

CANCER RESEARCH

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This study presents evidence that certain presumed loss-of-function variants in a cancer-predisposition gene can retain function due to their direct impact on RNA splicing.

METABOLISM AND CHEMICAL BIOLOGY

- 1387** Inhibition of *BCL2* Family Members Increases the Efficacy of Copper Chelation in *BRAF*^{V600E}-Driven Melanoma
A C Ye-Jin Kim, Tiffany Tsang, Grace R. Anderson, Jessica M. Posimo, and Donita C. Brady
This study unveils a novel collateral drug sensitivity elicited by combining copper chelators and BH3 mimetics for treatment of *BRAF*^{V600E} mutation-positive melanoma.

- 1401** Dual Oxidase-Induced Sustained Generation of Hydrogen Peroxide Contributes to Pharmacologic Ascorbate-Induced Cytotoxicity
Adrienne R. Gibson, Brianne R. O'Leary, Juan Du, Ehab H. Sarsour, Amanda L. Kalen, Brett A. Wagner, Jeffrey M. Stolwijk, Kelly C. Falls-Hubert, Matthew S. Alexander, Rory S. Carroll, Douglas R. Spitz, Garry R. Buettner, Prabhat C. Goswami, and Joseph J. Cullen
A high dose of vitamin C, in addition to delivering an acute exposure of H₂O₂ to tumor cells, activates DUOX in pancreatic cancer cells, which provide sustained production of H₂O₂.

MOLECULAR CELL BIOLOGY

- 1414** *UBR5* Is Coamplified with *MYC* in Breast Tumors and Encodes an Ubiquitin Ligase That Limits *MYC*-Dependent Apoptosis
Xi Qiao, Ying Liu, Maria Llamazares Prada, Aravind K. Mohan, Abhishekh Gupta, Alok Jaiswal, Mukund Sharma, Joni Merisaari, Heidi M. Haikala, Kati Talvinen, Laxman Yetukuri, Joanna W. Pytvänäinen, Juha Klefström, Pauliina Kronqvist, Annika Meinander, Tero Aittokallio, Ville Hietakangas, Martin Eilers, and Jukka Westermarck
These findings identify *UBR5* as a novel *MYC* regulator, the inactivation of which could be very important for understanding of *MYC* dysregulation in cancer cells.
- 1428** Oncogenic *ERG* Represses *PI3K* Signaling through Downregulation of *IRS2*
A C Ninghui Mao, Dong Gao, Wenhao Hu, Sunyana Gadal, Haley Hieronymus, Shangqian Wang, Young Sun Lee, Patrick Sullivan, Zeda Zhang, Danielle Choi, Neal Rosen, Charles L. Sawyers, Anuradha Gopalan, Yu Chen, and Brett S. Carver
This work provides insight on how initiating oncogenic events may directly influence the selection of secondary concomitant alterations to promote tumorigenesis.
- 1438** Enhanced Lipid Accumulation and Metabolism Are Required for the Differentiation and Activation of Tumor-Associated Macrophages
Pan Su, Qiang Wang, Enguang Bi, Xingzhe Ma, Lintao Liu, Maojie Yang, Jianfei Qian, and Qing Yi
This study highlights the role of lipid metabolism in the differentiation and function of TAMs and suggests targeting TAM fatty acid oxidation as a potential therapeutic modality for human cancers.

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TUMOR BIOLOGY AND IMMUNOLOGY

1451 ***In Silico* Models Accurately Predict *In Vivo* Response for IL6 Blockade in Head and Neck Cancer**

Fereshteh Nazari, Alexandra E. Oklejas, Jacques E. Nör, Alexander T. Pearson, and Trachette L. Jackson

A mathematical model is used to rapidly evaluate dosing strategies for IL6 pathway modulation. These results may lead to nonintuitive dosing or timing treatment schedules to optimize synergism between drugs.

1461 **Cancer Cell-Derived Matrisome Proteins Promote Metastasis in Pancreatic Ductal Adenocarcinoma**

Chenxi Tian, Daniel Öhlund, Steffen Rickelt, Tommy Lidström, Ying Huang, Liangliang Hao, Renee T. Zhao, Oskar Franklin, Sangeeta N. Bhatia, David A. Tuveson, and Richard O. Hynes

This study provides insights into the biological roles of cancer cell-derived matrisome proteins in PDAC and supports the notion that these proteins are protumorigenic and better therapeutic targets.

1475 **Proteomic Profiling of the ECM of Xenograft Breast Cancer Metastases in Different Organs Reveals Distinct Metastatic Niches**

Jess D. Hebert, Samuel A. Myers, Alexandra Naba, Genevieve Abbruzzese, John M. Lamar, Steven A. Carr, and Richard O. Hynes

Tumor and stromal cells together create distinct ECM niches in breast cancer metastases to various tissues, providing new insight into how tumor cells adapt to survive in different tissue environments.

1486 **Truncated ASPP2 Drives Initiation and Progression of Invasive Lobular Carcinoma via Distinct Mechanisms**

Koen Schipper, Anne Paulien Drenth, Eline van der Burg, Samuel Cornelissen, Sjoerd Klarenbeek, Micha Nethe, and Jos Jonkers

Truncated ASPP2 cooperates with E-cadherin and PTEN loss to drive breast cancer initiation and progression via two distinct mechanisms. ASPP2-induced actomyosin relaxation drives tumor initiation, while ASPP2-mediated YAP activation enhances tumor progression.

TRANSLATIONAL SCIENCE

1498 **Clonal ZEB1-Driven Mesenchymal Transition Promotes Targetable Oncologic Antiangiogenic Therapy Resistance**

Ankush Chandra, Arman Jahangiri, William Chen, Alan T. Nguyen, Garima Yagnik, Matheus P. Pereira, Saket Jain, Joseph H. Garcia, Sumedh S. Shah, Harsh Wadhwa, Rushikesh S. Joshi, Jacob Weiss, Kayla J. Wolf, Jung-Ming G. Lin, Sören Müller, Jonathan W. Rick, Aaron A. Diaz, Luke A. Gilbert, Sanjay Kumar, and Manish K. Aghi

Bevacizumab resistance in GBM is associated with mesenchymal/glycolytic shifts involving YKL-40 and ZEB1. Targeting ZEB1 reduces bevacizumab-resistant GBM phenotypes.

1512 **Extensive Clonal Branching Shapes the Evolutionary History of High-Risk Pediatric Cancers**

Natalie Andersson, Bjorn Bakker, Jenny Karlsson, Anders Valind, Linda Holmquist Mengelbier, Diana C.J. Spierings, Floris Fojer, and David Gisselsson

Different pediatric cancers with a high risk of relapse share a common generic pattern of extensively branching evolution of somatic mutations.

1524 **An ABC Transporter Drives Medulloblastoma Pathogenesis by Regulating Sonic Hedgehog Signaling**

Juwina Wijaya, BaoHan T. Vo, Jingjing Liu, Beisi Xu, Gang Wu, Yao Wang, Junmin Peng, Jin Zhang, Laura J. Janke, Brent A. Orr, Jiyang Yu, Martine F. Roussel, and John D. Schuetz

These findings identify ABCC4 transporter as a new target in SHH-MB, prompting the development of inhibitors or the repurposing of existing drugs to target ABCC4.

1538 **Thermal Proteome Profiling Identifies Oxidative-Dependent Inhibition of the Transcription of Major Oncogenes as a New Therapeutic Mechanism for Select Anticancer Compounds**

Sylvain Peugeot, Jiawei Zhu, Gema Sanz, Madhurendra Singh, Massimiliano Gaetani, Xinsong Chen, Yao Shi, Amir Ata Saei, Torkild Visnes, Mikael S. Lindström, Ali Rihani, Lidia Moyano-Galceran, Joseph W. Carlson, Elisabet Hjerpe, Ulrika Joneborg, Kaisa Lehti, Johan Hartman, Thomas Helleday, Roman Zubarev, and Galina Selivanova

These findings highlight agents that target transcriptional addiction in cancer cells and suggest combination treatments that target RNA processing and DNA repair pathways simultaneously as effective cancer therapies.

1551 **Single-Cell Proteomic Profiling Identifies Combined AXL and JAK1 Inhibition as a Novel Therapeutic Strategy for Lung Cancer**

Josephine A. Taverna, Chia-Nung Hung, Daniel T. DeArmond, Meizhen Chen, Chun-Lin Lin, Pawel A. Osmulski, Maria E. Gaczynska, Chiou-Miin Wang, Nicholas D. Lucio, Chih-Wei Chou, Chun-Liang Chen, Alia Nazarullah, Shellye R. Lampkin, Lianqun Qiu, David J. Bearss, Steven Warner, Clifford J. Whatcott, Lars Mouritsen, Mark Wade, Steven Weitman, Ruben A. Mesa, Nameer B. Kirma, Wei-Ting Chao, and Tim H.-M. Huang

Single-cell proteomic profiling of clinical samples may facilitate the optimal selection of novel drug targets, interpretation of early-phase clinical trial data, and development of predictive biomarkers valuable for patient stratification.

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CONVERGENCE AND TECHNOLOGIES

- 1564 Modeling Acquired Resistance to the Second-Generation Androgen Receptor Antagonist Enzalutamide in the TRAMP Model of Prostate Cancer**
Marianna Cerasuolo, Federica Maccarinelli, Daniela Coltrini, Ali Mokhtar Mahmoud, Viviana Marolda, Gaia Cristina Ghedini, Sara Rezzola, Arianna Giacomini, Luca Triggiani, Magdalena Kostrzewa, Roberta Verde, Debora Paris, Dominique Melck, Marco Presta, Alessia Ligresti, and Roberto Ronca
Merging mathematical modeling with experimental data, this study presents the "TRAMP-based platform" as a novel experimental tool to study the *in vitro* and *in vivo* evolution of prostate cancer resistance to enzalutamide.

- 1578 Towards Multidrug Adaptive Therapy**
Jeffrey West, Li You, Jingsong Zhang, Robert A. Gatenby, Joel S. Brown, Paul K. Newton, and Alexander R.A. Anderson
Driving tumor evolution into periodic, repeatable treatment cycles provides a path forward for multidrug adaptive therapy.

POPULATION AND PREVENTION SCIENCE

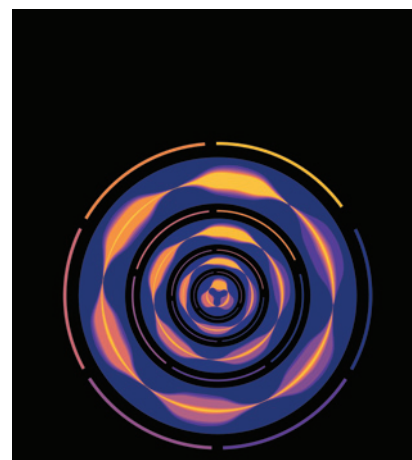
- 1590 Heritability of Mammographic Breast Density, Density Change, Microcalcifications, and Masses**
Natalie Holowko, Mikael Eriksson, Ralf Kuja-Halkola, Shadi Azam, Wei He, Per Hall, and Kamila Czene
These findings provide novel data on the heritability of microcalcifications, masses, and density change, which are all associated with breast cancer risk that can indicate women at short-term risk.

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ABOUT THE COVER

Colored arcs indicate concomitant delivery of multiple targeted treatments. Subclonal evolution begins at the top, evolving clockwise in a circular Muller diagram with treatment and subsequent resistant subclonal expansion. This circular design illustrates a potential path forward to multidrug adaptive therapy, driving tumor evolution into periodic, repeatable treatment "cycles." A cycle (defined as a treatment regimen that steers the tumor to return to initial tumor composition) can be repeated *ad infinitum* to steer and trap tumor evolution in periodic (and controllable) dynamics. Concentric circular evolutionary diagrams represent individual patients with varied treatments available. For details, see article by West and colleagues on page 1578.



- 1601 Across-Site Differences in the Mechanism of Alcohol-Induced Digestive Tract Carcinogenesis: An Evaluation by Mediation Analysis**
Yuriko N. Koyanagi, Etsuji Suzuki, Issei Imoto, Yumiko Kasugai, Isao Oze, Tomotaka Ugai, Madoka Iwase, Yoshiaki Usui, Yukino Kawakatsu, Michi Sawabe, Yutaka Hirayama, Tsutomu Tanaka, Tetsuya Abe, Seiji Ito, Koji Komori, Nobuhiro Hanai, Masahiro Tajika, Yasuhiro Shimizu, Yasumasa Niwa, Hidemi Ito, and Keitaro Matsuo
These findings support that genetic alcohol avoidance is a factor against alcohol-induced cancers.

EDITOR'S NOTE

- 1611 Editor's Note: p73 and p63 Sustain Cellular Growth by Transcriptional Activation of Cell Cycle Progression Genes**
Konstantinos Lefkimmatis, Mariano Francesco Caratozzolo, Paola Merlo, Anna Maria D'Erchia, Beatriz Navarro, Massimo Levrero, Elisabetta Sbisa', and Apollonia Tullo