Molecular Drivers of the Non–T-cell-Inflamed Tumor Microenvironment in Urothelial Bladder Cancer
Randy F. Sweis, Stefani Spranger, Riyue Bao, Gladell P. Paner, Walter M. Stadler, Gary Steinberg, and Thomas F. Gajewski

Immunotherapy resistance is a reality for many cancer patients. Three tumor-intrinsic molecular pathways, β-catenin, PPARγ, and FGFR3, were identified and linked to the exclusion of T cells from urothelial tumors. Targeting these pathways may enhance immune checkpoint efficacy.

Prolonged Benefit from Ipilimumab Correlates with Improved Outcomes from Subsequent Pembrolizumab
Amanda Shreders, Richard Joseph, Chengwei Peng, Fei Ye, Shilin Zhao, Igor Puzanov, Jeffrey A. Sosman, and Douglas B. Johnson

Anti–PD-1 therapies are becoming first-line treatments for metastatic melanoma, but how prior immune therapy affects anti–PD-1 efficacy is unknown. Prior ipilimumab was found to predict response to anti–PD-1, which could help select patients for therapy.

Expanded and Activated Natural Killer Cells for Immunotherapy of Hepatocellular Carcinoma
Takahiro Kamiya, Yu-Hsiang Chang, and Dario Campana

Hepatocellular carcinoma (HCC) is often incurable. Human NK cells with enhanced cytotoxicity against HCC were expanded in vitro, generating efficient killers of HCC in culture and in mice, supporting the infusion of such cells for treatment of HCC.

Immune-Derived PD-L1 Gene Expression Defines a Subgroup of Stage II/III Colorectal Cancer Patients with Favorable Prognosis Who May Be Harmed by Adjuvant Chemotherapy

A subgroup of patients with colorectal cancer was defined by high PD-L1 gene expression on their tumor-infiltrating immune cells. These patients may be harmed by standard chemotheraphy and may benefit from immunotherapy that targets the PD-1 immune checkpoint.

Enhanced Tumor Control with Combination mTOR and PD-L1 Inhibition in Syngeneic Oral Cavity Cancers
Ellen C. Moore, Harrison A. Cash, Andria M. Caruso, Ravindra Uppaluri, James W. Hodge, Carter Van Waes, and Clint T. Allen

Inhibition of mTOR is felt to be systemically immunosuppressive. However, the antitumor immunity induced by checkpoint inhibition in an immunogenic model of oral cavity cancer was enhanced by the mTOR inhibitor rapamycin via a T cell–dependent mechanism.

Antitumor Efficacy of Radiation plus Immunotherapy Depends upon Dendritic Cell Activation of Effector CD8+ T Cells
Simon J. Dovedi, Grawnya Lipowska-Bhalla, Stephen A. Beers, Eleanor J. Cheadle, Lijun Mu, Martin J. Glennie, Timothy M. Illidge, and Jamie Honeychurch

Radiotherapy plus CD40 or TLR7 stimulation leads to long-term clearance of B- and T-cell lymphomas. These curative responses after combining radiotherapy with an immunomodulatory agent depended upon the priming of tumor-specific CD8+ T cells by dendritic cells.
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<td><em>Most effective antibody immunotherapy relies on ADCC. A potent ADCC-enhanced antibody is described that, in comparison with Abs with altered affinities for Fc receptors, significantly improved the growth control of tumors expressing cancer-antigen GD2.</em></td>
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### ADDENDUM

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<td>ADDENDUM: T Cells Expressing CD19/CD20 Bispecific Chimeric Antigen Receptors Prevent Antigen Escape by Malignant B Cells</td>
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### ABOUT THE COVER

Patients with advanced hepatocellular carcinoma (liver cancer) have a median life expectancy of 8 to 11 months. These tumors are frequently associated with viral hepatitis. Natural killer (NK) cells recognize virally infected cells and malignant cells, so to develop an immunotherapy, the authors expanded and activated NK cells *ex vivo*. These cells, when reinfused into immunodeficient mice hosting human tumors, enabled many mice to survive and efficiently killed tumor cells. The cover is based on a fluorescence confocal image (far right) of PLC/PRF/5 hepatocarcinoma cells (green) surrounded by expanded, activated human NK cells (red). Cover by Lewis Long; image captured by T. Kamiya. Read more starting on page 574 in this issue of *Cancer Immunology Research.*