# Cancer Research

## Table of Contents

### BREAKING INSIGHTS

1717  
**Highlights from Recent Cancer Literature**

### REVIEWS

1719  
**Wnt/PCP Signaling Contribution to Carcinoma Collective Cell Migration and Metastasis**  

1730  
**Exploiting DNA Replication Stress for Cancer Treatment**  
Tajinder Ubhi and Grant W. Brown

1740  
**Estrogen Receptor Covalent Antagonists: The Best Is Yet to Come**  
Craig Furman, Ming-Hong Hao, Sudeep Prajapati, Dominic Reynolds, Victoria Rimkunas, Guo Z. Zheng, Ping Zhu, and Manav Korpal

### CANCER RESEARCH HIGHLIGHTS

1746  
**Quest for Tangible Biomarkers for Triple-Negative Breast Cancer**  
Dipali Sharma  
*See related article, p. 1784*

1749  
**DUDBbing Ferroptosis in Cancer Cells**  
Boyi Gan  
*See related article, p. 1913*

1751  
**Genome–Epigenome–Senescence: Is TET1 a Caretaker of p53-Injured Lung Cancer Cells?**  
Yutaka Kondo  
*See related article, p. 1758*

1753  
**When Failure Is Worse Than Giving Up: The Case of CTL**  
Mario Paolo Colombo and Daniele Lecis  
*See related article by Stein and colleagues; Cancer Res 79(7):1507–19*

1756  
**Lulling the Cancer Cell into an Eternal Sleep**  
Caroline C. Farrington and Goutham Narla  
*See related article, p. 1831*

### GENOME AND EPIGENOME

1758  
**p53-Suppressed Oncogene TET1 Prevents Cellular Aging in Lung Cancer**  
Piotr T. Filipczak, Shuguang Leng, Carmen S. Tellez, Kieu C. Do, Marcie J. Grimes, Cynthia L. Thomas, Stephanie R. Walton-Filipczak, Maria A. Picchi, and Steven A. Belinsky  
*Significance: These studies identify TET1 as an oncogene in lung cancer whose gain of function following loss of p53 may be exploited by targeted therapy-induced senescence. See related commentary, p. 1751* 

### METABOLISM AND CHEMICAL BIOLOGY

1769  
**Stabilized Peptide HDAC Inhibitors Derived from HDAC1 Substrate H3K56 for the Treatment of Cancer Stem–Like Cells In Vivo**  
Dongyuan Wang, Wenjun Li, Rongtong Zhao, Longjian Chen, Na Liu, Yuan Tian, Hui Zhao, Mingheng Xie, Fei Lu, Qi Fang, Wei Liang, Feng Yin, and Zigang Li  
*Significance: The selective antiproliferative effects of stabilized peptide HDAC inhibitors towards cancer stem-like cells provide a therapeutic alternative that avoids the high nonspecific toxicity of current drugs.*

1784  
**WWOX Inhibits Metastasis of Triple-Negative Breast Cancer Cells via Modulation of miRNAs**  
Saleh Khawaled, Sung Suk Suh, Suhaib K. Abdeen, Jonathan Monin, Rosario Distefano, Giovanni Nigita, Carlo M. Croce, and Rami I. Aqeilan  
*Significance: These findings highlight the mechanism by which the tumor suppressor WWOX regulates metastasis of triple-negative breast cancer. See related commentary, p. 1746*

1799  
**Concurrent Targeting of Glutaminolysis and Metabotropic Glutamate Receptor 1 (GRM1) Reduces Glutamate Bioavailability in GRM1⁺ Melanoma**  
Raj Shah, Simar J. Singh, Kevinn Eddy, Fabian V. Filipp, and Suzie Chen  
*Significance: These findings demonstrate that targeting glutaminolytic glutamate bioavailability is an effective therapeutic strategy for GRM1-activated tumors.*

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research

---

Cancer Research

Table of Contents

American Association for Cancer Research

---

April 15, 2019 • Volume 79 • Number 8

Cancer Research / C15

Table of Contents

American Association for Cancer Research
1810 Antibody-Mediated Endocytosis of Polysialic Acid Enables Intracellular Delivery and Cytotoxicity of a Glycan-Directed Antibody–Drug Conjugate
Emily C. Cox, Dana N. Thornlow, Michaela A. Jones, Jordan L. Fuller, Judith H. Merritt, Matthew J. Paszek, Christopher A. Alabi, and Matthew P. DeLisa

Significance: These findings describe a glycan-specific antibody-drug conjugate that establishes polySia as a viable cell surface target within the tumor glycocalyx.

1822 Targeted Metabolomics Identifies the Cytochrome P450 Monoxygenase Eicosanoid Pathway as a Novel Therapeutic Target of Colon Tumorigenesis
Weicang Wang, Jun Yang, Matthew L. Edin, Yuxin Wang, Ying Luo, Debin Wan, Haixia Yang, Chun-Qing Song, Wen Xue, Katherine Z. Sanidad, Mingyue Song, Heather A. Bisbee, Jennifer A. Bradbury, Guanjun Nan, Jianan Zhang, Pei-an Betty Shih, Kin Sing Stephen Lee, Lisa M. Minter, Daeyoung Kim, Hang Xiao, Jun-Yan Liu, and Guodong Zhang

Significance: This study finds that the previously unappreciated CYP monooxygenase eicosanoid pathway is deregulated in colon cancer and contributes to colon tumorigenesis.

MOLECULAR CELL BIOLOGY

1831 Spleen Tyrosine Kinase–Mediated Autophagy Is Required for Epithelial–Mesenchymal Plasticity and Metastasis in Breast Cancer

Significance: These findings present inhibition of spleen tyrosine kinase as a therapeutic option to limit breast cancer metastasis by promoting systemic tumor dormancy.

1844 MiR-644a Disrupts Oncogenic Transformation and Warburg Effect by Direct Modulation of Multiple Genes of Tumor-Promoting Pathways

Significance: This study demonstrates that miR-644a therapeutically influences the CRPC tumor microenvironment by suppressing androgen signaling and additional genes involved in metabolism, proliferation, Warburg effect, and EMT to potentiate the enzalutamide therapy.

1857 T-Type Ca_{3.1} Channels Mediate Progression and Chemotherapeutic Resistance in Glioblastoma
Anna Visa, Marta C. Sallán, Oscar Maisques, Lía Alza, Elisabet Talavera, Ricardo López-Ortega, María Santacana, Judit Herreros, and Carles Cantí

Significance: These findings identify Ca_{3.1} calcium channels as a molecular target to regulate autophagy and prevent progression and chemotherapeutic resistance in glioblastoma.

1869 Retrodifferentiation of Human Tumor Hepatocytes to Stem Cells Leads to Metabolic Reprogramming and Chemoresistance
Karim Fekir, Hélène Dubois-Pot-Schneider, Romain Désert, Yoann Daniel, Denise Glaise, Claudine Rausch, Fabrice Morel, Bernard Fromenty, Orlando Musso, Florian Cabiblic, and Anne Corlu

Significance: Restoring mitochondrial function in human hepatocellular carcinomas overcomes cancer resistance.

1884 MDH1 and MPP7 Regulate Autophagy in Pancreatic Ductal Adenocarcinoma
Maria New, Tim Van Acker, Jun-Ichi Sakamaki, Ming Jiang, Rebecca E. Saunders, Jaclyn Long, Victoria M.-Y. Wang, Axel Behrens, Joana Cerveira, Padmanan Sudhakar, Tamas Korcsmaros, Harold B.J. Jefferies, Kevin M. Ryan, Michael Howell, and Sharon A. Tooze

Significance: This study identifies and characterizes MPP7 and MDH1 as novel regulators of autophagy, which is thought to be responsible for pancreatic cancer cell survival.

1913 The Deubiquitylase OTUB1 Mediates Ferroptosis via Stabilization of SLC7A11
Tong Liu, Le Jiang, Omid Tavana, and Wei Gu

Significance: This study identifies OTUB1 as a key regulator of ferroptosis and implicates it as a potential target in cancer therapy.

See related commentary, p. 1749
TUMOR BIOLOGY AND IMMUNOLOGY

1925 Spatiotemporal Regulation of Tumor Angiogenesis by Circulating Chromogranin A Cleavage and Neuropilin-1 Engagement
Alice Dallatomasina, Anna Maria Gasparri, Barbara Colombo, Angelina Sacchi, Mimma Bianco, Tiziana Daniele, Antonio Esposito, Fabio Pastorino, Mirco Ponzoni, Fabrizio Marcucci, Flavio Curnis, and Angelo Corti

Significance: This work reveals that the interaction between fragmented chromogranin A and neuropilin-1 is required for tumor growth and represents a novel potential therapeutic target.

1938 Nicotinamide Phosphoribosyltransferase Acts as a Metabolic Gate for Mobilization of Myeloid-Derived Suppressor Cells
Cristina Travelli, Francesca Maria Consommi, Sabina Sangaletti, Mariangela Storto, Sara Morlacchi, Ambra A. Grolla, Uladbanda Galli, Gian Cesare Tron, Paola Pottararo, Lorenza Rimassa, Tiziana Pressiani, Massimiliano Mazzone, Rosalinda Trovato, Stefano Ugel, Vincenzo Bron, Claudio Tripodo, Mario P. Colombo, Armando A. Genazzani, and Antonio Sica

Significance: These findings identify NAMPT as a metabolic gate of MDSC’s precursor function, providing new opportunities to reverse tumor immunosuppression and restore clinical efficacy of immunotherapy in cancer patients.

1952 Acidification of Tumor at Stromal Boundaries Drives Transcriptome Alterations Associated with Aggressive Phenotypes
Nazanin Rohani, Liangliang Hao, Maria S. Alexis, Brian A. Joughin, Konstantin Krismer, Mira N. Moufarrej, Anthony R. Solis, Douglas A. Lauffenburger, Michael B. Yaffe, Christopher B. Burge, Santega N. Bhatia, and Frank B. Gertler

Significance: This study expands our understanding of acidosis within the tumor microenvironment and indicates that acidosis induces potentially therapeutically actionable changes to alternative splicing.

1967 MYC Drives Group 3 Medulloblastoma through Transformation of Sox2+ Astrocyte Progenitor Cells
Ran Tao, Najiba Murad, Zhenhua Xu, Peng Zhang, Konstantin Okonechnikov, Marcel Kool, Samuel Rivero-Hinojosa, Christopher Lazaruski, Pan Zheng, Yang Liu, Charles G. Eberhart, Brian R. Rood, Roger Packer, and Yanxin Pei

Significance: Insights from a new model identified LDHA as a novel target for group 3 medulloblastoma, paving the way for the development of effective therapies against this disease.

TRANSITIONAL SCIENCE

2021 Optical Radiomic Signatures Derived from Optical Coherence Tomography Images Improve Identification of Melanoma
Zahra Turani, Emad Fatemizadeh, Tatiana Blumetti, Steven Daveluy, Ana Flavia Moraes, Wei Chen, Darius Mehergan, Peter E. Andersen, and Mohammadreza Nasiavi

Significance: This study describes a noninvasive, safe, simple-to-implement, and accurate method for the detection and differentiation of malignant melanoma versus benign nevus.
MUC1-C Integrates Chromatin Remodeling and PARP1 Activity in the DNA Damage Response of Triple-Negative Breast Cancer Cells

Masaaki Yamamoto, Caining Jin, Tsuyoshi Hata, Yota Yasumizu, Yan Zhang, Deli Hong, Takahiro Maeda, Masaaki Miyo, Masayuki Hiraki, Yozo Suzuki, Kunihiko Hinohara, Hasan Rajabi, and Donald Kufe

Significance: These findings demonstrate that targeting MUC1-C disrupts epigenetics of the PARP1 complex, inhibits PARP1 activity, and is synergistic with olaparib in TNBC cells.

Biomaterial Scaffolds Recruit an Aggressive Population of Metastatic Tumor Cells In Vivo


Significance: These findings suggest that metastatic tumor cells captured by a biomaterial scaffold may serve as a diagnostic for molecular staging of metastasis.

Label-Free Raman Spectroscopy Reveals Signatures of Radiation Resistance in the Tumor Microenvironment

Santosh K. Paidi, Paola Monterroso Diaz, Sina Dadgar, Samir V. Jenkins, Charles M. Quick, Robert J. Griffin, Ruud P.M. Dings, Narasimhan Rajaram, and Ishan Barman

Significance: These findings highlight the sensitivity of label-free Raman spectroscopy to changes induced by radiation therapy and indicate the potential to predict radiation resistance prior to commencing therapy.

Transcriptome-Wide Association Study Identifies New Candidate Susceptibility Genes for Glioma


Significance: This study identifies new genes associated with glioma risk, increasing understanding of how these tumors develop.

ACE: A Workbench Using Evolutionary Genetic Algorithms for Analyzing Association in TCGA

Alan R. Gilmore, Matthew Alderdice, Rienan I. Savage, Paul G. O’Reilly, Aiden C. Roddy, Philip D. Dunne, Mark Lawler, Simon S. McDade, David J. Waugh, and Darragh G. McArt

Significance: ACE uses an evolutionary algorithm approach to perform large searches for associations between any combination of data in the TCGA database.

InCAR: A Comprehensive Resource for lncRNAs from Cancer Arrays

Yueyuan Zheng, Qingxian Xu, Mengni Liu, Huanjing Hu, Yubin Xie, Zhixiang Zuo, and Jian Ren

Significance: InCAR, a new interactive tool of reannotated public cancer-related microarray data, provides expression profiles and prognostic landscapes of lncRNAs across thousands of samples and multiple cancer types.

Correction: Gene Regulatory Network Analysis Identifies Sex-Linked Differences in Colon Cancer Drug Metabolism

Camila M. Lopes-Ramos, Mariele L. Kuijjer, Shuji Ogino, Charles S. Fuchs, Dawn L. DeMeo, Kimberly Glass, and John Quackenbush

Retraction: Transactivation of the EGR1 Gene Contributes to Mutant p53 Gain of Function

Lilach Weisz, Amir Zalcenstein, Perry Stambolsky, Yehudit Cohen, Naomí Goldinger, Moshé Oren, and Varda Rotter
ABOUT THE COVER

The image shows the activated actin cytoskeleton (red) and accumulation of mRNA processing bodies (green) present in 4T1 metastatic breast cancer cells that have been genetically deleted for the autophagy protein, ATG7. This image is part of the study from Shinde and colleagues, which describes the relocalization of spleen tyrosine kinase (SYK) into these processing bodies (P-bodies) during the induction of epithelial-mesenchymal transition. Similar to genetic inhibition of autophagy, pharmacologic inhibition of SYK activity prevents P-body clearance, inhibiting the later steps of metastatic outgrowth. For details, see article by Shinde and colleagues on page 1831.