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 DUBbing 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.
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.

Targeted Metabolomics Identifies the Cytochrome P450 Monooxygenase 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.

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

Aparna Shinde, Shana D. Hardy, Dongwook Kim, Saeed Salehin Akhand, Mohit Kumar Jolly, Wen-Hung Wang, Joshua C. Anderson, Ryan B. Khodadadi, Wells S. Wang, Junan Liu, Herbert Levine, Christopher D. Willey, 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.

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.
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 Sangalletti, Mariangela Storto, Sara Mozzacchi, Ambra A. Croilla, Ubalda Cali, Gian Cesare Tron, Paola Portarore, Lorenza Rimassa, Tiziana Pressiani, Massimiliano Mazzone, Rosalinda Trovato, 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, 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.

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 Mehregan, 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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<td>2031</td>
<td>MUC1-C Integrates Chromatin Remodeling and PARP1 Activity in the DNA Damage Response of Triple-Negative Breast Cancer Cells</td>
<td>Masaaki Yamamoto, Caining Jin, Tsuyoshi Hata, Yota Yasumizu, Yan Zhang, Deli Hong, Takahiro Maeda, Masaaki Miyo, Masayuki Hitaki, Yozo Suzuki, Kunihiko Hinohara, Hasan Rajabi, and Donald Kufe</td>
<td>These findings demonstrate that targeting MUC1-C disrupts epigenetics of the PARP1 complex, inhibits PARP1 activity, and is synergistic with olaparib in TNBC cells.</td>
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<td>2042</td>
<td>Biomaterial Scaffolds Recruit an Aggressive Population of Metastatic Tumor Cells In Vivo</td>
<td>Grace G. Bushnell, Tejaswini P. Hardas, Rachel M. Hartfield, Yining Zhang, Robert S. Oakes, Scott Ronquist, Haiming Chen, Indika Rajapakse, Max S. Wicha, Jacqueline S. Jeruss, and Lonnie D. Shea</td>
<td>These findings suggest that metastatic tumor cells captured by a biomaterial scaffold may serve as a diagnostic for molecular staging of metastasis.</td>
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<td>2054</td>
<td>Label-Free Raman Spectroscopy Reveals Signatures of Radiation Resistance in the Tumor Microenvironment</td>
<td>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</td>
<td>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.</td>
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<td>2065</td>
<td>Transcriptome-Wide Association Study Identifies New Candidate Susceptibility Genes for Glioma</td>
<td>Isabelle Aikins, Ben Kinnersley, Quinn T. Oststrom, Karim Labreche, Dora Ilyasova, Georgina N. Armstrong, Jeanette E. Eckel-Passow, Minouk J. Schoemaker, Markus M. Nöthen, Jill S. Barnholz-Sloan, Anthony J. Swoerdlow, Matthias Simon, Preetha Rajaraman, Stephen J. Chanock, Joellen Shildkraut, Jonine L. Bernstein, Per Hoffmann, Karl-Heinz Jöckel, Rose K. Lai, Elizabeth B. Claus, Sara H. Olson, Christoffer Johansen, Margaret R. Wrensch, Beatrice Melin, Robert B. Jenkins, Marc Sanson, Melissa L. Bondy, and Richard S. Houlston</td>
<td>This study identifies new genes associated with glioma risk, increasing understanding of how these tumors develop.</td>
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**RESOURCE REPORTS**

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<td>2072</td>
<td>ACE: A Workbench Using Evolutionary Genetic Algorithms for Analyzing Association in TCGA</td>
<td>Alan R. Gilmore, Matthew Alderdice, Kieran I. Savage, Paul G. O’Reilly, Aideen C. Roddy, Philip D. Dunne, Mark Lawler, Simon S. McDade, David J. Waugh, and Danzagh G. McArt</td>
<td>ACE uses an evolutionary algorithm approach to perform large searches for associations between any combination of data in the TCGA database.</td>
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<td>2076</td>
<td>InCAR: A Comprehensive Resource for IncRNAs from Cancer Arrays</td>
<td>Yueyuan Zheng, Qingxuan Xu, Mengni Liu, Huanjing Hu, Yubin Xie, Zhixiang Zuo, and Jian Ren</td>
<td>A comprehensive resource tool of reannotated public cancer-related microarray data, provides expression profiles and prognostic landscapes of IncRNAs across thousands of samples and multiple cancer types.</td>
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<td>2084</td>
<td>Correction: Gene Regulatory Network Analysis Identifies Sex-Linked Differences in Colon Cancer Drug Metabolism</td>
<td>Camila M. Lopes-Ramos, Mariele L. Kuijier, Shuji Ogino, Charles S. Fuchs, Dawn L. DeMeo, Kimberly Glass, and John Quackenbush</td>
<td><strong>Significance:</strong> This study identifies sex-linked differences in colon cancer drug metabolism.</td>
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<td>2085</td>
<td>Retraction: Transactivation of the EGR1 Gene Contributes to Mutant p53 Gain of Function</td>
<td>Lilach Weisz, Amir Zalcenstein, Perry Stambolsky, Yehudit Cohen, Naomii Goldlinger, Monse Oren, and Varda Rotter</td>
<td><strong>Significance:</strong> This study identifies new genes associated with glioma risk, increasing understanding of how these tumors develop.</td>
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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.