

CANCER RESEARCH

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2085 Moving beyond PARP Inhibition in ATM-Deficient Prostate Cancer
Jeremy S. Setton and Simon N. Powell
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2087 Molecular Imaging of the Tumor Microenvironment Reveals the Relationship between Tumor Oxygenation, Glucose Uptake, and Glycolysis in Pancreatic Ductal Adenocarcinoma
Kazutoshi Yamamoto, Jeffrey R. Brender, Tomohiro Seki, Shun Kishimoto, Nobu Oshima, Rajani Choudhuri, Stephen S. Adler, Elaine M. Jagoda, Keita Saito, Nallathamby Devasahayam, Peter L. Choyke, James B. Mitchell, and Murali C. Krishna
Novel multimodal molecular imaging techniques reveal the potential of three interrelated imaging biomarkers to profile the tumor microenvironment and interrelationships of hypoxia, glucose uptake, and glycolysis.

2094 ATM Loss Confers Greater Sensitivity to ATR Inhibition Than PARP Inhibition in Prostate Cancer



Shahzad Rafiei, Kenyon Fitzpatrick, David Liu, Mu-Yan Cai, Haitham A. Elmarakeby, Jihye Park, Cora Ricker, Bose S. Kochupurakkal, Atish D. Choudhury, William C. Hahn, Steven P. Balk, Justin H. Hwang, Eliezer M. Van Allen, and Kent W. Mouw

ATM loss occurs in a subset of prostate tumors. This study shows that deleting ATM in prostate cancer models does not significantly increase sensitivity to PARP inhibition but does sensitize to ATR inhibition.

See related commentary, p. 2085

GENOME AND EPIGENOME

2101 Loss of Apc Rapidly Impairs DNA Methylation Programs and Cell Fate Decisions in Lgr5⁺ Intestinal Stem Cells

Marco Bruschi, Laure Garnier, Elouan Cleroux, Alicia Giordano, Michael Dumas, Anaïs F. Bardet, Thomas Kergrohen, Stanislas Quesada, Pierre Cesses, Michael Weber, François Gerbe, and Philippe Jay

This study demonstrates the functional impact of changes in DNA methylation to determine the colorectal cancer cell phenotype following loss of *Apc* function.

2114 Hispanic/Latino Patients with Gastric Adenocarcinoma Have Distinct Molecular Profiles Including a High Rate of Germline *CDH1* Variants

Sam C. Wang, Yunku Yeu, Sunita T.G. Hammer, Shu Xiao, Min Zhu, Changjin Hong, Jean R. Clemencau, Lynn Y. Yoon, Ibrahim Nassour, Jeanne Shen, Deepak Agarwal, Scott I. Reznik, John C. Mansour, Adam C. Yopp, Hao Zhu, Tae Hyun Hwang, and Matthew R. Porembka

Gastric cancer in Hispanic/Latino patients has unique genomic profiles that may contribute to the aggressive clinical phenotypes seen in these patients.

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- 2125 Peptidylarginine Deiminase IV Regulates Breast Cancer Stem Cells via a Novel Tumor Cell–Autonomous Suppressor Role**
Nellie Moshkovich, Humberto J. Ochoa, Binwu Tang, Howard H. Yang, Yuan Yang, Jing Huang, Maxwell P. Lee, and Lalage M. Wakefield
These findings demonstrate a novel activity of the citrullinating enzyme PADI4 in suppressing breast cancer stem cells through epigenetic repression of stemness master transcription factors NANOG and OCT4.

- 2138 CircFOXK2 Promotes Growth and Metastasis of Pancreatic Ductal Adenocarcinoma by Complexing with RNA-Binding Proteins and Sponging MiR-942**
Chi Hin Wong, Ut Kei Lou, Youjia Li, Stephen L. Chan, Joanna HM Tong, Ka-Fai To, and Yangchao Chen
This study reveals a prominent role for the circRNA circFOXK2 in PDAC progression, suggesting that circFOXK2 might be a novel diagnostic marker for PDAC.

METABOLISM AND CHEMICAL BIOLOGY

- 2150 GPD1 Enhances the Anticancer Effects of Metformin by Synergistically Increasing Total Cellular Glycerol-3-Phosphate**
A C Jianjiang Xie, Jianheng Ye, Zhiduan Cai, Yong Luo, Xuejin Zhu, Yulin Deng, Yuanfa Feng, Yingke Liang, Ren Liu, Zhaodong Han, Yuxiang Liang, Yu Zheng, Rujun Mo, Yangjia Zhuo, Yongding Wu, Funeng Jiang, Jianguo Zhu, Chin-Lee Wu, and Weide Zhong
GPD1 overexpression enhances the anticancer effect of metformin through synergistic inhibition of mitochondrial function, thereby providing new insight into metformin-mediated cancer therapy.

- 2163 Golgi-Localized PAQR4 Mediates Antiapoptotic Ceramidase Activity in Breast Cancer**
Line Pedersen, Pouda Panahandeh, Muntequa I. Siraji, Stian Knappskog, Per Eystein Lønning, Ruth Gordillo, Philipp E. Scherer, Anders Molven, Knut Teigen, and Nils Halberg
Induction of and cellular dependency on *de novo* sphingolipid synthesis via PAQR4 highlights a central vulnerability in breast cancer that may serve as a viable therapeutic target.

MOLECULAR CELL BIOLOGY

- 2175 Hypomethylation-Linked Activation of PLCE1 Impedes Autophagy and Promotes Tumorigenesis through MDM2-Mediated Ubiquitination and Destabilization of p53**
Yunzhao Chen, Huahua Xin, Hao Peng, Qi Shi, Menglu Li, Jie Yu, Yanxia Tian, Xueping Han, Xi Chen, Yi Zheng, Jun Li, Zhihao Yang, Lan Yang, Jianming Hu, Xuan Huang, Zheng Liu, Xiaoxi Huang, Hong Zhou, Xiaobin Cui, and Feng Li
These findings identify hypomethylation-mediated activation of PLCE1 as a potential oncogene that blocks cellular autophagy of esophageal carcinoma by facilitating the MDM2-dependent ubiquitination of p53 and subsequent degradation.

- 2190 Rapalog-Mediated Repression of Tribbles Pseudokinase 3 Regulates Pre-mRNA Splicing**
Bojana Stefanovska, Cecile Edith Vicier, Thibault Dayris, Vasily Ogryzko, Veronique Scott, Ibrahim Bouakka, Suzette Delalogue, Anna Rocca, Olivia Le Saux, Olivier Trédan, Thomas Bachelot, Fabrice André, and Olivia Fromigué
Independent of mTOR signaling, rapalogs induce cytotoxicity by dysregulating spliceosome function via repression of TRIB3, the loss of which may, in the long term, contribute to therapeutic resistance.

- 2204 USP10 Promotes Proliferation of Hepatocellular Carcinoma by Deubiquitinating and Stabilizing YAP/TAZ**
Hong Zhu, Fangjie Yan, Tao Yuan, Meijia Qian, Tianyi Zhou, Xiaoyang Dai, Ji Cao, Meidan Ying, Xiaowu Dong, Qiaojun He, and Bo Yang
These findings identify USP10 as a DUB of YAP/TAZ and its role in hepatocellular carcinoma progression, which may serve as a potential therapeutic target for hepatocellular carcinoma treatment.

- 2217 A Feedback Loop Comprising EGF/TGF α Sustains TFCP2-Mediated Breast Cancer Progression**
Yi Zhao, Neha Kaushik, Jae-Hyeok Kang, Nagendra Kumar Kaushik, Seung Han Son, Nizam Uddin, Min-Jung Kim, Chul Geun Kim, and Su-Jae Lee
TFCP2 is a new antimetastatic target that controls TNBC progression via a positive feedback loop between EGF/TGF α and the AKT signaling axis.

- 2230 PSF Promotes ER-Positive Breast Cancer Progression via Posttranscriptional Regulation of *ESR1* and *SCFD2***
Yuichi Mitobe, Kaori Iino, Ken-ichi Takayama, Kazuhiro Ikeda, Takashi Suzuki, Kenjiro Aogi, Hidetaka Kawabata, Yutaka Suzuki, Kuniko Horie-Inoue, and Satoshi Inoue
This study defines oncogenic roles of RNA-binding protein PSF, which exhibits posttranscriptional regulation in ER-positive breast cancer.

- 2243 H2A Monoubiquitination Links Glucose Availability to Epigenetic Regulation of the Endoplasmic Reticulum Stress Response and Cancer Cell Death**
Yilei Zhang, Jiejun Shi, Xiaoguang Liu, Zhenna Xiao, Guang Lei, Hyemin Lee, Pranavi Koppula, Weijie Cheng, Chao Mao, Li Zhuang, Li Ma, Wei Li, and Boyi Gan
These findings link glucose deprivation and H2A ubiquitination to regulation of the ER stress response in tumor growth and demonstrate pharmacologic susceptibility to inhibition of polycomb and glucose transporters.

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TUMOR BIOLOGY AND IMMUNOLOGY

2257 The Interplay between Slow-Cycling, Chemoresistant Cancer Cells and Fibroblasts Creates a Proinflammatory Niche for Tumor Progression

Jaebom Cho, Hyo-Jong Lee, Su Jung Hwang, Hye-Young Min, Han Na Kang, A-Young Park, Seung Yeob Hyun, Jeong Yeon Sim, Ho Jin Lee, Hyun-Ji Jang, Young-Ah Suh, Sungyoul Hong, Young Kee Shin, Hye Ryun Kim, and Ho-Young Lee
Cotargeting COX2 and Src may be an effective strategy to prevent cancer progression after chemotherapy.

2273 Long Noncoding RNA MRPL23-AS1 Promotes Adenoid Cystic Carcinoma Lung Metastasis

Chu-Wen Chen, Min Fu, Zhi-Hao Du, Fei Zhao, Wen-Wen Yang, Li-Hua Xu, Sheng-Lin Li, and Xi-Yuan Ge
This study identifies a novel metastasis-promoting lncRNA MRPL23-AS1, which mediates the transcriptional silencing of E-cadherin through forming a RNA-protein complex with EZH2.

2286 Systematic Establishment of Robustness and Standards in Patient-Derived Xenograft Experiments and Analysis

A C Yvonne A. Evrard, Anuj Srivastava, Jelena Randjelovic, The NCI PDXNet Consortium, James H. Doroshow, Dennis A. Dean II, Jeffrey S. Morris, and Jeffrey H. Chuang

The PDXNet Consortium shows that PDX drug responses and sequencing results are reproducible across diverse experimental protocols, establishing the potential for multisite preclinical studies to translate into clinical trials.

2298 Targeting Glycosylated PD-1 Induces Potent Antitumor Immunity

Linlin Sun, Chia-Wei Li, Ezra M. Chung, Riyao Yang, Yong-Soo Kim, Andrew H. Park, Yun-Ju Lai, Yi Yang, Yu-Han Wang, Jielin Liu, Yufan Qiu, Kay-Hooi Khoo, Jun Yao, Jennifer L. Hsu, Jong-Ho Cha, Li-Chuan Chan, Jung-Mao Hsu, Heng-Huan Lee, Stephen S. Yoo, and Mien-Chie Hung

These findings demonstrate that glycosylation of PD-1 is functionally significant and targeting glycosylated PD-1 may serve as a means to improve immunotherapy response.

2311 Infiltrating Mast Cell-Mediated Stimulation of Estrogen Receptor Activity in Breast Cancer Cells Promotes the Luminal Phenotype

Maria Teresa Majorini, Valeria Cancila, Alice Rigoni, Laura Botti, Matteo Dugo, Tiziana Triulzi, Loris De Cecco, Enrico Fontanella, Elena Jachetti, Elda Tagliabue, Claudia Chiodoni, Claudio Tripodo, Mario P. Colombo, and Daniele Lecis

Mast cells impact breast cancer outcome by directly affecting the phenotype of tumor cells through stimulation of the estrogen receptor pathway.

2325 RUNX1 Is a Driver of Renal Cell Carcinoma Correlating with Clinical Outcome

A C Nicholas Rooney, Susan M. Mason, Laura McDonald, J. Henry M. Däbritz, Kirsteen J. Campbell, Ann Hedley, Steven Howard, Dimitris Athineos, Colin Nixon, William Clark, Joshua D.G. Leach, Owen J. Sansom, Joanne Edwards, Ewan R. Cameron, and Karen Blyth

These data reveal a novel unexplored oncogenic role for *RUNX* genes in kidney cancer and indicate that targeting the effects of RUNX transcriptional activity could be relevant for clinical intervention in ccRCC.

TRANSLATIONAL SCIENCE

2340 FGF Trapping Inhibits Multiple Myeloma Growth through c-Myc Degradation-Induced Mitochondrial Oxidative Stress

Roberto Ronca, Gaia C. Ghedini, Federica Maccarinelli, Antonio Sacco, Silvia L. Locatelli, Eleonora Foglio, Sara Taranto, Elisabetta Grillo, Sara Matarazzo, Riccardo Castelli, Giuseppe Paganini, Vanessa Desantis, Nadia Cattane, Annamaria Cattaneo, Marco Mor, Carmelo Carlo-Stella, Angelo Belotti, Aldo M. Roccaro, Marco Presta, and Arianna Giacomini

This study provides new insights into the mechanisms by which FGF antagonists promote multiple myeloma cell death.

2355 Targeted Inhibition of the E3 Ligase SCF^{Skp2/Cks1} Has Antitumor Activity in *RB1*-Deficient Human and Mouse Small-Cell Lung Cancer

Hongling Zhao, Niloy J. Iqbal, Vineeth Sukrithan, Cari Nicholas, Yingjiao Xue, Cindy Yu, Joseph Locker, Juntao Zou, Edward L. Schwartz, and Liang Zhu

There are no effective therapies for SCLC. The identification of an actionable target downstream of *RB1*, inactivated in SCLC and other advanced tumors, could have a broad impact on its treatment.

2368 IRE1 α Disruption in Triple-Negative Breast Cancer Cooperates with Antiangiogenic Therapy by Reversing ER Stress Adaptation and Remodeling the Tumor Microenvironment

A C Jonathan M. Harnoss, Adrien Le Thomas, Mike Reichelt, Ofer Guttman, Thomas D. Wu, Scot A. Marsters, Anna Shemorry, David A. Lawrence, David Kan, Ehud Segal, Mark Merchant, Klara Totpal, Lisa M. Crocker, Kathryn Mesh, Monika Dohse, Margaret Solon, Zora Modrusan, Joachim Rudolph, Hartmut Koeppen, Peter Walter, and Avi Ashkenazi
Pharmacologic IRE1 α kinase inhibition reverses ultrastructural distension of the ER, normalizes the tumor vasculature, and remodels the cellular TME attenuating TNBC growth in mice.

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2380 BRD4 Levels Determine the Response of Human Lung Cancer Cells to BET Degraders That Potently Induce Apoptosis through Suppression of Mcl-1

Dan Zong, Jiajia Gu, Giovanna C. Cavalcante, Weilong Yao, Guojing Zhang, Shaomeng Wang, Taofeek K. Owonikoko, Xia He, and Shi-Yong Sun

The current study demonstrates the potential of novel BET degraders in the treatment of lung cancer and warrants clinical validation of BET degraders in lung cancer with high levels of BRD4.

2407 Hybrid Epithelial–Mesenchymal Phenotypes Are Controlled by Microenvironmental Factors

Gianluca Selvaggio, Sara Canato, Archana Pawar, Pedro T. Monteiro, Patrícia S. Guerreiro, M. Manuela Brás, Florence Janody, and Claudine Chaouiya

A multidisciplinary study sheds light on microenvironmental signals controlling cancer cell plasticity along EMT and suggests that hybrid and mesenchymal phenotypes arise through independent molecular paths.

CONVERGENCE AND TECHNOLOGIES

2394 Model-Based Inference and Classification of Immunologic Control Mechanisms from TKI Cessation and Dose Reduction in Patients with CML

Tom Hähnel, Christoph Baldow, Joëlle Guilhot, François Guilhot, Susanne Saussele, Satu Mustjoki, Stefanie Jilg, Philipp J. Jost, Stephanie Dulucq, François-Xavier Mahon, Ingo Roeder, Artur C. Fassoni, and Ingmar Glauche

This mathematical modeling approach provides strong evidence that different immunological configurations in patients with CML determine their response to therapy cessation and that dose reductions can help to prospectively infer different risk groups.

See **related commentary**, p. 2083

CORRECTION

2421 Correction: Hypoxia-Induced WSB1 Promotes the Metastatic Potential of Osteosarcoma Cells

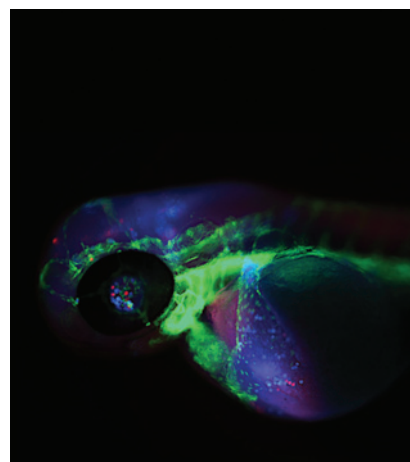
Ji Cao, Yijie Wang, Rong Dong, Guanyu Lin, Ning Zhang, Jing Wang, Nengming Lin, Yongchuan Gu, Ling Ding, Meidan Ying, Qiaojun He, and Bo Yang

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ABOUT THE COVER

The FGF system plays a pivotal role in multiple myeloma growth and dissemination. FGF antagonists promote mitochondrial oxidative stress and apoptosis in myeloma cells by inducing proteasomal degradation of the c-Myc oncoprotein. Inhibition of the FGF system prevents the homing of grafted human myeloma cells to the bone marrow-like caudal niche of zebrafish embryos. This study provides new insights into the mechanisms by which FGF antagonists promote multiple myeloma cell death. For details, see article by Ronca and colleagues on page 2340.



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