

WHAT WE'RE READING

- 1 A Sampling of Highlights from the Literature

MEETING REPORT

- 2 Translating Science into Survival: Report on the Fourth International Cancer Immunotherapy Conference

Mustafa Diken, Srivani Ravoori, and Arthur N. Brodsky

CANCER IMMUNOLOGY MINIATURE

- 6 Autoantibody Development under Treatment with Immune-Checkpoint Inhibitors

Emma C. de Moel, Elisa A. Rozeman, Ellen H. Kapiteijn, Els M.E. Verdegaal, Annette Grummels, Jaap A. Bakker, Tom W.J. Huizinga, John B. Haanen, René E.M. Toes, and Diane van der Woude

Ipilimumab induced autoantibodies in a fifth of melanoma patients. Patients who developed autoantibodies, especially thyroid autoantibodies, experienced more irAEs and had a survival and response benefit, suggesting that breaking of B-cell tolerance could indicate therapy toxicity and efficacy.

RESEARCH ARTICLES

- 12 Collapse of the Plasmacytoid Dendritic Cell Compartment in Advanced Cutaneous Melanomas by Components of the Tumor Cell Secretome

Raffaella Vescovi, Matilde Monti, Daniele Moratto, Lucia Paolini, Francesca Consoli, Luisa Benerini, Laura Melocchi, Stefano Calza, Mariella Chiudinelli, Giulio Rossi, Mattia Bugatti, Michele Maio, Ester Fonsatti, Camillo Farisoglio, Michele Simbolo, Camillo Almici, Rosanna Verardi, Aldo Scarpa, Paolo Bergese, Ausilia Manganoni, Fabio Facchetti, and William Vermi
Plasmacytoid dendritic cells (PDCs) can regulate anti-cancer immune responses. Factors in the melanoma secretome drive the PDC compartment to collapse during disease progression, and rescue of PDCs could aid existing spontaneous and drug-induced adaptive immune responses.

- 29 *Batf3*-Dependent Genes Control Tumor Rejection Induced by Dendritic Cells Independently of Cross-Presentation

Derek J. Theisen, Stephen T. Ferris, Carlos G. Briseño, Nicole Kretzer, Arifumi Iwata, Kenneth M. Murphy, and Theresa L. Murphy

In addition to stabilizing cDC1 dendritic cell lineage commitment, BATF3 controls a set of genes required for cDC1 cells to promote tumor rejection. These BATF3-controlled genes, which are independent of cross-presentation, may be targets in the development of immunotherapies.

- 40 Leveraging TCR Affinity in Adoptive Immunotherapy against Shared Tumor/Self-Antigens

Aaron M. Miller, Milad Bahmanof, Dietmar Zehn, Ezra E.W. Cohen, and Stephen P. Schoenberger

Adoptive cellular therapy (ACT) with a low-affinity T-cell receptor (TCR) that recognizes a self-antigen yields antitumor cytotoxicity but not autoimmune damage. A better understanding of TCR affinity could ultimately minimize autoimmunity while increasing ACT therapeutic efficacy.

- 50 High-Throughput Stability Screening of Neoantigen/HLA Complexes Improves Immunogenicity Predictions

Dylan T. Blaha, Scott D. Anderson, Daniel M. Yoakum, Marlies V. Hager, Yuanyuan Zha, Thomas F. Gajewski, and David M. Kranz

Using a rapid, high-throughput method, peptide/HLA thermal stability was determined for a variety of peptides and peptide variants. This approach allows for predicting neoantigens that can best serve as targets for a robust T-cell response against cancer.

- 62 Mapping the MHC Class I-Spliced Immunopeptidome of Cancer Cells

Juliane Liepe, John Sidney, Felix K.M. Lorenz, Alessandro Sette, and Michele Mishto

Unconventional spliced peptides can be presented by cancer cells. This survey of peptide characteristics in the immunopeptidome of colon and breast carcinoma cell lines may help to predict and identify an unforeseen pool of antigenic targets for immunotherapy.

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- 77** **Peripheral Blood TCR Repertoire Profiling May Facilitate Patient Stratification for Immunotherapy against Melanoma**
 Sabrina A. Hogan, Anaïs Courtier, Phil F. Cheng, Nicoletta F. Jaberg-Bentele, Simone M. Goldinger, Manuarii Manuel, Solène Perez, Nadia Plantier, Jean-François Mouret, Thi Dan Linh Nguyen-Kim, Marieke I.G. Raaijmakers, Pia Kvistborg, Nicolas Pasqual, John B.A.G. Haanen, Reinhard Dummer, and Mitchell P. Levesque
Analysis of TCR repertoire clonality in blood samples collected from patients with melanoma before treatment may predict their eventual response to anti-PD1 and anti-CTLA4 therapy. Such a biomarker could help clinicians refine treatment courses for melanoma patients.
- 86** **Computational Immune Monitoring Reveals Abnormal Double-Negative T Cells Present across Human Tumor Types**
 Allison R. Greenplate, Daniel D. McClanahan, Brian K. Oberholtzer, Deon B. Doxie, Caroline E. Roe, Kirsten E. Diggins, Nalin Leelatian, Megan L. Rasmussen, Mark C. Kelley, Vivian Gama, Peter J. Siska, Jeffrey C. Rathmell, P. Brent Ferrell, Douglas B. Johnson, and Jonathan M. Irish
An analysis toolkit was developed for characterizing immunological changes over time in clinical samples. Use of this toolkit revealed the presence of a double-negative T-cell subset in melanoma, glioblastoma, and renal cell carcinoma but not in healthy tissues.
- 100** **Phase I Trial of Autologous CAR T Cells Targeting NKG2D Ligands in Patients with AML/MDS and Multiple Myeloma**
 Susanne H. Baumeister, Joana Murad, Lillian Werner, Heather Daley, Helene Trebeden-Negre, Joanina K. Gicobi, Adam Schmucker, Jake Reder, Charles L. Sentman, David E. Gilham, Frédéric F. Lehmann, Ilene Galinsky, Heidi DiPietro, Kristen Cummings, Nikhil C. Munshi, Richard M. Stone, Donna S. Neuberg, Robert Soiffer, Glenn Dranoff, Jerome Ritz, and Sarah Nikiforow
NKG2D-CAR T-cell therapy is safe and feasible. Infused cells were transiently detected and exhibited in vitro responses to autologous tumors. However, objective responses to low doses were only seen in lymphodepleted patients, warranting studies to improve efficacy.
- 113** **Reduced Breast Tumor Growth after Immunization with a Tumor-Restricted MUC1 Glycopeptide Conjugated to Tetanus Toxoid**
 Natascha Stergiou, Nikola Gaidzik, Anne-Sophie Heimes, Sarah Dietzen, Pol Besenius, Jörg Jäkel, Walburgis Brenner, Marcus Schmidt, Horst Kunz, and Edgar Schmitt
Tumor-associated MUC1 is a target for the development of breast cancer vaccines due to its tumor-specific overexpression and aberrant glycosylation. Immunization with synthetically produced tumor-associated MUC1 glycopeptides conjugated to tetanus toxoid resulted in reduced tumor burden in mice.
- 123** **Calnexin Impairs the Antitumor Immunity of CD4⁺ and CD8⁺ T Cells**
 Yichen Chen, Da Ma, Xi Wang, Juan Fang, Xiangqi Liu, Jingjing Song, Xinye Li, Xianye Ren, Qiusheng Li, Qunxing Li, Shuqiong Wen, Liqun Luo, Juan Xia, Jun Cui, Gucheng Zeng, Lieping Chen, Bin Cheng, and Zhi Wang
T-cell numbers and effector functions are diminished by calnexin, an ER chaperone protein, possibly through PD-1 upregulation, in OSCC patients and in a mouse melanoma model. These results suggest calnexin could be targeted to improve immunotherapy responses.
- 136** **PARP1 Suppresses the Transcription of PD-L1 by Poly(ADP-Ribosyl)ating STAT3**
 Ling Ding, Xi Chen, Xiaqing Xu, Yuli Qian, Guikai Liang, Fengqi Yao, Zhangting Yao, Honghai Wu, Jieqiong Zhang, Qiaojun He, and Bo Yang
PARP1-mediated poly(ADP-ribosyl)ation of STAT3 drives its dephosphorylation, leading to the inhibition of PD-L1 transcription across multiple cancer types. In patients, PARP1 and PD-L1 expression are inversely correlated. These data highlight a conserved regulatory mechanism for PD-L1 expression.
- 150** **PD-L1 microSPECT/CT Imaging for Longitudinal Monitoring of PD-L1 Expression in Syngeneic and Humanized Mouse Models for Cancer**
 Sandra Heskamp, Peter J. Wierstra, Janneke D.M. Molkenboer-Kuenen, Gerwin W. Sandker, Soley Thordardottir, Jeannette Cany, Daniel Olive, Johan Bussink, Otto C. Boerman, Harry Dolstra, Erik H.J.G. Aarntzen, and Willemijn A. Hobo
PD-L1 microSPECT/CT is a technique to detect PD-L1 expression in syngeneic murine models and humanized mice, allowing the monitoring of therapy-induced changes in tumor PD-L1 expression. In the future, this technique could enable patient selection for PD-1/PD-L1-targeted therapies.
- 162** **Correction: Stromal Cell PD-L1 Inhibits CD8⁺ T-cell Antitumor Immune Responses and Promotes Colon Cancer**
- 163** **Acknowledgment to Reviewers**

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ABOUT THE COVER

Although T cells infiltrate melanomas, they usually fail to clear the tumor. Plasmacytoid DCs (PDCs) can regulate T-cell function and, in addition, can eliminate melanomas by TLR-mediated mechanisms. Vescovi et al. show that infiltration by PDCs occurs early in primary cutaneous melanoma and their localization is at the invasive margin, where the PDCs can interact with CD8⁺ T cells. However, in advanced and metastatic disease, PDCs do not infiltrate into tumor tissues and PDCs in circulation are reduced. This is due to a collapse of the PDC compartment during cancer progression, caused by soluble factors in the melanoma secretome that lead to PDC death and impaired differentiation from progenitor cells. These data highlight that rescuing PDCs could help in inducing antitumor responses. Read more in this issue on page 12. Original image is a primary cutaneous melanoma with little infiltration of PDCs from Fig. 1H. Artwork by Lewis Long.

