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 Rinkunas, Guo Z. Zheng, Ping Zhu, and Manav Korpal

GENOME AND EPIGENOME

1758 p53-Suppressed Oncogene TET1 Prevents Cellular Aging in Lung Cancer
Piotr T. Filipczak, Shuguang Leng, Carmen S. Tellez, Kieru 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

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, Suhail 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.
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

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

1831 Spleen Tyrosine Kinase–Mediated Autophagy Is Required for Epithelial–Mesenchymal Plasticity and Metastasis in Breast Cancer
Aparna Shinde, Shana D. Hardy, Dongwook Kim, Saed Salehi-Askand, Mohit Kumar Jolly, Wen-Hung Wang, Joshua C. Anderson, Ryan B. Khodadadi, Wells S. Xiao, Herbert Levine, Christopher D. Willey, Casey J. Krusemark, Robert L. Geahlen, and Michael K. Wendt

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

See related commentary, p. 1756

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 Ca3.1 Channels Mediate Progression and Chemotherapeutic Resistance in Glioblastoma
Anna Visa, Marta C. Sallán, Oscar Maisques, Lia Alza, Elisabet Talavera, Ricardo López-Ortega, Maria Santacana, Judith Herreros, and Carles Canti

Significance: These findings identify Ca3.1 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 Desert, Yoann Daniel, Denise Glaise, Claudine Rauh, Fabrice Morel, Bernard Froment, Orlando Musso, Florian Cabillic, and Anne Corlu

Significance: Retrodifferentiation 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, Padmanand Sudhakar, Tamás Korcsmaros, Harold B.J. Jeffries, Kevin M. Ryan, Michael Howell, and Sharon A. Tooz

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 Consomni, Sabina Sangaletti, Mariangela Storto, Sara Mottacchi, Ambra A. Croilla, Ulbadina Galli, Gian Cesare Tron, Paola Portararo, Lorenza Rimassa, Tiziana Presiani, Massimiliano Mazzone, Stefano Ugel, Vincenzo Bronte, 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. Solits, Douglas A. Lauffenburger, Michael B. Yaffe, Christopher B. Burge, Sangeeta 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, Zhenghua Xu, Peng Zhang, Konstantin Okonechnikov, Marcel Kool, Samuel Rivero-Hinojosa, Christopher Lazarски, Pan Zheng, Yang Liu, Charles G. Eberhart, Brian R. Roord, 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.

1981  A Feedback Loop between Hypoxia and Matrix Stress Relaxation Increases Oxygen-Axis Migration and Metastasis in Sarcoma

Significance: These findings demonstrate that mechanical (stress relaxation) and chemical (hypoxia) properties of the tumor microenvironment jointly accelerate sarcoma motility and metastasis via increased expression of collagen matrix cross-linker PLOD2.

1996  Immuno-oncological Efficacy of RXDX-106, a Novel TAM (TYRO3, AXL, MER) Family Small-Molecule Kinase Inhibitor

Significance: The pan-TAM small-molecule kinase inhibitor RXDX-106 activates both innate and adaptive immunity to inhibit tumor growth and progression, indicating its clinical potential to treat a wide variety of cancers.

2009  EZH2 Inhibitor GSK126 Suppresses Antitumor Immunity by Driving Production of Myeloid-Derived Suppressor Cells
Shuo Huang, Zhongyu Wang, Jie Zhou, Jian Huang, Li Zhou, Jing Luo, Yisong Y. Wan, Haixia Long, and Bo Zhu

Significance: This study uncovers a potential mechanism behind disappointing results of a phase 1 clinical trial of EZH2 inhibitor GSK126 and identifies a translatable combinational strategy to overcome it.

TRANSLATIONAL 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 Mehsregan, Peter E. Andersen, and Mohammadreza Nasiriavanaki

Significance: This study describes a noninvasive, safe, simple-to-implement, and accurate method for the detection and differentiation of malignant melanoma versus benign nevus.
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## RESOURCE REPORTS

### 2072
ACE: A Workbench Using Evolutionary Genetic Algorithms for Analyzing Association in TCGA
Alan R. Gilmore, Matthew Alderdice, Kieran I. Savage, Paul G. O'Reilly, Aiden C. Roddy, Philip D. Dunne, Mark Lawler, Simon S. McDade, David J. Waugh, and Darren G. McArt

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

### 2076
InCAR: A Comprehensive Resource for IncRNAs from Cancer Arrays
Yueyuansheng, 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 IncRNAs across thousands of samples and multiple cancer types.

## CORRECTION

### 2084
Correction: Gene Regulatory Network Analysis Identifies Sex-Linked Differences in Colon Cancer Drug Metabolism
Camila M. Lopes-Ramos, Mariele I. Kuijjer, Shuji Ogino, Charles S. Fuchs, Dawn L. DeMeo, Kimberly Glass, and John Quackenbush

### 2085
Retraction: Transactivation of the EGR1 Gene Contributes to Mutant p53 Gain of Function
Lilach Weisz, Amir Zalcenstein, Perry Stambolsky, Yehudit Cohen, Naomi Goldfinger, Moshe Oren, and Varda Rotter

## POPULATION AND PREVENTION SCIENCE

### 2065
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.

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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.