### 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, Lynette P. Steele, Aat A. Mulder, Diana J.M. van den Wollenberg, Timothy J. Kotike, 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 CD56superbrightCD16+ 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. Hirst, and Ali A. Ashkar  
NK cells are usually ineffective as therapeutics against solid tumors. Expansion of autologous CD56superbright 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, Amrendra Kumar, Anna E. Vilgelm, Sheau-Chiann Chen, Gregory D. Ayers, Sergey V. Novitskiy, Sebastian Joycean, 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+ T-cell Proliferation and Effector Cytokine Production in a Mouse Tumor Model  
Simran S. Sabharwal, David B. Rosen, Jeff Grein, Dana Tedesco, Barbara Joyce-Shaikh, Roanna Ueda, Marie Semana, Mirchele Bauer, Kathy Bang, Christopher Stevenson, Daniel J. Cua, and Luis A. Zúñiga  
GITR stimulation treatment enhances CD8+ 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 Lu, 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.

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, Gianpiero 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, neutralized adenosine-mediated suppression, resulting in reduced tumor growth, increased antitumor responses, and increased T-cell activation. 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.