BREAKING ADVANCES

2055 Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

2057 Human Cancers Express a Mutator Phenotype: Hypothesis, Origin, and Consequences
Lawrence A. Loeb

2060 Jacob, Monod, the Lac Operon, and the PaJaMa Experiment—Gene Expression Circuitry Changing the Face of Cancer Research
Stephen B. Baylin

REVIEWS

2063 The Role of Cholesterol in Cancer
Omer F. Kuzu, Mohammad A. Noory, and Gavin P. Robertson

2071 Implications of Extracellular Vesicle Transfer on Cellular Heterogeneity in Cancer: What Are the Potential Clinical Ramifications?
Anoek Zomer and Jacco van Rheenen

PRIORITY REPORTS

2076 STING Promotes the Growth of Tumors Characterized by Low Antigenicity via IDO Activation
Henrique Lemos, Eslam Mohamed, Lei Huang, Rong Ou, Gabriela Pacholczyk, Ali S. Arbab, David Munn, and Andrew L. Mellor

Précis: While the DNA sensor STING can activate powerful antitumor immune responses, this study shows that it can also tolerate the immune microenvironment of weakly antigenic tumors, with implications to broaden the numbers of tumors that may respond strongly to cancer immunotherapy.

2082 Frequency and Dynamics of Leukemia-Initiating Cells during Short-term Ex Vivo Culture Informs Outcomes in Acute Myeloid Leukemia Patients
Emmanuel Griessinger, Fernando Anjos-Afonso, Jacques Vargafig, David C. Taussig, François Lassailly, Thomas Prebet, Véronique Imbert, Marielle Nebout, Norbert Vey, Christian Chabannon, Andrew Filby, Frederic Bollet-Quivogne, John G. Gribben, Jean-François Peyron, and Dominique Bonnet

Précis: This study describes an accessible approach to reliably capture the intrinsic biological features of leukemic stem cells, offering a clinically relevant tool for the prognostic assessment of patient outcome upon AML diagnosis.

2087 TALEN-Mediated Inactivation of PD-1 in Tumor-Reactive Lymphocytes Promotes Intratumoral T-cell Persistence and Rejection of Established Tumors
Laurie Menger, Anna Sleczynska, Katharina Bergerhoff, Frederick Ance Vargas, Julianne Smith, Laurent Poirot, Martin Pule, Javier Hererro, Karl S. Peggs, and Sergio A. Quezada

Précis: This proof-of-concept study demonstrates that advanced adoptive T-cell therapies for cancer can be enhanced by genomic editing strategies to bypass immune checkpoints.

INTEGRATED SYSTEMS AND TECHNOLOGIES

2094 In Vivo Visualization and Characterization of Epithelial–Mesenchymal Transition in Breast Tumors
Zhen Zhao, Xiaoping Zhu, Kemi Cui, James Mancuso, Richard Federley, Kari Fischer, Gao-jun Teng, Vivek Mittal, Dingcheng Gao, Hong Zhao, and Stephen T.C. Wong

Précis: An in vivo method to visualize features of epithelial-mesenchymal transition reveals tumor cell-microenvironment interactions that foster metastatic behaviors and therapeutic strategies best suited to suppress them.

2105 Transcriptome Analysis of Triple-Negative Breast Cancer Reveals an Integrated mRNA-IncRNA Signature with Predictive and Prognostic Value
Yi-Zhou Jiang, Yi-Rong Liu, Xiao-En Xu, Xi Jin, Xin Hu, Ke-Da Yu, and Zhi-Ming Shao

Précis: This prospective observational study reports a simple biomarker signature of triple-negative breast cancer that can predict risks of disease relapse and the clinical benefit of commonly employed taxane chemotherapy, addressing needs in a disease that can be aggressive in some but not all patients.
Inherent and Tumor-Driven Immune Tolerance in the Prostate Microenvironment Impairs Natural Killer Cell Antitumor Activity
Christine Pasero, Gwenaëlle Gravis, Mathilde Guerin, Samuel Granjaud, Jeanne Thomassin-Piana, Palma Rocchi, Maria Paciencia-Gros, Flora Poizat, Mélanie Bentobji, Francine Azario-Cheillan, Jochen Walz, Naji Salem, Serge Brunelle, Alessandro Moretta, and Daniel Olive
Précis: This study suggests that immune escape in prostate cancer entails a suppression of natural killer cell activity, suggesting strategies to restore their function as a pivotal therapeutic approach in patients.
Identification of RNA-Binding Protein LARP4B as a Tumor Suppressor in Glioma
Hideto Koso, Hungtsung Yi, Paul Sheridan, Satoru Miyano, Yasushi Ino, Tomoki Todo, and Sumiko Watanabe

Précis: An RNA-binding protein absent from most human gliomas is found to function as a tumor suppressor in this setting, revealing new insights into posttranscriptional mechanisms of cell growth and apoptotic control.

2265 Melanoma Cells Block PEDF Production in Fibroblasts to Induce the Tumor-Promoting Phenotype of Cancer-Associated Fibroblasts
Nkerchinyere G. Nwani, Maria L. Deguiz, Benilde Jimenez, Elena Vinokour, Oleksii Dubrovskyi, Andrey Ugolkov, Andrew P. Mazat, and Olga V. Volpert

Précis: Melanoma cells override tumor suppression programs in neighboring stromal cells by a mechanism that facilitates the conversion of normal fibroblasts into cancer-associated fibroblasts, fostering a tumor promoting environment.

PREVENTION AND EPIDEMIOLOGY

2288 A Meta-analysis of Individual Participant Data Reveals an Association between Circulating Levels of IGF-I and Prostate Cancer Risk

Précis: This study encompasses the largest collaborative analysis of individual data as yet in addressing the relationship between insulin-like growth factors and prostate cancer risk.
## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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<tr>
<th>Page</th>
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<td>2301</td>
<td>Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor–Positive Breast Cancer</td>
<td>Maria Teresa Herrera-Abreu, Marta Palafox, Uzma Asghar, Martin A. Rivas, Rosalind J. Cutts, Isaac Garcia-Murillas, Alex Pearson, Marta Guzman, Olga Rodriguez, Judit Grueso, Meritxell Bellet, Javier Cortés, Richard Elliott, Sunil Pancholi, José Baselga, Mitch Dowsett, Lesley-Ann Martin, Nicholas C. Turner, and Violeta Serra</td>
<td>Précis: These results illustrate that breast cancer cells can adapt quickly to cell-cycle blockades imposed by CDK4/6 inhibitors being used in clinical practice, acquiring resistance mechanisms that enable alternate means of S phase entry, yet also highlighting strategies to prevent the acquisition of therapeutic resistance to these agents.</td>
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<td>2314</td>
<td>MCAM and LAMA4 Are Highly Enriched in Tumor Blood Vessels of Renal Cell Carcinoma and Predict Patient Outcome</td>
<td>Joseph W. Wragg, Jonathan P. Finnity, Jane A. Anderson, Henry J.M. Ferguson, Emilio Porfiri, Rupesh I. Bhatt, Paul G. Murray, Victoria L. Heath, and Roy Bicknell</td>
<td>Précis: Newly identified markers of blood vessels in renal tumors may offer an opportunity to selectively target the tumor vasculature in this setting.</td>
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<td>2327</td>
<td>Resistance to Anti-VEGF Therapy Mediated by Autocrine IL6/STAT3 Signaling and Overcome by IL6 Blockade</td>
<td>Alexandra Eichten, Jia Su, Alexander P. Adler, Li Zhang, Ella Ioffe, Asma A. Parveen, George D. Yancopoulos, John Rudge, Israel Lowy, Hsin Chieh Lin, Douglas MacDonald, Christopher Daly, Xunbao Duan, and Gavin Thurston</td>
<td>Précis: These findings suggest that cancer patients undergoing anti-VEGF therapy may benefit from analysis of circulating IL6 levels as a predictive response marker, as well as cotreatment with an IL6 receptor targeting antibody.</td>
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<td>2340</td>
<td>The Error-Prone DNA Polymerase ξ Promotes Temozolomide Resistance in Glioblastoma through Rad17-Dependent Activation of ATR-Chk1 Signaling</td>
<td>Chenghao Peng, Zhengxin Chen, Shuai Wang, Hong-Wei Wang, Wenyin Qiu, Lin Zhao, Ran Xu, Hui Luo, Yuanxuan Chen, Dan Chen, Yongping You, Ning Liu, and Huibo Wang</td>
<td>Précis: Increased activity of a DNA repair pathway that can reverse the damage created by temozolomide, a chemotherapeutic drug used to treat glioblastoma, may explain why drug resistance in this setting tends to be clinically problematic.</td>
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<td>2354</td>
<td>p28-Mediated Activation of p53 in G2–M Phase of the Cell Cycle Enhances the Efficacy of DNA Damaging and Antimitotic Chemotherapy</td>
<td>Tohru Yamada, Tapas K. Das Gupta, and Craig W. Beattie</td>
<td>Précis: Delivery of a small p53-activating peptide that can safely increase the cytotoxicity of DNA damaging or antimitotic cancer drugs may offer one more twist on p53-based strategies to widen the therapeutic window for cancer drug responses.</td>
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<td>2366</td>
<td>Hypoxic Signaling and the Cellular Redox Tumor Environment Determine Sensitivity to MTH1 Inhibition</td>
<td>Lars Bräutigam, Linda Pudelko, Ann-Sofie Jerth, Helge Gad, Mohit Narwal, Robert Gustafsson, Stella Karsten, Jordi Carreras Puigvert, Evert Homan, Cansten Berndt, Ulrika Warman Berglund, Pal Stenmark, and Thomas Helleday</td>
<td>Précis: This study illustrates how zebrafish can serve as a useful model to investigate the relationship between redox imbalance and hypoxic signaling in oncogenesis at the level of the tumor microenvironment.</td>
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<td>2376</td>
<td>Cancer Differentiating Agent Hexamethylene Bisacetamide Inhibits BET Bromodomain Proteins</td>
<td>Lisa M. Nilsson, Lydia C. Green, Somssundar Veppil, Muralidharan, Daqiu Demir, Martin Welin, Joydeep Bhadury, Derek T. Logan, Bjorn Wahle, and Jonas A. Nilsson</td>
<td>Précis: These findings suggest a new perspective on patient recruitment to ongoing BET inhibitor clinical trials.</td>
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<td>2384</td>
<td>The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase</td>
<td>Edel McGarry, David Gaboriau, Michael D. Rainey, Umberto Restuccia, Angela Bach, and Corrado Santocanale</td>
<td>Précis: These findings highlight a role for an important deubiquitinylating enzyme in maintaining genomic stability during DNA replication, offering new mechanistic clues to its tumor suppressor functions in various cancers.</td>
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TUMOR AND STEM CELL BIOLOGY

2394 Inflammation-Dependent IL18 Signaling Restricts Hepatocellular Carcinoma Growth by Enhancing the Accumulation and Activity of Tumor-Infiltrating Lymphocytes
Geoffrey J. Markowitz, Pengyuan Yang, Jing Fu, Gregory A. Michelotti, Rui Chen, Jianhua Sui, Bin Yang, Wen-Hao Qin, Zheng Zhang, Fu-Sheng Wang, Anna Mae Diehl, Qi-Jing Li, Hongyang Wang, and Xiao-Fan Wang
Précis: These findings resolve a long-standing contradiction regarding a tumor suppressive role for IL18 in established liver cancers.

2406 Cyclin E Associates with the Lipogenic Enzyme ATP-Citrate Lyase to Enable Malignant Growth of Breast Cancer Cells
Kimberly S. Lucenay, Iman Doostan, Cansu Karakas, Tuyen Bui, Zhiyong Ding, Gordon B. Mills, Kelly K. Hunt, and Khandan Keyomarsi
Précis: These findings establish a novel relationship between cyclin E and lipid metabolism pathways in breast cancer oncogenesis, with potential implications for therapeutic interventions.

2419 KLF4-Mediated Suppression of CD44 Signaling Negatively Impacts Pancreatic Cancer Stemness and Metastasis
Yongmin Yan, Zhiwei Li, Xiangyu Kong, Zhiliang Jia, Xiangsheng Zuo, Nihai Gagea, Suyun Huang, Daoyan Wei, and Keping Xie
Précis: These findings elucidate the tumor suppressive mechanism by which KLF4 regulates the stemness and metastatic potential of pancreatic cancer cells, strengthening the preclinical rationale for early phase clinical trials of targeted KLF4 activation in aggressive solid tumors.

2432 Pharmacological Targeting of the Histone Chaperone Complex FACT Preferentially Eliminates Glioblastoma Stem Cells and Prolongs Survival in Preclinical Models
Josephine Kam Tai Dermawan, Masahito Hiromi, Daniel J. Silver, Qiulian Wu, Poorva Sandesh, Andrew E. Sloan, Andrei A. Purmal, Katerina V. Gurova, Jeremy N. Rich, Justin D. Lathia, George R. Stark, and Monica Venere
Précis: These findings offer a preclinical proof of concept for development of an anticancer drug class termed curaxins, which appear to preferentially kill stem cells in glioblastoma that are thought to be responsible for the aggressiveness of this disease.

2443 Drosophila Brat and Human Ortholog TRIM3 Maintain Stem Cell Equilibrium and Suppress Brain Tumorigenesis by Attenuating Notch Nuclear Transport
Subhas Mukherjee, Carol Tucker-Burden, Changming Zhang, Kenneth Moberg, Renee Read, Costas Hadjiyanis, and Daniel J. Beat
Précis: Investigations in a Drosophila brain tumor model reveal an evolutionarily conserved mechanism, which controls the self-renewal of glioma stem-like cells, suggesting new potential strategies to attack Notch-driven tumorigenesis.

2453 Cyclin A1 and P450 Aromatase Promote Metastatic Homing and Growth of Stem-like Prostate Cancer Cells in the Bone Marrow
Regina Miftakhova, Andreas Hedblom, Julius Semenas, Brian Robinson, Athanasios Simoulin, Johan Malin, Albert Bizovanov, David M. Heery, Nigel P. Morgan, Norman J. Maitland, Cinzia Allegrucci, and Jenny L. Persson
Précis: These results suggest that local production of steroids and MMPs in the bone marrow may provide a suitable microenvironment for prostate cancer stem-like cells to establish metastatic growths, with implications for how to target bone metastases in patients with advanced prostate cancer.

2465 A Three-Dimensional Organoid Culture System Derived from Human Glioblastomas Recapitulates the Hypoxic Gradients and Cancer Stem Cell Heterogeneity of Tumors Found In Vivo
Christopher G. Hubert, Maricruz Rivera, Lisa C. Spangler, Qiulian Wu, Stephen C. Mack, Brian C. Prager, Marta Couce, Roger E. McLendon, Andrew E. Sloan, and Jeremy N. Rich
Précis: This study presents an important new tool to probe the diversity of glioblastoma cell phenotypes and microenvironmental nuances, which contribute to progression, by enabling investigations in a highly disease-relevant and tractable ex vivo culture system.

2478 Activated KRAS Cooperates with MLL-AF4 to Promote Extramedullary Engraftment and Migration of Cord Blood CD34+ HSPC But Is Insufficient to Initiate Leukemia
Cristina Prieto, Ronald W. Stam, Antonio Agraz-Doblas, Paola Ballerini, Mireia Camos, Julio Castaño, Rolf Marschalek, Alderheid Bursen, Ignacio Varela, Clara Bueno, and Pablo Menendez
Précis: These findings support genomic studies conducted in other leukemias that show KRAS mutations are subclonal and lost at relapse.
RETRCTIONS

2490 Retraction: Immunity to Murine Prostatic Tumors: Continuous Provision of T-Cell Help Prevents CD8 T-Cell Tolerance and Activates Tumor-Infiltrating Dendritic Cells

2491 Retraction: High-Avidity T Cells Are Preferentially Tolerized in the Tumor Microenvironment

CORRECTION

2492 Correction: Lens Epithelium-Derived Growth Factor Is an Hsp70-2 Regulated Guardian of Lysosomal Stability in Human Cancer

ABOUT THE COVER

In commemoration of the 75th anniversary of Cancer Research, the Journal Editors have identified some of the most impactful articles published throughout the Journal’s history. This year, Cancer Research has published and will continue to publish commentaries from authors, Editors, and other leaders in the field, reflecting on these important articles and how the field has continued to advance. This issue’s cover offers a look back at some classic and distinctive covers from the Journal’s rich history, featuring some key players, locations, and findings, and highlighting the impact the Journal has had in advancing cancer research and the mission of the AACR. For a more in-depth look at Cancer Research through the years, an interactive Anniversary timeline, and an archive of all Commentaries, please visit http://cancerres.aacrjournals.org/site/misc/75th_anniversary/CR75_timeline.html#timeline.
Cancer Research

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