

WHAT WE'RE READING

- 167 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

- 168 Revolutionizing Cancer Immunology: The Power of Next-Generation Sequencing Technologies
Meromit Singer and Ana C. Anderson

PRIORITY BRIEFS


- 174 **A Synthetic DNA, Multi-Neoantigen Vaccine Drives Predominately MHC Class I CD8⁺ T-cell Responses, Impacting Tumor Challenge**
Elizabeth K. Duperret, Alfredo Perales-Puchalt, Regina Stoltz, Hiranjith G.H., Nitin Mandloi, James Barlow, Amitabha Chaudhuri, Niranjana Y. Sardesai, and David B. Weiner
A multi-neoantigen DNA cancer vaccine was designed and tested against multiple tumor types. The vaccine was efficiently delivered and elicited CD8⁺ T-cell responses, highlighting how this platform could be used to target a variety of neoantigens in cancer.
- 183 **Antagonism of IAPs Enhances CAR T-cell Efficacy**
Jessica Michie, Paul A. Beavis, Andrew J. Freeman, Stephin J. Vervoort, Kelly M. Ramsbottom, Vignesh Narasimhan, Emily J. Lelliott, Najoua Lalaoui, Robert G. Ramsay, Ricky W. Johnstone, John Silke, Phillip K. Darcy, Ilia Voskoboinik, Conor J. Kearney, and Jane Oliaro
Antagonizing "inhibitor of apoptosis proteins" (IAPs) with the clinical SMAC-mimetic, birinapant, enhances the antitumor activity of CAR T cells in a TNF-dependent, perforin-independent manner. The data illustrate the potential for this combination therapy to enhance antitumor efficacy.

RESEARCH ARTICLES

- 193 **Intracellular Activation of Complement C3 Leads to PD-L1 Antibody Treatment Resistance by Modulating Tumor-Associated Macrophages**
Haoran Zha, Xinxin Wang, Ying Zhu, Diangang Chen, Xiao Han, Fei Yang, Jianbao Gao, Chunyan Hu, Chi Shu, Yi Feng, Yulong Tan, Jinyu Zhang, Yongsheng Li, Yisong Y. Wan, Bo Guo, and Bo Zhu
Intracellular activation of complement C3 by tumor cells was found to suppress CD8⁺ T-cell responses by modulating tumor-associated macrophages. The data suggest that a combined strategy of PD-L1 blockade with C3 targeting may enhance antitumor immunity.

- 208 **CD16⁺NKG2A^{high} Natural Killer Cells Infiltrate Breast Cancer–Draining Lymph Nodes**
Alexandra Frazao, Meriem Messaoudene, Nicolas Nunez, Nicolas Dulphy, France Roussin, Christine Sedlik, Laurence Zitvogel, Eliane Piaggio, Antoine Toubert, and Anne Caignard
NK cells infiltrating breast cancer–draining lymph nodes express activating NK receptors, the inhibitory NKG2A receptor, and PD-1 and are capable of degranulation and tumor cell lysis. These findings support potential therapeutic development targeting these cells.
- 219 **An Antibody Designed to Improve Adoptive NK-Cell Therapy Inhibits Pancreatic Cancer Progression in a Murine Model**
Jaemin Lee, Tae Heung Kang, Wonbeak Yoo, Hyunji Choi, Seongyea Jo, Kyungsu Kong, Sang-Rae Lee, Sun-Uk Kim, Ji-Su Kim, Duck Cho, Janghwan Kim, Jeong-Yoon Kim, Eun-Soo Kwon, and Seokho Kim
The homing of natural killer (NK) cells is often inhibited by pancreatic cancer tumors. A mesothelin-directed antibody conjugated to a cleavable NK cell–recruiting chemokine increased NK-cell infiltration of PDAC tumors, reduced tumor burden, and improved survival.
- 230 **A Mechanism of Resistance to Antibody-Targeted Immune Attack**
Dalal S. Aldeghaither, David J. Zahavi, Joseph C. Murray, Elana J. Fertig, Garrett T. Graham, Yong-Wei Zhang, Allison O'Connell, Junfeng Ma, Sandra A. Jablonski, and Louis M. Weiner
Antibody targeting of the EGFR on tumor cells is a form of immunotherapy that works by inducing NK-cell killing through antibody–NK-cell interactions. Resistance develops via the downregulation of the interaction molecules; thus, NK cells are not activated.
- 244 **Mouse PVRIG Has CD8⁺ T Cell–Specific Coinhibitory Functions and Dampens Antitumor Immunity**
Benjamin Murter, Xiaoyu Pan, Eran Ophir, Zoya Alteber, Meir Azulay, Rupashree Sen, Ofer Levy, Liat Dassa, Ilan Vaknin, Tal Fridman-Kfir, Ran Salomon, Achinoam Ravet, Ada Tam, Doron Levin, Yakir Vaknin, Evgeny Tatirovsky, Arthur Machlenkin, Drew Pardoll, and Sudipto Ganguly
Expression of PVRIG, an immune checkpoint target, is upregulated on activated and tumor-infiltrating CD8⁺ T cells in mice. Disrupting the PVRIG (receptor)/PVRL2 (ligand) pathway using PVRIG-deficient mice or monoclonal antibodies inhibited tumor growth.
See related article, p. 257.

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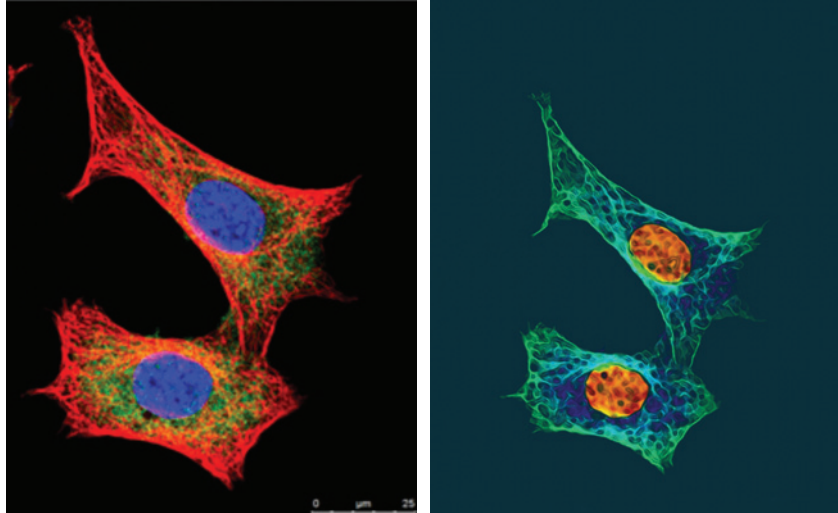
- 257** **PVRIG and PVRL2 Are Induced in Cancer and Inhibit CD8⁺ T-cell Function**
 Sarah Whelan, Eran Ophir, Maya F. Kotturi, Ofer Levy, Sudipto Ganguly, Ling Leung, Ilan Vaknin, Sandeep Kumar, Liat Dassa, Kyle Hansen, David Bernados, Benjamin Murter, Abha Soni, Janis M. Taube, Amanda Nickles Fader, Tian-Li Wang, Ie-Ming Shih, Mark White, Drew M. Pardoll, and Spencer C. Liang
PVRIG acts as an immune checkpoint in human tumors that express its ligands. A PVRIG antagonistic antibody, COM701, may be useful as monotherapy or combined with other immunotherapies. COM701 is in clinical trials for patients with solid tumors.
[See related article, p. 244.](#)
- 269** **Late-Stage Tumor Regression after PD-L1 Blockade Plus a Concurrent OX40 Agonist**
Fanny Polesso, Andrew D. Weinberg, and Amy E. Moran
PD-L1 blockade with concurrent OX40 agonism enhanced frequency and functionality of antigen-specific CD8⁺ T cells in mouse models of large tumors. Th1 skewing, CD8⁺ T cell metabolism, and antitumor immunity were augmented, and tumor regression was promoted.
- 282** **Semaphorin4D Inhibition Improves Response to Immune-Checkpoint Blockade via Attenuation of MDSC Recruitment and Function**
Paul E. Clavijo, Jay Friedman, Yvette Robbins, Ellen C. Moore, Ernest Smith, Maurice Zauderer, Elizabeth E. Evans, and Clint T. Allen
Neutralization of Semaphorin4D within the tumor microenvironment inhibited recruitment and function of myeloid-derived suppressor cells, sensitizing carcinomas to CTLA-4 or PD-1 blockade. Semaphorin4D mAb may be useful as an adjuvant for immune checkpoint immunotherapies.
- 292** **LncRNA-MM2P Identified as a Modulator of Macrophage M2 Polarization**
Ji Cao, Rong Dong, Li Jiang, Yanling Gong, Meng Yuan, Jieqiong You, Wen Meng, Zhanlei Chen, Ning Zhang, Qinjie Weng, Hong Zhu, Qiaojun He, Meidan Ying, and Bo Yang
A long noncoding RNA (lncRNA), called lncRNA-MM2P, is specifically expressed in M2 macrophages, and its knockdown prevents polarization. This lncRNA could serve as a marker for protumoral tumor-associated macrophages and highlights the role of lncRNAs in macrophage polarization.
- 306** **Autocrine TGFβ Is a Survival Factor for Monocytes and Drives Immunosuppressive Lineage Commitment**
Alba Gonzalez-Junca, Kyla E. Driscoll, Ilenia Pellicciotta, Shisuo Du, Chen Hao Lo, Ritu Roy, Renate Parry, Iliana Tenvooren, Diana M. Marquez, Matthew H. Spitzer, and Mary Helen Barcellos-Hoff
TGFB1 expression in lung adenocarcinoma correlates with myeloid markers and poor prognosis in patients. TGFβ promotes immunosuppressive myeloid cell differentiation at the expense of DCs, and inhibition of TGFβ reverses this effect, promoting antigen-presenting DC maturation.
- 321** **IL13-Mediated Dectin-1 and Mannose Receptor Overexpression Promotes Macrophage Antitumor Activities through Recognition of Sialylated Tumor Cells**
Mohamad Alaeddine, Mélissa Prat, Véréna Poinso, Valérie Gouazé-Andersson, Hélène Authier, Etienne Meunier, Lise Lefèvre, Camille Alric, Christophe Dardenne, José Bernad, Laurent Alric, Bruno Segui, Patricia Balard, François Couderc, Bettina Couderc, Bernard Pipy, and Agnès Coste
Cytotoxicity of tumor-associated macrophages may be enhanced through IL13 activation, enhanced expression of C-type lectin receptors (CLRs), and subsequent recognition of tumor cells through sialic acid. These results identify CLRs as potential therapeutic targets to improve antitumor responses.
- 335** **Lactate-Mediated Acidification of Tumor Microenvironment Induces Apoptosis of Liver-Resident NK Cells in Colorectal Liver Metastasis**
Cathal Harmon, Mark W. Robinson, Fiona Hand, Dalal Almuaili, Keno Mentor, Diarmaid D. Houlihan, Emir Hoti, Lydia Lynch, Justin Geoghegan, and Cliona O'Farrelly
In colorectal liver metastasis, liver-resident NK cells are depleted from the tumor microenvironment. NK-cell apoptosis is induced by metabolic changes resulting from tumor-derived lactate. Targeting tumor metabolism represents a promising therapeutic avenue to restore liver NK-cell activity.

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ABOUT THE COVER

Complement is known to play a role in antitumor immunity. However, specific complement molecules can be enriched in the tumor microenvironment where they can regulate the function of tumor and immune cells to promote tumor progression, and thus, interfere with immune-checkpoint blockade efficacy. Zha et al. show that expression and activation of complement C3 in murine tumor cells created an immunosuppressive milieu by facilitating the accumulation and suppressive function of tumor-associated macrophages, mediated by signaling through the C3a receptor. Deletion of C3 in the tumor cells enhanced the efficacy of checkpoint blockade, illustrating the potential of targeting tumor cell-derived complement to boost responses to immune-checkpoint blockade. Read more in this issue on page 193. Original image from Fig. 1D. Artwork by Lewis Long.



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