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, Islam 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 Vargafigi, David C. Tausig, François Lassalilly, 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 Sledzinska, Katharina Bergerhoff, Frederick Arce 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.
2115 Redundant Innate and Adaptive Sources of IL17 Production Drive Colon Tumorigenesis
Précis: These findings suggest redundant sources for the cytokine IL17 in bacteria-induced colon carcinogenesis, stressing the importance of therapeutically targeting IL17 itself rather than its cellular sources.

2125 Myeloid-Derived Suppressor Cells Express Bruton’s Tyrosine Kinase and Can Be Depleted in Tumor-Bearing Hosts by Ibrutinib Treatment
Précis: The Bruton’s tyrosine kinase inhibitor ibrutinib impairs the generation and function of myeloid-derived suppressor cells in multiple malignancies, supporting a preclinical rationale for its use as an immunotherapy.

2137 Agonist-Mediated Activation of STING Induces Apoptosis in Malignant B Cells
Chih-Hang Anthony Tang, Joseph A. Zandell, Sujeewa Ranatunga, Cindy Lin, Yulia Nefedova, Juan R. Del Valle, and Chih-Chi Andrew Hu
Précis: These findings show how STING agonists can be used directly to eradicate neoplastic B cells, suggesting their potential therapeutic value in treatment of B-cell malignancies.

2145 Inherent and Tumor-Driven Immune Tolerance in the Prostate Microenvironment Impairs Natural Killer Cell Antitumor Activity
Christine Pasero, Gwenaëlle Gravis, Mathilde Guerin, Samuel Granjaund, Jeanne Thomassin-Naggara, Palma Rocchi, Maria Pacienza-Gros, Flora Poziat, Mélanie Bentobi, Francine Azario-Cheillan, Jochen Walz, Naji Salem, Serge Brunelle, Alessandro Moretta, and Daniel Oliva
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.

2155 Activation of the MDA-5–IPS-1 Viral Sensing Pathway Induces Cancer Cell Death and Type I IFN-Dependent Antitumor Immunity
Xiaofei Yu, Hongxia Wang, Xia Li, Chunqing Guo, Fang Yuan, Paul B. Fisher, and Xiang-Yang Wang
Précis: These findings reveal a role for a viral sensing pathway in the induction of antitumor immunity, offering an opportunity for therapeutic targeting in novel cancer immunotherapy modalities.

2166 Detection of an Immunogenic HERV-E Envelope with Selective Expression in Clear Cell Kidney Cancer
Elena Cherkasova, Claire Scrivani, Susan Doh, Quinn Weisman, Yoshiyuki Takahashi, Nanar Harashima, Hisayuki Yokoyma, Ramaprasad Srinivasan, W. Marston Linehan, Michael J. Lerman, and Richard W. Childs
Précis: These findings define a promising disease-specific targeting strategy for the development of kidney cancer immunotherapy.

2176 ILK Induction in Lymphoid Organs by a TNFα–NF-κB–Regulated Pathway Promotes the Development of Chronic Lymphocytic Leukemia
Précis: These findings support the development of targeted therapies for cancer that aberrantly express the multifunctional kinase ILK.

2186 Genomic Profiling of Pediatric Acute Myeloid Leukemia Reveals a Changing Mutational Landscape from Disease Diagnosis to Relapse
Précis: These findings reveal a complex evolution in the mutational landscape of a common pediatric leukemia, suggesting potentially actionable therapeutic targets.
2219 Prolyl Hydroxylase 3 Attenuates MCL-1–Mediated ATP Production to Suppress the Metastatic Potential of Colorectal Cancer Cells

Praveen Kumar Radhakrishnan, Nadine Ruh, Jonathan M. Harnoss, Judit Kiss, Martin Mollenhauer, Anna-Lena Scherr, Lisa K. Platter, Thomas Schmidt, Klaus Podar, Joseph T. Opferman, Jürgen Weitz, Henning Schulze-Bergkamen, Bruno C. Koehler, Alexis Ulrich, and Martin Schneider

Précis: This study shows that the molecular oxygen sensor PHD3 functions as a metastasis suppressor in colorectal cancer, with caution for use of PHD inhibitors as therapeutics in patients with advanced cancers.

2231 Immunoregulatory Protein B7-H3 Reprograms Glucose Metabolism in Cancer Cells by ROS-Mediated Stabilization of HIF1α

Sangbin Lim, Hao Liu, Luciana Madeira da Silva, Ritu Arora, Zixing Liu, Yifeng Lin, Wensheng Lin, Gary A. Piazza, Oystein Fodstad, and Ming Tan

Précis: This seminal work defines a broader and previously unrecognized role for the T-cell immunoregulatory protein B7-H3 in cancer cell metabolism, suggesting the therapeutic use of metabolic inhibitors in malignancies that overexpress B7-H3.

2243 PR55α Subunit of Protein Phosphatase 2A Supports the Tumorigenic and Metastatic Potential of Pancreatic Cancer Cells by Sustaining Hyperactive Oncogenic Signaling

Ashley L. Hein, Parthasarathys Seshacharyulu, Satyanarayana Rachaganti, Yuri M. Sheinin, Michel M. Ouellette, Moorthy P. Ponnusamy, Marc C. Mumby, Surinder K. Batra, and Ying Yan

Précis: These findings offer preclinical proof of principle for a regulatory subunit of the protein phosphatase 2a holoenzyme as a candidate therapeutic target in pancreatic cancer.

2254 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

Nkerih Yere G. Nwani, Maria L. Deguiz, Benilde Jimenez, Elena Vinokour, Oleksii Dubrovskiy, 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.

2277 Stomach-Specific Activation of Oncogenic KRAS and STAT3-Dependent Inflammation Cooperatively Promote Gastric Tumorigenesis in a Preclinical Model

Stefan Thiem, Moritz F. Eissmann, Joachim Elzer, Anna Jonas, Tracy L. Putozeki, Ashleigh Poh, Paul Nguyen, Adele Preaudet, Dustin Flanagan, Elizabeth Vincan, Paul Waring, Michael Buchert, Andrew Jarnicki, and Matthias Ernst

Précis: This study describes a new preclinical model of gastric cancer that underscores the importance of both oncogene activation and aberrant inflammation in gastric epithelial cells to the onset and progression of tumorigenesis.
THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2301 Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor–Positive Breast Cancer
Maria Teresa Herrera-Abreu, Marta Palafox, Uzma Asghar, Martín A. Rivas, Rosalind J. Cutts, Isaac García-Murillas, Alex Pearson, Marta Guzman, Olga Rodriguez, Judit Grueso, Meritxell Bellet, Javier Cortés, Richard Elliott, Sunil Pancholi, Jose Baselga, Mitch Dowsett, Lesley-Ann Martin, Nicholas C. Turner, and Violeta Serra

Précis: These results illustrate that breast cancer cells can adapt quickly to cell-cycle blockades imposed by CDK4/6 inhibitors being used in clinic, 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.

2314 MCAM and LAMA4 Are Highly Enriched in Tumor Blood Vessels of Renal Cell Carcinoma and Predict Patient Outcome

Précis: Newly identified markers of blood vessels in renal tumors may offer an opportunity to selectively target the tumor vasculature in this setting.

2327 Resistance to Anti-VEGF Therapy Mediated by Autocrine IL6/STAT3 Signaling and Overcome by IL6 Blockade
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

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.

2340 The Error-Prone DNA Polymerase ε Promotes Temozolomide Resistance in Glioblastoma through Rad17-Dependent Activation of ATR-Chk1 Signaling
Chenghao Peng, Zhengxin Chen, Shuai Wang, Hong-Wei Wang, Wengjin Qiu, Lin Zhao, Ran Xu, Hui Luo, Yuanyuan Chen, Dan Chen, Yongping You, Ning Liu, and Huibo Wang

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.

2354 p28-Mediated Activation of p53 in G2–M Phase of the Cell Cycle Enhances the Efficacy of DNA Damaging and Antimitotic Chemotherapy
Tohru Yamada, Tapas K. Das Gupta, and Craig W. Beattie

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.

2366 Hypoxic Signaling and the Cellular Redox Tumor Environment Determine Sensitivity to MTH1 Inhibition
Lars Bräutigam, Linda Pudelko, Ann-Sofie Jerth, Helge Gad, Mohit Narwal, Robert Gustafsson, Stella Karsten, Jordi Carreras Puigvert, Evert Homan, Cansten Berndt, Ulrika Warpman Berglund, Pal Stenmark, and Thomas Hellsted

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.

2376 Cancer Differentiating Agent Hexamethylene Bisacetamide Inhibits BET Bromodomain Proteins
Lisa M. Nilsson, Lydia C. Green, Somrindar Veppil Muralidharan, Dajsu Demir, Martin Welin, Joydeep Bhadury, Derek T. Logan, Bjorn Wahle, and Jonas A. Nilsson

Précis: These findings suggest a new perspective on patient recruitment to ongoing BET inhibitor clinical trials.

2384 The Deubiquitinase USP9X Maintains DNA Replication Fork Stability and DNA Damage Checkpoint Responses by Regulating CLASPIN during S-Phase
Edel McGarry, David Gaboriau, Michael D. Rainey, Umberto Restuccia, Angela Bach, and Corrado Santocanale

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.
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, 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, Qiqian Wu, Poorva Sandlesh, 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 Hadjipanayis, and Daniel J. Beat

Précis: Investigations in a Drosophila brain tumor model reveal an evolutionarily conserved mechanism, which controls the self-renewal of gloma 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 Mitakhova, Andreas Hedblom, Julius Semenas, Brian Robinson, Athanasios Simoulias, Johan Malin, Albert Rizvanov, David M. Heery, Nigel P. Morgan, Norman J. Maitland, Cinzia Allegriucci, 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 bony 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, Briana 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, Aldeheid 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.
RETRACEMENTS

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.