun Zhou, Evisa Gjini, Ana Lako, Mikel Lipschitz, Christine J. Pak, Sara Abdelrahman, Scott Rodig, and F. Stephen Hodi  
*Outcomes for metastatic melanoma patients treated with checkpoint blockade were poor when circulating Ang-2 was high. Ang-2 promoted recruitment of tumor macrophages and upregulated PD-L1, making it a predictive and/or prognostic biomarker and potential target to combine with checkpoint blockade.*

- 29 Rational Selection of Syngeneic Preclinical Tumor Models for Immunotherapeutic Drug Discovery  
Suzanne I.S. Mosely, John E. Prime, Richard C.A. Sainson, Jens-Oliver Koopmann, Dennis Y.Q. Wang, Danielle M. Greenawalt, Miika J. Ahdesmaki, Rebecca Leyland, Stefanie Mullins, Luciano Pacelli, Danielle Marcus, Judith Anderton, Amanda Watkins, Jane Coates Ulrichsen, Philip Brohawn, Brandon W. Higgs, Matthew McCourt, Hazel Jones, James A. Harper, Michelle Morrow, Viia Valge-Archer, Ross Stewart, Simon J. Dovedi, and Robert W. Wilkinson  
*Murine syngeneic tumor models are used to study responses to antitumor immunotherapies. To rationalize model selection, the underlying genetic and immunologic biology of the models was analyzed, allowing parallels to be drawn between models and human disease phenotypes.*

- 42 Bortezomib Relieves Immune Tolerance in Nasopharyngeal Carcinoma via STAT1 Suppression and Indoleamine 2,3-Dioxygenase Downregulation  
Guan-Min Jiang, Hong-Sheng Wang, Jun Du, Wei-Feng Ma, Hui Wang, Yu Qiu, Qiu-Gui Zhang, Wei Xu, Hui-Fang Liu, and Jian-Ping Liang  
*The proteasome inhibitor bortezomib can synergize with other chemotherapies to kill nasopharyngeal carcinoma cells. Bortezomib released the immune suppression imposed by IFN $\gamma$ -induced IDO (indoleamine 2,3-dioxygenase) through inhibition of NF- $\kappa$ B translocation, IRF-1 production, and STAT1 signaling.*

- 52 Human Dendritic Cells Mitigate NK-Cell Dysfunction Mediated by Nonselective JAK1/2 Blockade  
Shane A. Curran, Justin A. Shyer, Erin T. St. Angelo, Lillian R. Talbot, Sneha Sharma, David J. Chung, Glenn Heller, Katharine C. Hsu, Brian C. Betts, and James W. Young  
*Broad JAK inhibitors can improve graft-versus-host disease caused by stem cell transplants, but they reduce NK-cell numbers and activity. Selective inhibitors of JAK2, in concert with moDCs or Langerhans cells, preserve STAT5 signaling and NK-cell proliferation and function.*

- 61 IL4 from T Follicular Helper Cells Downregulates Antitumor Immunity  
Hidekazu Shirota, Dennis M. Klinman, Shuku-ei Ito, Hiroyasu Ito, Masato Kubo, and Chikashi Ishioka  
*The source and role of IL4 in tumors is not clear. T follicular helper cells in the tumor-draining lymph nodes produced most of the IL4, which profoundly influenced the tumor microenvironment, enhancing M2-macrophage polarization and suppressing antitumor immunity.*

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- 72** **Optimization of Peptide Vaccines to Induce Robust Antitumor CD4 T-cell Responses**  
Takumi Kumai, Sujin Lee, Hyun-Il Cho, Hussein Sultan, Hiroya Kobayashi, Yasuaki Harabuchi, and Esteban Celis  
*Previous work on peptide vaccines has focused primarily on boosting either antibody or CTL responses. Here, a vaccine strategy was optimized that elicited strong and effective CD4 T-cell responses with therapeutic antitumor effects in a murine melanoma model.*

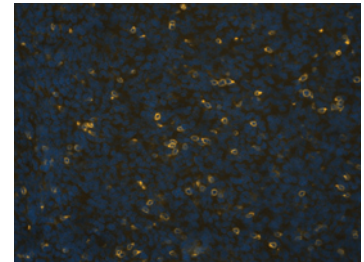
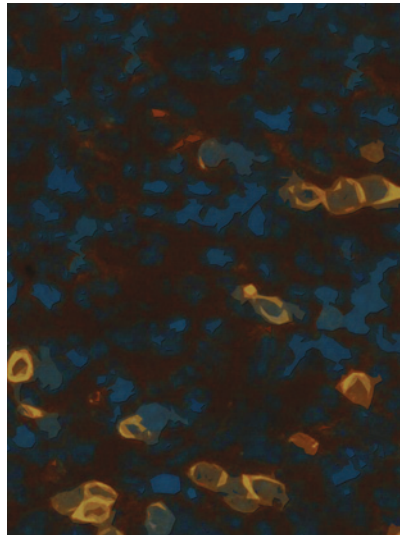
- 84** **Somatic Mutations and Neoepitope Homology in Melanomas Treated with CTLA-4 Blockade**  
Tavi Nathanson, Arun Ahuja, Alexander Rubinsteyn, Bulent Arman Aksoy, Matthew D. Hellmann, Diana Miao, Eliezer Van Allen, Taha Merghoub, Jedd D. Wolchok, Alexandra Snyder, and Jeff Hammerbacher  
*This is a reanalysis of data described in Snyder et al., N Eng J Med 2014;371:2189–99, that also provides an open-source tool for comparing epitopes. No predictor of response to anti-CTLA-4 therapy was more accurate than mutation burden.*

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## ABOUT THE COVER

Syngeneic mouse models are used extensively to acquire a better understanding of tumor-immune system interactions and the effects of immunotherapeutic interventions. Because selection of the most suitable mouse model for a particular study is not always straightforward, Mosely et al. compared the tumor microenvironment of a number of syngeneic tumor model systems in immunocompetent mice for genomic signatures and immunophenotype. An example of the tumor microenvironment, the CT26 tumor model shown on the far right, illustrates the presence of CD3<sup>+</sup> T cells infiltrating the tumor. Visualized with immunohistochemistry, the T cells are identified with an antibody to CD3 and detected with the Alexa-568 fluorochrome (pale yellow). The DNA in cell nuclei is labeled blue with DAPI. Read more in the article by Mosely et al. in this issue of *Cancer Immunology Research*, starting on page 29. Images provided by Arthur Lewis and Lee Brown, Translational Sciences Pathology, MedImmune. Artwork by Lewis Long.



# Cancer Immunology Research

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