

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 Aryn 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
Pauline Maby, David Tougeron, Mohamad Hamieh, Bernhard Mlecnik, Hafid Kora, Gabriela Bindea, Helen K. Angell, Tessa Fredriksen, Nicolas Elie, Emilie Fauquembergue, Aurélie Drouet, Jérôme Leprince, Jacques Benichou, Jacques Mauillon, Florence Le Pessot, Richard Sesboüé, Jean-Jacques Tuech, Jean-Christophe Sabourin, Pierre Michel, Thierry Frébourg, Jérôme Galon, and Jean-Baptiste Latouche
- 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. Hollander, Cheryl A. Sherman-Baust, Robert P. Wersto, Yoshihiko Araki, Ichiro Miyoshi, Li Yang, Giorgio Trinchieri, and Arya Biragyn

Précis: B regulatory cells in the cancer microenvironment mediate TGF β 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^{-/-}IL2R γ ^{null} Immunodeficient Mice

Miguel F. Sanmamed, Inmaculada Rodriguez, Kurt A. Schalper, Carmen Oñate, Arantza Azpilikueta, Maria E. Rodriguez-Ruiz, Aizea Morales-Kastresana, Sara Labiano, Jose L. Pérez-Gracia, Salvador Martín-Algarra, Carlos Alfaro, Guillermo Mazzolini, 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, Munitta Muthana, Ioanna Keklikoglou, 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.

Table of Contents

3492 **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.

3505 **Tuning Sensitivity of CAR to EGFR Density Limits Recognition of Normal Tissue While Maintaining Potent Antitumor Activity**



Hillary G. Caruso, Lenka V. Hurton, Amer Najjar, David Rushworth, Sonny Ang, Simon Olivares, Tiejuan Mi, Kirsten Switzer, Harjeet Singh, Helen Huls, Dean A. Lee, Amy B. Heimberger, Richard E. Champlin, and Laurence J.N. Cooper

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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

3519 **CRMP5 Controls Glioblastoma Cell Proliferation and Survival through Notch-Dependent Signaling**

Aubin Moutal, Jérôme Honnorat, Patrick Massoma, Pauline Désormeaux, Caroline Bertrand, Céline Malleval, Chantal Watrin, Naura Chounlamountri, Marie-Eve Mayeur, Roger Besançon, Nicolas 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.

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, 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.

3543 **Defects in the Fanconi Anemia Pathway and Chromatid Cohesion in Head and Neck Cancer**

Chantal Stoepler, Najim Ameziane, Petra van der Lelij, Irsan E. Kooi, Anneke B. Oostra, Martin A. Rooimans, Saskia E. van Mil, Arjen Brink, Ralf Dietrich, Jesper A. Balk, Bauke Ylstra, Hans Joenje, Stephan M. Feller, and Ruud H. Brakenhoff

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.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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, 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.

3568 **Novel Cancer Therapeutics with Allosteric Modulation of the Mitochondrial C-Raf–DAPK Complex by Raf Inhibitor Combination Therapy**



Yi-Ta Tsai, Mei-Jen Chuang, Shou-Hung Tang, Sheng-Tang Wu, Yu-Chi Chen, Guang-Huan Sun, Pei-Wen Hsiao, Shih-Ming Huang, Hwei-Jen Lee, Cheng-Ping Yu, Jar-Yi Ho, Hui-Kuan Lin, Ming-Rong Chen, Chung-Chih Lin, Sun-Yran Chang, Victor C. Lin, Dah-Shyong Yu, and Tai-Lung Cha

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.



Table of Contents

3583 **CHK1 Inhibition Synergizes with Gemcitabine Initially by Destabilizing the DNA Replication Apparatus**



Siang-Boon Koh, Aurélie Courtin, Richard J. Boyce, Robert G. Boyle, Frances M. Richards, and Duncan I. Jodrell

Précis: This work informs how cell cycle checkpoint kinase inhibitors cooperate with DNA damaging drugs, finding that cancer cells are destroyed not by frank G₂-M phase abrogation, as has been hypothesized widely, but rather by promoting a cumulative genotoxicity that deregulates DNA synthesis.

3596 **Affinity-Tuned ErbB2 or EGFR Chimeric Antigen Receptor T Cells Exhibit an Increased Therapeutic Index against Tumors in Mice**



Xiaojun Liu, Shuguang Jiang, Chongyun Fang, Shiyu Yang, Devvora Olalere, Edward C. Pequignot, Alexandria P. Cogdill, Na Li, Melissa Ramones, Brian Granda, Li Zhou, Andreas Loew, Regina M. Young, Carl H. June, and Yangbing Zhao

Précis: 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.

TUMOR AND STEM CELL BIOLOGY

3608 **IL6/JAK1/STAT3 Signaling Blockade in Endometrial Cancer Affects the ALDH^{hi}/CD126⁺ Stem-like Component and Reduces Tumor Burden**



Marten van der Zee, Andrea Sacchetti, Medine Cansoy, Rosalie Joosten, Miriam Teeuwssen, Claudia Heijmans-Antonissen, Patricia C. Ewing-Graham, Curt W. Burger, Leen J. Blok, and Riccardo Fodde

Précis: These results provide a preclinical rationale to target IL6 or its downstream effector functions as a novel therapeutic option in endometrial cancer, with immediate potential implications for a clinical evaluation of IL6-blocking antibodies or JAK inhibitors in this setting.

3623 **RAS/MAPK Activation Drives Resistance to Smo Inhibition, Metastasis, and Tumor Evolution in Shh Pathway-Dependent Tumors**

Xuesong Zhao, Tatyana Ponomaryov, Kimberly J. Ormell, Pengcheng Zhou, Sukriti K. Dabral, Ekaterina Pak, Wei Li, Scott X. Atwood, Ramon J. Whitson, Anne Lynn S. Chang, Jiang Li, Anthony E. Oro, Jennifer A. Chan, Joseph F. Kelleher, and Rosalind A. Segal

Précis: These findings point to a significant role for RAS/MAPK pathway alternations in acquired drug resistance and tumor evolution of Sonic Hedgehog pathway-driven cancers.

3636 **Microenvironment-Modulated Metastatic CD133⁺/CXCR4⁺/EpCAM⁻ Lung Cancer-Initiating Cells Sustain Tumor Dissemination and Correlate with Poor Prognosis**



Giulia Bertolini, Lucia D'Amico, Massimo Moro, Elena Landoni, Paola Perego, Rosalba Miceli, Laura Gatti, Francesca Andriani, Donald Wong, Roberto Caserini, Monica Tortoreto, Massimo Milione, Riccardo Ferracini, Luigi Mariani, Ugo Pastorino, Ilaria Roato, Gabriella Sozzi, and Luca Roz

Précis: 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.

3650 **Keratin-17 Promotes p27^{KIP1} Nuclear Export and Degradation and Offers Potential Prognostic Utility**



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

Précis: This important study establishes that keratin-17 functions specially among keratins as an oncoprotein by controlling the ability of the tumor suppressor p27KIP1 to influence cervical cancer pathogenesis.

3663 **Androgen Receptor Splice Variants Dimerize to Transactivate Target Genes**

Duo Xu, Yang Zhan, Yanfeng Qi, Bo Cao, Shanshan Bai, Wei Xu, Sanjiv S. Gambhir, Peng Lee, Oliver Sartor, Erik K. Flemington, Haitao Zhang, Chang-Deng Hu, and Yan Dong

Précis: 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.

Table of Contents

3672 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 TWIST1, which regulates epithelial-mesenchyme transition in cancer cells.

3682 Cell Death Identification in Anticancer Therapy—Response

Santiago Rello-Varona, David Herrero-Martín, Roser López-Alemany, and Oscar M. Tirado

CORRECTIONS

3683 Correction: Long Noncoding RNA GAPLINC Regulates CD44-Dependent Cell Invasiveness and Associates with Poor Prognosis of Gastric Cancer

3684 Correction: Host Immune Defense Peptide LL-37 Activates Caspase-Independent Apoptosis and Suppresses Colon Cancer

LETTERS TO THE EDITOR

3681 Cell Death Identification in Anticancer Therapy—Letter

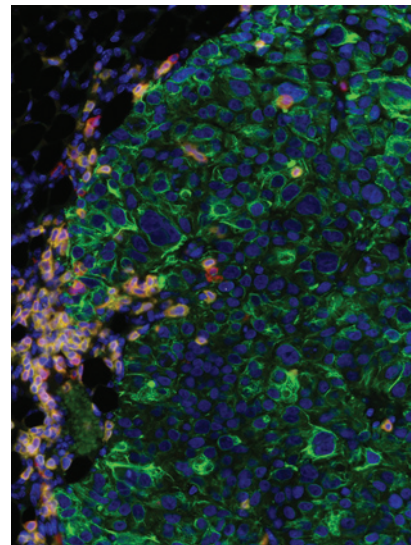
J. Martin Brown, Bradly G. Wouters, and David G. Kirsch

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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.



Cancer Research

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