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3442 Stem Cell Transfusion Restores Immune Function in Radiation-Induced Lymphopenic C57BL/6 Mice
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### MICROENVIRONMENT AND IMMUNOLOGY

3446 Correlation between Density of CD8⁺ T-cell Infiltrate in Microsatellite Unstable Colorectal Cancers and Frameshift Mutations: A Rationale for Personalized Immunotherapy

   Précis: Colorectal cancer patients whose tumors harbor unstable DNA microsatellite repeats, representing about 15% of all cases of colorectal cancers, express frameshift mutation-derived neoantigens, constituting a special opportunity for developing new personalized immunotherapy strategies.

3479 Perivascular M2 Macrophages Stimulate Tumor Relapse after Chemotherapy
   Russell Hughes, Bin-Zhi Qian, Charlotte Rowan, Munita Muthana, Joanna Kekikoglou, Oakley C. Olson, Simon Tazzyman, Sarah Danson, Christina Addison, Mark Clemons, Ana Maria Gonzalez-Angulo, Johanna A. Joyce, Michele De Palma, Jeffrey W. Pollard, and Claire E. Lewis

   Précis: These findings rationalize a strategy to leverage chemotherapeutic efficacy by selectively targeting perivascular, relapse-promoting macrophages.

3456 Immunosuppressive and Prometastatic Functions of Myeloid-Derived Suppressive Cells Rely upon Education from Tumor-Associated B Cells
   Monica Bodogai, Kanako Moritoh, Catalina Lee-Chang, Christine M. Hollander, Cheryl A. Sherman-Baust, Robert P. Herbst, Yoshihiko Araki, Ichiro Miyoshi, Li Yang, Giorgio Trinchieri, and Aya Biragyn

   Précis: B regulatory cells in the cancer microenvironment mediate TGFβ signaling events that help program the immune suppressive and prometastatic functions of MDSC, a central driver of immune escape in cancer.

3466 Nivolumab and Urelumab Enhance Antitumor Activity of Human T Lymphocytes Engrafted in Rag2⁻/⁻/IL2Rγnull Immunodeficient Mice

   Précis: Traditional human tumor xenograft models can not address the revolution in cancer research being driven by advances in immunology; this study addresses the pressing need to develop new preclinical models that are immunocompetent for the study of human tumors.

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Cancer Research

American Association for Cancer Research

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AIP1 Expression in Tumor Niche Suppresses Tumor Progression and Metastasis
Weidong Ji, Yonghao Li, Yun He, Mingzhu Yin, Huanjiao Jenny Zhou, Titus J. Boggon, Haifeng Zhang, and Wang Min

Précis: Expression of the suppressor gene AIP1 in the microenvironment of a premetastatic niche is found to suppress EMT, angiogenesis, and metastatic progression, illustrating a role for tumor suppression genes not only in tumor cells but also stromal cells of the tumor microenvironment.

Tuning Sensitivity of CAR to EGFR Density Limits Recognition of Normal Tissue While Maintaining Potent Antitumor Activity

Précis: A re-engineered CAR T-cell receptor decreases risks of on-target off-tissue toxicity by enabling preferential recognition of EGFR on the basis of its overexpressed levels in cancer.

CRMP5 Controls Glioblastoma Cell Proliferation and Survival through Notch-Dependent Signaling
Aubin Moutal, Jérôme Honnorat, Patrick Massoma, Pauline Désormeaux, Caroline Bertrand, Céline Mallevial, Chantal Watrin, Naura Choulambomu, Marie-Eve Mayeur, Roger Besanyon, Niclas Naudet, Léa Magadoux, Rajesh Khanna, François Ducray, David Meyronet, and Nicole Thomasset

Précis: This study offers insights into glioblastoma proliferation controlled by the Notch receptor, highlighting a new biomarker for pretherapeutic screening or follow-up programs.

Pancreatic Cancer Cell Migration and Metastasis Is Regulated by Chemokine-Biased Agonism and Bioenergetic Signaling
Ishan Roy, Donna M. McAllister, Egal Gorse, Kate Dixon, Clinton T. Piper, Noah P. Zimmerman, Anthony E. Getschman, Susan Tsai, Dannielle D. Engle, Douglas B. Evans, Brian F. Volkman, Balaraman Kalyanaraman, and Michael B. Dwinell

Précis: Provocative biological findings offer a preclinical rationale for further investigation of the promigratory chemokine CXCL12 for preventing metastasis in pancreatic cancer.

Defects in the Fanconi Anemia Pathway and Chromatid Cohesion in Head and Neck Cancer

Précis: Defects defined in a subset of head and neck cancers might be exploited for targeted treatments in a therapeutic setting of rapidly rising incidence.

ErbB3–ErbB2 Complexes as a Therapeutic Target in a Subset of Wild-type BRAF/NRAS Cutaneous Melanomas
Claudia Capparelli, Sheera Rosenbaum, Lisa D. Berman-Booty, Amel Salhi, Nadège Gaborit, Tingting Zhan, Inna Chervoneva, Jason Roszik, Scott E. Woodman, Michael A. Davies, Yulius Y. Setiady, Iman Osman, Yosef Yarden, and Andrew E. Aplin

Précis: This study addresses the lack of effective targeted therapeutic options for BRAF/NRAS wild-type melanomas, offering a preclinical basis for new treatment strategies in a subset of these melanomas.

Novel Cancer Therapeutics with Allosteric Modulation of the Mitochondrial C-Raf-DAPK Complex by Raf Inhibitor Combination Therapy

Précis: These findings suggest a novel predictive biomarker for responses to combination therapy with Raf kinase inhibitors, which have a variety of antimetabolic and immune modulatory effects beyond the inhibition of growth and survival in cancer cells.
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<td><strong>Précis:</strong> A newly engineered CAR T-cell receptor can better discriminate therapeutic targets in normal versus tumor tissues, potentially expanding the utility of this adoptive cell therapy for cancer.</td>
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<td>IL6/JAK1/STAT3 Signaling Blockade in Endometrial Cancer Affects the ALDH&lt;sup&gt;hi&lt;/sup&gt;/CD126&lt;sup&gt;+&lt;/sup&gt; Stem-like Component and Reduces Tumor Burden</td>
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<td>3623</td>
<td>RAS/MAPK Activation Drives Resistance to Smo Inhibition, Metastasis, and Tumor Evolution in Shh Pathway–Dependent Tumors</td>
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<td><strong>Précis:</strong> These findings point to a significant role for RAS/MAPK pathway alterations in acquired drug resistance and tumor evolution of Sonic Hedgehog pathway-driven cancers.</td>
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<td>3636</td>
<td>Microenvironment-Modulated Metastatic CD133&lt;sup&gt;-&lt;/sup&gt;/CXCR4&lt;sup&gt;-&lt;/sup&gt;/EpCAM&lt;sup&gt;-&lt;/sup&gt; Lung Cancer–Initiating Cells Sustain Tumor Dissemination and Correlate with Poor Prognosis</td>
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<td><strong>Précis:</strong> These results highlight the CXCR4 signaling axis as a target for disrupting the development of chemotherapy-resistant cells in the metastatic niche, suggesting an effective therapeutic strategy to improve the clinical management of lung cancer patients.</td>
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<td>Keratin-17 Promotes p27&lt;sup&gt;KIP1&lt;/sup&gt; Nuclear Export and Degradation and Offers Potential Prognostic Utility</td>
<td>Luisa F. Escobar-Hoyos, Ruchi Shah, Lucia Roa-Peña, Elizabeth A. Vanner, Nilofar Najafian, Anna Banach, Erik Nielsen, Ramsey Al-Khalil, Ali Akalin, David Talmage, and Kenneth R. Shroyer</td>
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<td><strong>Précis:</strong> This important study establishes that keratin-17 functions specially among keratins as an oncoprotein by controlling the ability of the tumor suppressor p27&lt;sup&gt;KIP1&lt;/sup&gt; to influence cervical cancer pathogenesis.</td>
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<td><strong>Précis:</strong> These results clarify how variant splice forms of the androgen receptor function to drive the malignant character of advanced prostate cancer, providing key mechanistic insights that will promote rational drug design for more effective treatment of this deadly disease.</td>
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Epigenetic Activation of TWIST1 by MTDH Promotes Cancer Stem–like Cell Traits in Breast Cancer
Yajun Liang, Jing Hu, Jiatao Li, Yingjie Liu, Jingyi Yu, Xueqian Zhuang, Lili Mu, Xiangyin Kong, Dengli Hong, Qifeng Yang, and Guohong Hu

Précis: A prometastatic molecule of uncertain molecular function, known as metadherin, AEG-1, or LYRIC, is found to control a transcriptional program driven by TWIST, which regulates epithelial-mesenchymal transition in cancer cells.

Cell Death Identification in Anticancer Therapy—Letter
J. Martin Brown, Bradly G. Wouters, and David G. Kirsch

Correction: Long Noncoding RNA GAPLINC Regulates CD44-Dependent Cell Invasiveness and Associates with Poor Prognosis of Gastric Cancer

Correction: Host Immune Defense Peptide LL-37 Activates Caspase-Independent Apoptosis and Suppresses Colon Cancer

About the Cover
Combination immunotherapy with anti-hCD137 (urelumab) and anti-hPD-1 (nivolumab) monoclonal antibodies (mAb) in a humanized mouse model enhances the human T-cell infiltrate in xenografted tumors. Using multiplexed quantitative immunofluorescence, we profiled T- and B-cells in the tumor microenvironment. In immunodeficient Rag2−/−IL2Rγ null mice subcutaneously bearing human gastric carcinoma and transferred with peripheral blood mononuclear cells from the same patient, urelumab and nivolumab increased the T-cell infiltrates that were penetrating into the tumor. The presence of T lymphocytes was associated with slow tumor progression. In contrast, tumor-infiltrating lymphocytes (TILs) were restricted to the tumor periphery when treatment consisted of control hIgG4 mAb or either urelumab or nivolumab as single agents. The combination of urelumab and nivolumab seems to help overcome a peripheral barrier so TILs can enter the tumor core. For details, see article by Sanmamed and colleagues on page 3466.