

WHAT WE'RE READING

1223 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

1224 Lessons Learned from Checkpoint Blockade Targeting PD-1 in Multiple Myeloma
Alexander M. Lesokhin, Susan Bal, and Ashraf Z. Badros

CANCER IMMUNOLOGY MINIATURES

1230 Intrinsic Resistance to Immune Checkpoint Blockade in a Mismatch Repair–Deficient Colorectal Cancer
Carino Gurjao, David Liu, Matan Hofree, Saud H. AlDubayan, Isaac Wakiro, Mei-Ju Su, Kristen Felt, Evisa Gjini, Lauren K. Brais, Asaf Rotem, Michael H. Rosenthal, Orit Rozenblatt-Rosen, Scott Rodig, Kimmie Ng, Eliezer M. Van Allen, Steven M. Corsello, Shuji Ogino, Aviv Regev, Jonathan A. Nowak, and Marios Giannakis
This case of PD-1 blockade resistance, despite microsatellite instability-high (MSI-H) molecular features, suggests that other biomarkers should be considered. Loss of β_2 -microglobulin expression and infiltration of NK cells and M2 macrophages may be informative in therapy selection.

PRIORITY BRIEF

1237 Systemic Interferon- γ Increases MHC Class I Expression and T-cell Infiltration in Cold Tumors: Results of a Phase 0 Clinical Trial
Shihong Zhang, Karan Kohli, R. Graeme Black, Lu Yao, Sydney M. Spadinger, Qianchuan He, Venu G. Pillarisetty, Lee D. Cranmer, Brian A. Van Tine, Cassian Yee, Robert H. Pierce, Stanley R. Riddell, Robin L. Jones, and Seth M. Pollack
Interferon- γ , an FDA approved drug, can drive inflammation of non-inflamed cancers, potentially facilitating immunotherapy with PD-1 inhibitors. A multicenter trial sponsored by the Cancer Immunotherapy Trials Network is based on these results.

RESEARCH ARTICLES



1244 Disrupting LILRB4/APOE Interaction by an Efficacious Humanized Antibody Reverses T-cell Suppression and Blocks AML Development
Xun Gui, Mi Deng, Hao Song, Yuanzhi Chen, Jingjing Xie, Zunling Li, Licai He, Fangfang Huang, Yixiang Xu, Yasuaki Anami, Hai Yu, Chenyi Yu, Leike Li, Zihao Yuan, Xiaoying Xu, Qihui Wang, Yan Chai, Tao Huang, Yi Shi, Kyoji Tsuchikama, X. Charlene Liao, Ningshao Xia, George F. Gao, Ningyan Zhang, Cheng Cheng Zhang, and Zhiqiang An
*When LILRB4 on acute myeloid leukemia cells (AML) binds to its ligand APOE, T-cell activation is suppressed. A humanized mAb to LILRB4 blocks LILRB4/APOE interaction and, through multiple modes of action, blocks AML development in mouse models.*1258 IRF1 Inhibits Antitumor Immunity through the Upregulation of PD-L1 in the Tumor Cell
Lulu Shao, Weizhou Hou, Nicole E. Scharping, Frank P. Vendetti, Rashmi Srivastava, Chandra Nath Roy, Ashley V. Menk, Yiyang Wang, Joe-Marc Chauvin, Pooja Karukonda, Stephen H. Thorne, Veit Hornung, Hassane M. Zarour, Christopher J. Bakkenist, Greg M. Delgoffe, and Saumendra N. Sarkar
*IFN signaling can mediate antitumor responses, with transcription factor IRF1 involved in tumor suppression. Tumor cell–expressed IRF1 was found to upregulate PD-L1, aiding tumor escape. Thus, tumor cell–specific targeting of IRF1 may be important in immunotherapy.*1267 An Improved Patient-Derived Xenograft Humanized Mouse Model for Evaluation of Lung Cancer Immune Responses
Ismail M. Meraz, Mourad Majidi, Feng Meng, RuPing Shao, Min Jin Ha, Shinya Neri, Bingliang Fang, Steven H. Lin, Peggy T. Tinkey, Elizabeth J. Shpall, Jeffrey Morris, and Jack A. Roth
Often drugs tested in preclinical models fail in the clinic. An improved humanized mouse model derived from nonexpanded CD34⁺ stem cells from cord blood allowed for robust engraftment and the testing of non-HLA–matched patient tumors with immune therapies.

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- 1280** **High Numbers of Circulating CD57⁺ NK Cells Associate with Resistance to HER2-Specific Therapeutic Antibodies in HER2⁺ Primary Breast Cancer**
Aura Muntasell, Sònia Servitja, Mariona Cabo, Begoña Bermejo, Sandra Pérez-Buira, Federico Rojo, Marcel Costa-García, Oriol Arpí, Manuela Moraru, Laia Serrano, Ignasi Tusquets, María Teresa Martínez, Gemma Heredia, Andrea Vera, María Martínez-García, Laura Soria, Laura Comerma, Sara Santana-Hernández, Pilar Eroles, Ana Rovira, Carlos Vilches, Ana Lluch, Joan Albanell, and Miguel López-Botet
CD57⁺ NK-cell numbers may be a biomarker to identify breast cancer patients with primary resistance to HER2-specific therapeutic antibodies. NK-cell aging may influence NK-cell antitumor function.
- 1293** **Enriched HLA-E and CD94/NKG2A Interaction Limits Antitumor CD8⁺ Tumor-Infiltrating T Lymphocyte Responses**
 Megat Abd Hamid, Ruo-Zheng Wang, Xuan Yao, Peiwen Fan, Xi Li, Xue-Mei Chang, Yaning Feng, Stephanie Jones, David Maldonado-Perez, Craig Waugh, Clare Verrill, Alison Simmons, Vincenzo Cerundolo, Andrew McMichael, Christopher Conlon, Xiyan Wang, Yanchun Peng, and Tao Dong
Enriched HLA-E expression on carcinomas and tumor-associated macrophages and DCs correlated with coexpression of the CD94/NKG2A inhibitory receptor on PD-1^{hi} TILs. These TILs had impaired responses to IL2 and poor effector function, contributing to immune evasion of tumors.
- 1307** **Activating KIRs on Educated NK Cells Support Downregulation of CD226 and Inefficient Tumor Immunosurveillance**
Concepción F. Guillamón, María V. Martínez-Sánchez, Lourdes Gimeno, José A. Campillo, Gerardo Server-Pastor, Jerónimo Martínez-García, Jorge Martínez-Escribano, Amparo Torroba, Belén Ferri, Daniel J. Abellán, Isabel Legaz, María R. López-Álvarez, María R. Moya-Quiles, Manuel Muro, and Alfredo Minguela
Tumors can induce CD226 down-modulation on educated NK cells "sensitized" by activating NK-cell receptors (KIRs). Patients with these hyporesponsive CD226^{low} NK cells and a genome rich in activating KIRs may potentially benefit from NK cell-stimulating therapies.
- 1318** **Histone Deacetylase Inhibition Sensitizes PD1 Blockade-Resistant B-cell Lymphomas**
Xiaoguang Wang, Brittany C. Waschke, Rachel A. Woolaver, Zhangguo Chen, Gan Zhang, Anthony D. Piscopio, Xuedong Liu, and Jing H. Wang
The isoform-selective histone-deacetylase inhibitor OKI-179 has promising pharmacokinetics and immune enhancing effects. Combined treatment with OKI-179/anti-PD1 effectively inhibited poorly immunogenic B-cell lymphomas, providing a rationale for developing combinatorial therapy using epigenetic agents with immune checkpoint inhibitors.
- 1332** **The E3 Ubiquitin Ligase Asb2 α in T Helper 2 Cells Negatively Regulates Antitumor Immunity in Colorectal Cancer**
Camille A. Spinner, Isabelle Lamsoul, Arnaud Métais, Chanaëlle Febrissy, Christel Moog-Lutz, and Pierre G. Lutz
Tumor cells can evade antitumor responses by altering the balance between Th1 and Th2 cells. Asb2 α repressed antitumor responses in a model of colitis-associated tumorigenesis. Without it, Th2 cells had blunted cytokine production and antitumor immunity was enhanced.
- 1345** **Tumor Lymphatic Function Regulates Tumor Inflammatory and Immunosuppressive Microenvironments**
Raghu P. Kataru, Catherine L. Ly, Jinyeon Shin, Hyeung Ju Park, Jung Eun Baik, Sonia Rehal, Sagrario Ortega, David Lyden, and Babak J. Mehrara
Function of lymphatic vessels near a tumor may contribute to tumor immune evasion and metastasis. Interventions that manipulate lymphatic function may aid control of tumor growth and progression.
- 1359** **Efficient Tumor Clearance and Diversified Immunity through Neopeptide Vaccines and Combinatorial Immunotherapy**
Karin L. Lee, Stephen C. Benz, Kristin C. Hicks, Andrew Nguyen, Sofia R. Gameiro, Claudia Palena, John Z. Sanborn, Zhen Su, Peter Ordentlich, Lars Rohlin, John H. Lee, Shahrooz Rabizadeh, Patrick Soon-Shiong, Kayvan Niazi, Jeffrey Schlom, and Duane H. Hamilton
A multifaceted approach utilizing a neopeptide vaccine in combination with an IL15 superagonist, PD-L1 blockade, and a tumor-targeting IL12 molecule promoted the expansion of antitumor T cell responses and efficient tumor clearance in a colon carcinoma mouse model.
- 1371** **Anti-CTLA-4 Activates Intratumoral NK Cells and Combined with IL15/IL15R α Complexes Enhances Tumor Control**
Emilio Sanseviero, Erin M. O'Brien, Jenna R. Karras, Tamer B. Shabaneh, Bulent Arman Aksoy, Wei Xu, Cathy Zheng, Xiangfan Yin, Xiaowei Xu, Giorgos C. Karakousis, Ravi K. Amaravadi, Brian Nam, Mary Jo Turk, Jeff Hammerbacher, Mark P. Rubinstein, Lynn M. Schuchter, Tara C. Mitchell, Qin Liu, and Erica L. Stone
Surface expression of CTLA-4 on intratumoral Tregs may facilitate their depletion by NK cells following anti-CTLA-4 therapy, which in combination with IL15/IL15 α complexes improves tumor control, compared to either monotherapy, in a mouse model of colon cancer.

CORRECTION

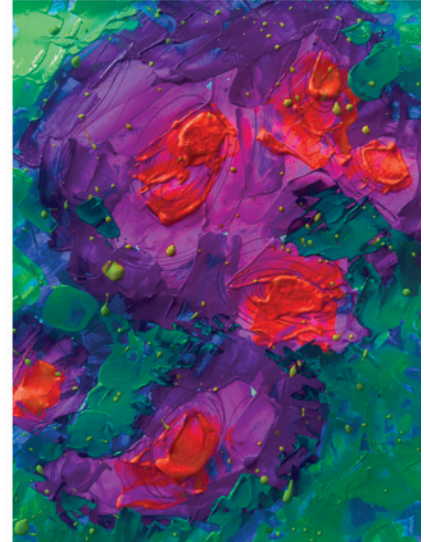
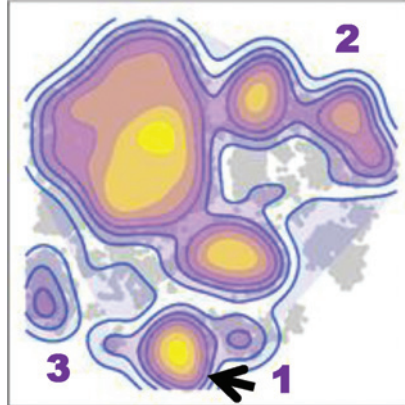
- 1381** **Correction: Automated Analysis of Lymphocytic Infiltration, Tumor Budding, and Their Spatial Relationship Improves Prognostic Accuracy in Colorectal Cancer**

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ABOUT THE COVER

Primary breast cancer biopsy tissue is not always available to assess the degree of immune-cell infiltration into HER2⁺ breast cancer tumors. Thus, one goal for cancer diagnostics is to find reliable measures based on circulating immune cells. Muntasell and Servitja et al. measure the absolute number of circulating CD57⁺ NK cells before treatment with HER2-specific antibodies and find that the higher the number of NK cells before treatment, the worse the patient's response to treatment. High amounts of CD57⁺NK cells in the blood inversely correlate with their density in tumors, suggestive of a tumor-homing or proliferative deficiency. Indeed, the authors find that CD57⁺ NK cells in the peripheral blood have both reduced tumor-homing chemokine receptor expression and low proliferation upon activation. The amount of these circulating cells could be used as a diagnostic marker of response to HER2 antibodies. Read more in this issue on page 1280. Original image from Fig. 3B. Artwork by Lewis Long.



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