BREAKING ADVANCES
3425 Highlights from Recent Cancer Literature

REVIEWS
3427 Prodding the Beast: Assessing the Impact of Treatment-Induced Metastasis
John M.L. Ebos

3436 Ligand-Independent EGFR Signaling
Gao Guo, Ke Gong, Bryan Wohlfeld, Kimmo J. Hatanpaa, Dawen Zhao, and Amyn A. Habib

PERSPECTIVE
3442 Stem Cell Transfusion Restores Immune Function in Radiation-Induced Lymphopenic C57BL/6 Mice
Vaishali Kapoor, Arpine Khudanyan, Pilar de la Puente, Jian Campian, Dennis E. Hallahan, Abdel Kareem Azab, and Dinesh Thotala

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.

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. Hollandier, Cheryl A. Sherman-Baust, Robert P. Wersto, Yoshihiko Araki, Ichiro Miyoshi, Li Yang, Giorgio Trinchieri, and Arya Irigan

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-/-IL2Rg-null Immunodeficient Mice
Miguel F. Sammamed, Inmaculada Rodriguez, Kurt A. Schaper, Carmen Ortiz, Arantza Aspilikueta, Maria E. Rodriguez-Ruiz, Aizea Morales-Rastresana, Sara Labiano, Jose L. Pérez-Gracia, Salvador Martín-Algarra, Carlos Alfaro, Guillermo Mazziolini, Francesca Sarno, Manuel Hidalgo, Alan J. Korman, Maria Jure-Kunkel, and Ignacio Melero

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.

3479 Perivascular M2 Macrophages Stimulate Tumor Relapse after Chemotherapy
Russell Hughes, Bin-Zhi Qian, Charlotte Rowan, Munita Muthana, Ioanna Kekilikoglou, 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.
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<td>AIP1 Expression in Tumor Niche Suppresses Tumor Progression and Metastasis</td>
<td>Weidong Ji, Yonghao Li, Yun He, Mingzhu Yin, Huanjiao Jenny Zhou, Titus J. Boggon, Haifeng Zhang, and Wang Min</td>
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**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.


**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.

| 3519 | 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 Choulemastouri, Marie-Eve Mayeur, Roger Besanyon, Nicolas Naude, 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.

| 3529 | 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, Danielle 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.


**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.

| 3554 | 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, Yuliys 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.


**Précis:** These findings suggest a novel predictive biomarker for responses to combination therapy with Raf kinase inhibitors, which have a variety of antimitabolic and immune modulatory effects beyond the inhibition of growth and survival in cancer cells.
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-mesenchyme transition in cancer cells.

LETTERS TO THE EDITOR

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

CORRECTIONS

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 (TIL) were restricted to the tumor periphery when treatment consisted of control hlgG4 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.