WHAT WE’RE READING

1121 A Sampling of Highlights from the Literature

CANCER IMMUNOLOGY AT THE CROSSROADS

1122 Predictive Biomarkers for Checkpoint Immunotherapy: Current Status and Challenges for Clinical Application
Nancy Tray, Jeffrey S. Weber, and Sylvia Adams

CANCER IMMUNOLOGY MINIATURE

1129 Successful Treatment of HIV-Associated Kaposi Sarcoma with Immune Checkpoint Blockade
Natalie Galanina, Aaron M. Goodman, Philip R. Cohen, Garrett M. Frampton, and Razelle Kurzrock
Patients with HIV-associated Kaposi sarcoma who were treated with immune checkpoint blockade were evaluated. Treatment was well tolerated, and objective response rates were seen in patients, highlighting the use of this immunotherapy strategy in this group of patients.

RESEARCH ARTICLES

1136 A2AR Antagonism with CPI-444 Induces Antitumor Responses and Augments Efficacy to Anti–PD-(L)1 and Anti–CTLA-4 in Preclinical Models
Stephen B. Willingham, Po Y. Ho, Andrew Hotson, Craig Hill, Emily C. Piccione, Jessica Hsieh, Liang Liu, Joseph J. Buggy, Ian McCaffery, and Richard A. Miller
Adenosine signaling in tumors can lead to suppression of antitumor responses. A new adenosine receptor antagonist, CPI-444, neutralized this suppression, resulting in tumor regression and immune memory, and when combined with immune checkpoint blockade, further enhanced antitumor responses.

1150 Cellular Cytotoxicity of Next-Generation CD20 Monoclonal Antibodies
Karl R. VanDerMeid, Michael R. Elliott, Andrea M. Baran, Paul M. Barr, Charles C. Chu, and Clive S. Zent
Primary tumor cells from CLL patients were used to compare the efficacy of ADCP and ADCC induced by different CD20-targeting monoclonal antibodies. Results highlight the use of ADCP assays as a better measure of monoclonal antibody-induced cellular cytotoxicity.

1161 Antibody-Neutralized Reovirus Is Effective in Oncolytic Virotherapy
Robert A. Berkeley, Lynnette P. Steele, Aat A. Mulder, Diana J.M. van den Wollenberg, Timothy J. Kotik, Jill Thompson, Matthew Coffey, Rob C. Hoeben, Richard G. Vile, Alan Melcher, and Elizabeth J. Ilett
Oncolytic viruses are thought to lose antitumor efficacy when bound to neutralizing antibodies. However, monocytes can internalize antibody-neutralized virus and transfer infectious virus to tumor cells, killing them. Thus, antibodies could be exploited for oncolytic virus therapy.

1174 Expanded CD56<sup>superbright</sup>CD16<sup>+</sup> NK Cells from Ovarian Cancer Patients Are Cytotoxic against Autologous Tumor in a Patient-Derived Xenograft Murine Model
Sophie M. Poznanski, Tina Nham, Marianne V. Chew, Amanda J. Lee, Joanne A. Hammill, Isabella Y. Fan, Martin Butcher, Jonathan L. Bramson, Dean A. Lee, Hal W. Hirt, and Ali A. Ashkar
NK cells are usually ineffective as therapeutics against solid tumors. Expansion of autologous CD56<sup>superbright</sup> NK cells before transfer into a mouse xenograft model effectively reduced the burden of established human ovarian tumors.

1186 Loss of CXCR4 in Myeloid Cells Enhances Antitumor Immunity and Reduces Melanoma Growth through NK Cell and FASL Mechanisms
Jinming Yang, Amarendra Kumar, Anna E. Vilgelm, Sheau-Chiann Chen, Gregory D. Ayers, Sergey V. Novitskiy, Sebastian Joyce, and Ann Richmond
NK-cell antitumor activity is enhanced by myeloid-CXCR4 deletion, revealing a pathway by which this receptor may contribute to tumor surveillance suppression and promotion of metastasis. This pathway provides a rationale for the clinical application of CXCR4 antagonists.

1199 GITR Agonism Enhances Cellular Metabolism to Support CD8<sup>+</sup> T-cell Proliferation and Effector Cytokine Production in a Mouse Tumor Model
Simran S. Sabharwal, David B. Rosen, Jeff Grein, Dana Tedesco, Barbara Joyce-Shaikhi, Roanna Ueda, Marie Semana, Mireille Bauer, Kathy Bang, Christopher Stevenson, Daniel J. Cua, and Luis A. Zúñiga
GITR stimulation treatment enhances CD8<sup>+</sup> T-cell metabolism, proliferation, and effector function. Characterization of the mechanism by which GITR agonist antibodies exert these effects provides insight into their future development in combination therapies.
Baseline Cytokine Profiles of Tuberculin-Specific CD4⁺ T Cells in Non–Muscle-Invasive Bladder Cancer May Predict Outcomes of BCG Immunotherapy
Samer Jallad, Philip Thomas, Melanie J. Newport, and Florian Kern
BCG immunotherapy helps preserve the bladder after surgery to remove certain bladder cancers but fails in about 30% of patients. A cytokine-secretion test identifies those most likely to fail, enabling choice of alternative treatments.

TLR2 Promotes Glioma Immune Evasion by Downregulating MHC Class II Molecules in Microglia
Jiawen Qian, Feifei Luo, Jiao Yang, Jun Liu, Ronghua Liu, Luman Wang, Chen Wang, Yuting Deng, Zhou Lu, Yuedi Wang, Mingfang Liu, Ji-Yang Wang, and Yiwei Chu
In the glioma tumor microenvironment, TLR2 activation of microglia induces downregulation of microglial MHC class II expression. Impaired MHC class II expression limits T cell–dependent antitumor immunity.

BET Bromodomain Inhibition Cooperates with PD-1 Blockade to Facilitate Antitumor Response in Kras-Mutant Non–Small Cell Lung Cancer
BET bromodomain inhibition combined with PD-1 blockade enhances T-cell activation and reduces regulatory T-cell infiltration, resulting in durable antitumor responses in a murine model of KRAS-mutant NSCLC. This suggests a promising avenue for future therapeutic development.

Maelstrom Directs Myeloid-Derived Suppressor Cells to Promote Esophageal Squamous Cell Carcinoma Progression via Activation of the Akt1/Rea/ILS Signaling Pathway
Pupu Li, Xinfeng Chen, Guohui Qin, Dongli Yue, Zhen Zhang, Yu Ping, Dan Wang, Xuan Zhao, Mengjia Song, Qitai Zhao, Jiayao Li, Shasha Liu, Dong Wang, Chaoqi Zhang, Jingxiao Liu, Ling Cao, Feng Li, Lan Huang, Liping Wang, Li Yang, Jianmin Huang, Hong Li, Bin Zhang, and Yi Zhang
Maelstrom directly and indirectly promotes growth of esophageal squamous cell carcinomas. MDSGs, recruited to the tumor’s microenvironment through IL8 signaling, produce TGFβ that then regulates maelstrom expression in the tumor cells by inducing Smad2/Smad3 phosphorylation.

Programmed Cell Death Ligand 1 (PD-L1) Signaling Regulates Macrophage Proliferation and Activation
Genevieve P. Hartley, Lyndah Chow, Dylan T. Ammons, William H. Wheat, and Steven W. Dow
Tumor treatment with antibodies to PD-L1 checkpoint molecules triggers activation and proliferation of tumor macrophages, inducing T cell–independent and –dependent control of tumor growth. Thus, the immunological effects of PD-L1 blockade differ from those of PD-1 blockade.

CD30-Redirected Chimeric Antigen Receptor T Cells Target CD30⁺ and CD30⁻ Embryonal Carcinoma via Antigen-Dependent and Fas/FasL Interactions
Lee K. Hong, Yuhui Chen, Christof C. Smith, Stephanie A. Montgomery, Benjamin G. Vincent, Gianpietro Dotti, and Barbara Savoldo
Tumor antigen heterogeneity limits CAR T-cell therapies. Although embryonal carcinomas express CD30, some tumor cells remain CD30⁻/dim. CD30-specific CAR T cells could be leveraged to also target and kill CD30⁻ tumor cells, through Fas/FasL interactions.

ABOUT THE COVER
The efficacy of immunotherapy can be limited by immunosuppressive mechanisms in the tumor microenvironment. One such mechanism that is exploited by tumor cells is the production of adenosine, which creates an immunosuppressive niche that inhibits the functions of multiple immune cell types. Willingham et al. developed an adenosine receptor antagonist, CPI-444. In multiple tumor models, comparison of mice with and without CPI-444 treatment demonstrates that the compound, administered as a single agent, neutralizes adenosine-mediated suppression, resulting in reduced tumor growth, increased antitumor responses, and increased T-cell activation. When combined with immune checkpoint blockade, antitumor responses and tumor reduction were enhanced. Thus, CPI-444 is a potential therapeutic for solid tumors. Read more in this issue on page 1136. Original image is of CD73 expression in non–small cell lung cancer. Artwork by Lewis Long.