**CANCER RESEARCH**

**TABLE OF CONTENTS**

**BREAKING INSIGHTS**

777  Highlights from Recent Cancer Literature

**REVIEWS**

779  Holding on to Junk Bonds: Intron Retention in Cancer and Therapy
Geoffray Monteuuis, Ulf Schmitz, Veronika Petrova, Padraic S. Kearney, and John E.J. Rasko

790  The Microbiome and Cancer: Creating Friendly Neighborhoods and Removing the Foes Within
Sheetal Parida and Dipali Sharma

801  Eph Receptors in the Immunosuppressive Tumor Microenvironment
Peter W. Janes, Mary E. Vail, Matthias Ernst, and Andrew M. Scott

806  Unraveling the Mysteries of PAX8 in Reproductive Tract Cancers
Daniele Chaves-Moreira, Patrice J. Morin, and Ronny Drapkin

**CANCER RESEARCH HIGHLIGHTS**

811  Adaptive Therapy and the Cost of Drug-Resistant Mutants
Dominik Wodarz
See related article, p. 1135

813  How Epigenetic Therapy Beats Adverse Genetics in Monosomy Karyotype AML
Heather M. O’Hagan, Feyruz V. Rassool, and Kenneth P. Nephew
See related article, p. 834

**CONTROVERSY AND CONSENSUS**

816  Assessing Drug Development Risk Using Big Data and Machine Learning
Vangelis Vergetis, Dimitrios Skaltsas, Vassilis G. Gorgoulis, and Aristotelis Tsirigos

**GENOME AND EPIGENOME**

820  BRD9 Is a Critical Regulator of Androgen Receptor Signaling and Prostate Cancer Progression
Aktan Alpsoy, Sagar M. Utturkar, Benjamin C. Carter, Alisha Dhiman, Sandra E. Torregrosa-Allen, Melanie P. Currie, Bennett D. Elzeby, and Emily C. Dykhuijen

Advanced prostate cancers resistant to androgen receptor antagonists are still susceptible to nontoxic BRD9 inhibitors, making them a promising alternative for halting AR signaling in progressed disease.

834  Decitabine Induces Gene Derepression on Monosomic Chromosomes: In Vitro and In Vivo Effects in Adverse-Risk Cytogenetics AML
Gabriele Greve, Julia Schüler, Björn A. Grünig, Bettina Berberich, Julia Stomper, Dennis Zimmer, Lea Gutenkunst, Ulrike Bönißch, Ruth Meier, Nadja Blagitko-Dorfs, Olga Grishina, Dietmar Pfeifer, Dieter Weichenhan, Christoph Plass, and Michael Lübbert
These findings unravel the molecular mechanism underlying the intriguing clinical activity of HMAs in AML/MDS patients with chromosome 7 deletions and other monosomal karyotypes.
See related commentary, p. 813

847  3D Functional Genomics Screens Identify CREBBP as a Targetable Driver in Aggressive Triple-Negative Breast Cancer
This study demonstrates that CREBBP genomic alterations drive aggressive TNBC, lung cancer, and lymphomas and may be selectively treated with clinical CDK4/6 inhibitors.
### TABLE OF CONTENTS

#### METABOLISM AND CHEMICAL BIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>860</td>
<td>Targeting p300/CBP Attenuates Hepatocellular Carcinoma Progression through Epigenetic Regulation of Metabolism</td>
<td>Ling-Yan Cai, Shi-Jie Chen, Sen-Hao Xiao, Qin-Juan Sun, Chen-Hong Ding, Bai-Nan Zheng, Xin-Yan Zhu, Shu-Qing Liu, Feng Yang, Ya-Xi Yang, Bing Zhou, Cheng Luo, Xin Zhang, and Wei-Fen Xie</td>
</tr>
</tbody>
</table>

This study demonstrates p300/CBP as a critical epigenetic regulator of glycolysis-related metabolic enzymes in HCC and identifies the p300/CBP inhibitor BO29-2 as a potential therapeutic strategy in this disease.

| 873  | Combinatorial Normalization of Liver-Derived Cytokine Pathways Alleviates Hepatic Tumor-Associated Cachexia in Zebrafish | Fei Fei, Shaoyang Sun, Qiang Li, Zhou Pei, Lei Wang, Ranran Zhang, Feihong Luo, Min Yu, and Xu Wang |

Disruption of leptin signaling with normalized Igf1 signaling significantly rescues anorexia, muscle wasting, and adipose wasting in Ras- and Myc-driven zebrafish models of HCC.

### MOLECULAR CELL BIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>885</td>
<td>Cancer-Induced Muscle Wasting Requires p38β MAPK Activation of p300</td>
<td>Thomas K. Sin, Guohua Zhang, Zicheng Zhang, James Z. Zhu, Yan Zuo, Jeffrey A. Frost, Min Li, and Yi-Ping Li</td>
</tr>
</tbody>
</table>

These findings demonstrate that prevention of p38β MAPK-mediated activation of p300 by the FDA-approved kinase inhibitor, nilotinib, ameliorates cancer cachexia, representing a potential therapeutic strategy against this syndrome.

| 898  | MDMX Recruits UbcH5c to Facilitate MDM2 E3 Ligase Activity and Subsequent p53 Degradation In Vivo | Jing Yang, Aiwen Jin, Jing Han, Xin Chen, Junnian Zheng, and Yanping Zhang |

This study provides the first *in vivo* evidence of MDMX facilitating MDM2-mediated p53 degradation, clarifying its role in the regulation of this critical tumor suppressor.

| 910  | A GRN Autocrine-Dependent FAM135B/AKT/mTOR Feedforward Loop Promotes Esophageal Squamous Cell Carcinoma Progression | Dezuo Dong, Weimin Zhang, Wenchang Xiao, Qingnan Wu, Yiren Cao, Xiaohan Gao, Lijie Huang, Yan Wang, Jie Chen, Weihu Wang, and Qinmin Zhan |

These findings investigate the mechanisms of FAM135B in promoting ESCC progression and suggest new potential prognostic biomarkers and therapeutic targets in patients with ESCC.

### TUMOR BIOLOGY AND IMMUNOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>923</td>
<td>DMDRMR-Mediated Regulation of m6A-Modified CDK4 by m6A Reader IGF2BP3 Drives ccRCC Progression</td>
<td>Yinmin Gu, Shaoxi Niu, Yang Wang, Lijiang Duan, Yongbo Pan, Zhou Tong, Xu Zhang, Zhenyu Yang, Bo Peng, Xiaodong Wang, Xiaoan Han, Yuxin Li, Tianyou Cheng, Yajuan Liu, Lina Zhang, Tongfeng Liu, Xiwen Yang, Minxuan Sun, Siyuan Jiang, Chang Zhang, Ning Zhang, Qinong Ye, and Shan Gao</td>
</tr>
</tbody>
</table>

This study demonstrates that the lncRNA DMDRMR acts as a cofactor for IGF2BP3 to stabilize target genes in an m6A-dependent manner, thus exerting essential oncogenic roles in ccRCC.

| 935  | Robust p53 Stabilization Is Dispensable for Its Activation and Tumor Suppressor Function         | Ning Kon, Michael Churchill, Huan Li, Siddhartha Mukherjee, James J. Manfredi, and Wei Gu |

Although robust p53 stabilization is critical for acute p53 responses such as DNA damage, this study underscores the important role of low basal p53 protein levels in p53 activation and tumor suppression.


These findings demonstrate that CUG-translated WT1 plays an oncogenic role *in vivo*, and GSK3β-mediated phosphorylation of cugWT1 induces its ubiquitination and degradation in concert with FBXW8.

| 956  | Targeting MARCO and IL37R on Immunosuppressive Macrophages in Lung Cancer Blocks Regulatory T Cells and Supports Cytotoxic Lymphocyte Function | Linnéa La Fleur, Johan Botling, Fei He, Catarina Pelicano, Chikai Zhou, Chenfei He, Giorgia Palano, Artur Mezheyevsiki, Patrick Micke, Jeffrey V. Ravetch, Mikael C. I. Karlsson, and Dhifaf Sarhan |

This study defines tumor-derived IL37 and the macrophage scavenger receptor MARCO as potential therapeutic targets to remodel the immune-suppressive microenvironment in patients with lung cancer.


This study reveals unrecognized roles of LXR in the transcriptional control of the tumor microenvironment and suggests use of a synthetic LXR agonist as a novel therapeutic strategy to stimulate antitumor activity.
### TABLE OF CONTENTS

#### TRANSLATIONAL SCIENCE

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>986</td>
<td>ORAI2 Promotes Gastric Cancer Tumorigenicity and Metastasis through PI3K/Akt Signaling and MAPK-Dependent Focal Adhesion Disassembly</td>
<td>Shayi Wu, Miao Chen, Jiao Huang, Feifei Zhang, Zhaojie Lv, Yongxu Jia, Yu-Zhu Cui, Liang-Zhan Sun, Ying Wang, Ying Tang, Krista R. Verhoeft, Yan Li, Yanru Qin, Xiang Lin, Xin-Yuan Guan, and Ka-On Lam</td>
</tr>
<tr>
<td>1001</td>
<td>Newly Identified Members of FGFR1 Splice Variants Engage in Cross-talk with AXL/AKT Axis in Salivary Adenoid Cystic Carcinoma</td>
<td>Joseph O. Humtsoe, Huyen-Su Kim, Brandon Leonard, Shizhang Ling, Blumusm Keam, Luigi Marchionni, Bahman Afsari, Michael Considine, Alexander V. Favorov, Elana J. Fertig, Hyunseok Kang, and Patrick K. Ha</td>
</tr>
<tr>
<td>1014</td>
<td>Therapeutic Targeting of Metadherin Suppresses Colorectal and Lung Cancer Progression and Metastasis</td>
<td>Minhong Shen, Shanshan Xie, Michelle Rowicki, Sven Michel, Yong Wei, Xiang Hang, Liling Wan, Xin Lu, Min Yuan, John F. Jin, Frank Jaschinski, Tianhau Zhou, Richard Klar, and Yibin Kang</td>
</tr>
<tr>
<td>1026</td>
<td>KIF15-Mediated Stabilization of AR and AR-V7 Contributes to Enzalutamide Resistance in Prostate Cancer</td>
<td>Lin Gao, Wenbo Zhang, Jing Zhang, Junmei Liu, Feifei Sun, Hui Liu, Jing Hu, Xin Wang, Xueli Wang, Peng Su, Shouzhen Chen, Sifen Qu, Benkang Shi, Xueting Xiong, Weifeng Chen, Xuesen Dong, and Bo Han</td>
</tr>
<tr>
<td>1063</td>
<td>ATG5-Dependent Autophagy Uncouples T-cell Proliferative and Effector Functions and Separates Graft-versus-Host Disease from Graft-versus-Leukemia</td>
<td>Katherine Oravecz-Wilson, Corinne Rossi, Cynthia Zajac, Yaping Sun, Lu Li, Thomas Decoville, Hideaki Fujiwara, Stephanie Kim, Daniel Peltier, and Pavan Reddy</td>
</tr>
<tr>
<td>1076</td>
<td>A Very Long-Acting PARP Inhibitor Suppresses Cancer Cell Growth in DNA Repair-Deficient Tumor Models</td>
<td>Shaun D. Fontaine, Gary W. Ashley, Peter J. Houghton, Raushan T. Kurmashava, Morgan Diolaiti, Alan Ashworth, Cody J. Peer, Ryan Nguyen, William D. Figg Sr., Denis R. Beckford-Vera, and Daniel V. Santi</td>
</tr>
</tbody>
</table>
## TABLE OF CONTENTS

### 1101 Identifying Clear Cell Renal Cell Carcinoma Coexpression Networks Associated with Opioid Signaling and Survival
Joseph R. Scarpa, Renzo G. DiNatale, Roy Mano, Andrew W. Silagy, Fengshen Kuo, Takeshi Irie, Patrick J. McCormick, Gregory W. Fischer, A. Ari Hakimi, and Joshua S. Mincer

This study suggests a possible molecular mechanism for opioid effects on cancer outcomes generally, with implications for personalization of analgesic regimens.

### 1111 MUC1-C Activates the BAF (mSWI/SNF) Complex in Prostate Cancer Stem Cells
Masayuki Hagiwara, Yota Yasumizu, Nami Yamashita, Hasan Rajabi, Atsushi Fushimi, Mark D. Long, Wei Li, Atrayee Bhattacharya, Rehan Ahmad, Mototsugu Oya, Song Liu, and Donald Kufe

These findings show that MUC1-C, which promotes prostate cancer progression, activates a novel pathway that drives the BAF remodeling complex, induces NOTCH1 and NANOG, and promotes self-renewal of prostate cancer stem cells.

### 1123 Optimal Timing for Cancer Screening and Adaptive Surveillance Using Mathematical Modeling
Kit Curtius, Anup Dewanjii, William D. Hazelton, Joel H. Rubenstein, and Georg E. Luebeck

This study demonstrates how mathematical modeling of cancer evolution can be used to optimize screening regimes, with the added potential to improve surveillance regimes.

### 1135 Turnover Modulates the Need for a Cost of Resistance in Adaptive Therapy
Maximilian A.R. Strobl, Jeffrey West, Yannick Viossat, Mehdi Damaghi, Mark Robertson-Tessi, Joel S. Brown, Robert A. Gatenby, Philip K. Maini, and Alexander R.A. Anderson

Tumor cell turnover modulates the speed of selection against drug resistance by amplifying the effects of competition and resistance costs; as such, turnover is an important factor in resistance management via adaptive therapy.

See related commentary, p. 811

### 1148 Patterns of Human Leukocyte Antigen Class I and Class II Associations and Cancer
Zhiwei Liu, Andriy Derkach, Kelly J. Yu, Meredith Yeager, Yu-Sun Chang, Chien-Jen Chen, Ulf Gyllensten, Qing Lan, Mei-Hsuan Lee, James D. McKay, Nathaniel Rothman, Hwai-I Yang, Allan Hildesheim, and Ruth M. Pfeiffer

GWAS of >71,000 individuals across 27 cancer types suggest that patterns of HLA Class I and Class II associations may provide etiologic insights for cancer.

### 1153 Time-Dependent Effects of Oral Contraceptive Use on Breast, Ovarian, and Endometrial Cancers
Torgny Karlsson, Therese Johansson, Julia Höglund, Veronica E. Ek, and Åsa Johansson

These results enable women and physicians to make more informed decisions considering oral contraceptive use, thus constituting an important step towards personalized medicine.

### 1163 Racial/Ethnic Disparities in All-Cause Mortality among Patients Diagnosed with Triple-Negative Breast Cancer
Fei Wang, Wei Zheng, Christina E. Bailey, Ingrid A. Mayer, Jennifer A. Pietenpol, and Xiao-Ou Shu

These findings highlight the need for equal healthcare to mitigate the black–white disparity and for investigations of contributors beyond healthcare for lower mortality among Asians and Hispanics.

### 1171 Interactive Classification of Whole-Slide Imaging Data for Cancer Researchers
Sanghoon Lee, Mohamed Amgad, Pooya Mobadersany, Matt McCormick, Brian P. Pollack, Habiba Ellandy, Hagar Hussein, David A. Gutman, and Lee A.D. Cooper

An interactive machine learning tool for analyzing digital pathology images enables cancer researchers to apply this tool to measure histologic patterns for clinical and basic science studies.

### 1178 The FABRIC Cancer Portal: A Ranked Catalogue of Gene Selection in Tumors Over the Human Coding Genome
Guy Kelman, Nadav Brandes, and Michal Linial

A new cancer portal quantifies and presents gene selection in tumors over the entire human coding genome across 33 cancer types and pan-cancer.

---

**AC icon indicates Author Choice**

For more information please visit www.aacrjournals.org
ABOUT THE COVER

Adaptive cancer therapy aims to delay cancer progression by exploiting competition between drug-sensitive and -resistant cells in the tumor. Drug dosing is adapted in a patient-specific fashion to maintain drug-sensitive cells that competitively suppress resistance (blue). This is in contrast to standard-of-care cancer treatment regimens that maximize cell kill and thereby cause the rapid competitive release of drug-resistant cells (orange). But, when will adaptive therapy work? Shown is a collage of so-called “phase plane” visualizations of a mathematical model with which the authors address this question. Each triangle represents a different parameterization. It was found that resource availability, resistance fraction, resistance cost, and cellular turnover integrate to modulate intratumoral competition. For details, see article by Strobl and colleagues on page 1135.