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. 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 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.

3479 Perivascular M2 Macrophages Stimulate Tumor Relapse after Chemotherapy
Russell Hughes, Bin-Zhi Qian, Charlotte Rowan, Muninta 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.
### MOLECULAR AND CELLULAR PATHOBIOLOGY

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### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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### Precis:
- **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
  - Precis: 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**
  - Precis: 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.

- **CRM5 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 Chouhamou, Marie-Eve Mayeur, Roger Besanyo, Nicolas Naudet, Léa Magadoux, Rajesh Khanna, François Ducray, David Meyronet, and Nicole Thomasset
  - Precis: 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. Zimmermann, Anthony E. Getschman, Susan Tsai, Dannielle D. Engle, Douglas B. Evans, Brian F. Volkman, Balaraman Kalyanaraman, and Michael B. Dwinell
  - Precis: Provocative biological findings offer a preclinical rationale for further investigation of the promigratory chemokine CXCL12 for preventing metastasis in pancreatic cancer.
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.

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.

IL6/JAK1/STAT3 Signaling Blockade in Endometrial Cancer Affects the ALDHhi/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.

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.
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.

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 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.