

## CANCER RESEARCH

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## CANCER RESEARCH HIGHLIGHTS

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## GENOME AND EPIGENOME

**4046** **Y Chromosome lncRNA Are Involved in Radiation Response of Male Non-Small Cell Lung Cancer Cells**

**AC** Tayvia Brownmiller, Jamie A. Juric, Abby D. Ivey, Brandon M. Harvey, Emily S. Westemeier, Michael T. Winters, Alyson M. Stevens, Alana N. Stanley, Karen E. Hayes, Samuel A. Sprowls, Amanda S. Gatesman Ammer, Mackenzie Walker, Erik A. Bey, Xiaoliang Wu, Zuan-Fu Lim, Lin Zhu, Sijin Wen, Gangqing Hu, Patrick C. Ma, and Ivan Martinez

This study describes previously unknown Y chromosome-expressed lncRNA regulators of radiation response in male NSCLC and show a correlation between loss of chromosome Y and radioresistance.

**4058** **CXCR4 in Tumor Epithelial Cells Mediates Desmoplastic Reaction in Pancreatic Ductal Adenocarcinoma**

Toshihiro Morita, Yuzo Kodama, Masahiro Shiokawa, Katsutoshi Kuriyama, Saiko Marui, Takeshi Kuwada, Yuko Sogabe, Tomoaki Matsumori, Nobuyuki Kakiuchi, Teruko Tomono, Atsushi Mima, Tatsuki Ueda, Motoyuki Tsuda, Yuki Yamauchi, Yoshihiro Nishikawa, Yojiro Sakuma, Yuji Ota, Takahisa Maruno, Norimitsu Uza, Takashi Nagasawa, Tsutomu Chiba, and Hiroshi Seno

The current study uncovers CXCR4 as a key regulator of desmoplastic reaction in PDAC and opens the way for new therapeutic approaches to overcome the chemoresistance in patients with PDAC.

## METABOLISM AND CHEMICAL BIOLOGY

**4071** **Aquaporin-7 Regulates the Response to Cellular Stress in Breast Cancer**

Chen Dai, Verodia Charlestin, Man Wang, Zachary T. Walker, Maria Cristina Miranda-Vergara, Beth A. Facchine, Junmin Wu, William J. Kaliney, Norman J. Dovichi, Jun Li, and Laurie E. Littlepage

Aquaporin-7 is identified as a critical regulator of nutrient availability and signaling that responds to cellular stresses, making it an attractive therapeutic target in breast cancer.

**4087** **Pyrvinium Pamoate Induces Death of Triple-Negative Breast Cancer Stem-Like Cells and Reduces Metastases through Effects on Lipid Anabolism**

**AC** Rosanna Dattilo, Carla Mottini, Emanuela Camera, Alessia Lamolinara, Noam Auslander, Ginevra Doglioni, Michela Muscolini, Wei Tang, Melanie Planque, Cristiana Ercolani, Simonetta Buglioni, Isabella Manni, Daniela Trisciuglio, Alessandra Boe, Sveva Grande, Anna Maria Luciani, Manuela Iezzi, Gennaro Ciliberto, Stefan Ambs, Ruggero De Maria, Sarah-Maria Fendt, Eytan Ruppim, and Luca Cardone

These findings provide preclinical evidence that a drug repurposing approach to prevent metastatic disease in TNBC exploits lipid anabolism as a metabolic vulnerability against CSCs in primary tumors.

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## MOLECULAR CELL BIOLOGY

**4103**     **Soft Microenvironments Induce Chemoresistance by Increasing Autophagy Downstream of Integrin-Linked Kinase**

Alişya A. Anlaş and Celeste M. Nelson

These findings characterize the persistence of dormant cells at metastatic sites, where soft microenvironments downregulate estrogen receptor expression and upregulate autophagy, thereby promoting therapy resistance in breast cancer cells.

**4114**     **Circadian Rhythm Is Disrupted by ZNF704 in Breast Carcinogenesis**

**A C**

Chao Yang, Jiajing Wu, Xinhua Liu, Yue Wang, Beibei Liu, Xing Chen, Xiaodi Wu, Dong Yan, Lulu Han, Shumeng Liu, Lin Shan, and Yongfeng Shang

This study indicates that ZNF704 could be a potential oncogenic factor, disrupting circadian rhythm of breast cancer cells and contributing to breast carcinogenesis.

## TUMOR BIOLOGY AND IMMUNOLOGY

**4129**     **Intratumoral Copper Modulates PD-L1 Expression and Influences Tumor Immune Evasion**

Florida Voli, Emanuele Valli, Luigi Lerra, Kathleen Kimpton, Federica Saletta, Federico M. Giorgi, Daniele Mercatelli, Jourdin R.C. Rouaen, Sylvie Shen, Jayne E. Murray, Aria Ahmed-Cox, Giuseppe Cirillo, Chelsea Mayoh, Paul A. Beavis, Michelle Haber, Joseph A. Trapani, Maria Kavallaris, and Orazio Vittorio

These findings characterize the role of copper in modulating PD-L1 expression and contributing to cancer immune evasion, highlighting the potential for repurposing copper chelators as enhancers of antitumor immunity.

**4145**     **A Division of Labor between YAP and TAZ in Non-Small Cell Lung Cancer**

Michal Shreberk-Shaked, Bareket Dassa, Sanju Sinha, Silvia Di Agostino, Ido Azuri, Saptaparna Mukherjee, Yael Aylon, Giovanni Blandino, Eytan Ruppman, and Moshe Oren

These findings show that oncogenic paralogs YAP and TAZ have distinct roles in NSCLC and are associated with differential response to anticancer drugs, knowledge that may assist lung cancer therapy decisions.

**4158**     **ARC Is a Critical Protector against Inflammatory Bowel Disease (IBD) and IBD-Associated Colorectal Tumorigenesis**

Qiushi Wang, Tianshun Zhang, Xiaoyu Chang, Do Young Lim, Keke Wang, Ruihua Bai, Ting Wang, Joohyun Ryu, Hanyong Chen, Ke Yao, Wei-Ya Ma, Lisa A. Boardman, Ann M. Bode, and Zigang Dong

This study uncovers a crucial role of ARC in the immune system and IBD, giving rise to a novel strategy for IBD and IBD-associated colon cancer therapy.

**4172**     **Ablation of the Brca1-Palb2 Interaction Phenocopies Fanconi Anemia in Mice**

Dongju Park, Stephen M. Bergin, Dan Jones, Peng Ru, Christopher S. Koivisto, Young-Jun Jeon, Gina M. Sizemore, Raleigh D. Kladney, Ashley Hadjis, Reena Shakya, and Thomas Ludwig

A new Brca1 mouse model for Fanconi anemia (FA) complementation group S provides a system in which to study phenotypes observed in human FA patients including bone marrow failure.

See related commentary, p. 4044

**4185**     **Cancer Cell CD44 Mediates Macrophage/Monocyte-Driven Regulation of Head and Neck Cancer Stem Cells**

Karina E. Gomez, FangLong Wu, Stephen B. Keysar, J. Jason Morton, Bettina Miller, Tugs-Saikhan Chimed, Phuong N. Le, Cera Nieto, Farshad N. Chowdhury, Anit Tyagi, Traci R. Lyons, Christian D. Young, Hongmei Zhou, Hilary L. Somerset, Xiao-Jing Wang, and Antonio Jimeno

These findings establish a mechanistic link between tumor cell CD44, TAM, and CSC properties at the tumor-stroma interface that can serve as a vital area of focus for target and drug discovery.

**4199**     **Metastasis-Associated Protein 2 Represses NF- $\kappa$ B to Reduce Lung Tumor Growth and Inflammation**

Nefertiti El-Nikhely, Annika Karger, Poonam Sarode, Indrabahadur Singh, Andreas Weigert, Astrid Wietelmann, Thorsten Stiewe, Reinhard Dammann, Ludger Fink, Friedrich Grimminger, Guillermo Barreto, Werner Seeger, Soni S. Pullamsetti, Ulf R. Rapp, and Rajkumar Savai

These findings strongly suggest a prominent role of MTA2 in primary tumor growth, lung metastasis, and NF- $\kappa$ B signaling modulatory functions.

**4212**     **SUMOylation of E2F1 Regulates Expression of EZH2**

Li Du, Marwan G. Fakhri, Steven T. Rosen, and Yuan Chen

These findings provide important biological insights into the mechanism of EZH2 overexpression in cancers and suggest that inhibiting SUMOylation may improve current cancer therapeutic approaches.

## TRANSLATIONAL SCIENCE

**4224**     **Endothelin-1-Mediated Drug Resistance in EGFR-Mutant Non-Small Cell Lung Carcinoma**

Inés Pulido, Stephen Ollosi, Salvador Aparisi, Jeffrey H. Becker, Alicia Aliena-Valero, Marta Benet, María L. Rodríguez, Adrián López, Eva Tamayo-Torres, Lourdes Chuliá-Peris, Juan Carlos García-Cañaveras, Margaret Soucheray, Annika V. Dalheim, Juan B. Salom, Wei Qiu, Simon Kaja, Javier Alcácer Fernández-Coronado, Sandra Alandes, Javier Alcácer, Fátima Al-Shahrour, Jeffrey A. Borgia, Oscar Juan, Michael I. Nishimura, Agustín Lahoz, Julián Carretero, and Takeshi Shimamura

EDNR antagonists can be repurposed to improve drug delivery in VEGFA-secreting tumors, which normally respond to TKI treatment by secreting EDN1, promoting vasoconstriction, and limiting blood and drug delivery.

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- 4233** **Leveraging Systematic Functional Analysis to Benchmark an *In Silico* Framework Distinguishes Driver from Passenger MEK Mutants in Cancer**  
Aphrothiti J. Hanrahan, Brooke E. Sylvester, Matthew T. Chang, Arijh Elzein, Jianjiong Gao, Weiwei Han, Ye Liu, Dong Xu, Sizhi P. Gao, Alexander N. Gorelick, Alexis M. Jones, Amber J. Kiliti, Moriah H. Nissan, Clare A. Nimura, Abigail N. Potesman, Zhan Yao, Yijun Gao, Wenhao Hu, Hannah C. Wise, Elena I. Gavrila, Alexander N. Shoushtari, Shakuntala Tiwari, Agnes Viale, Omar Abdel-Wahab, Taha Merghoub, Michael F. Berger, Neal Rosen, Barry S. Taylor, and David B. Solit  
Leveraging prospective functional characterization of MEK1/2 mutants, it was found that hotspot analysis, molecular dynamics simulation, and sequence paralogy are complementary tools that can robustly prioritize variants for biologic, therapeutic, and clinical validation.  
**See related commentary, p. 4042**
- 4244** **High PD-1/PD-L1 Checkpoint Interaction Infers Tumor Selection and Therapeutic Sensitivity to Anti-PD-1/PD-L1 Treatment**  
**AC** Lissete Sánchez-Magraner, James Miles, Claire L. Baker, Christopher J. Applebee, Dae-Jin Lee, Somaia Elsheikh, Shaimaa Lashin, Katriona Withers, Andrew G. Watts, Richard Parry, Christine Edmead, Jose Ignacio Lopez, Raj Mehta, Antoine Italiano, Stephen G. Ward, Peter J. Parker, and Banafshé Larijani  
Quantitation of immune checkpoint interaction by direct imaging demonstrates that immunotherapy-treated patients with metastatic NSCLC with a low extent of PD-1/PD-L1 interaction show significantly worse outcome.
- 4258** **Structural Optimization and Enhanced Prodrug-Mediated Delivery Overcomes Camptothecin Resistance in High-Risk Solid Tumors**  
Ferro Nguyen, Peng Guan, David T. Guerrero, Venkatadri Kolla, Koumudi Naraparaju, Lauren M. Perry, Danielle Soberman, Benjamin B. Pressly, Ivan S. Alferiev, Michael Chorny, and Garrett M. Brodeur  
SN22 is an effective and curative multivalent macromolecular agent in multiple solid tumor mouse models, overcoming common mechanisms of drug resistance with the potential to elicit fewer toxicities than most cancer therapeutics.
- 4266** **Extracellular Vesicle-Derived miR-124 Resolves Radiation-Induced Brain Injury**  
Ron J. Leavitt, Munjal M. Acharya, Janet E. Baulch, and Charles L. Limoli  
Radiation-induced neurocognitive decrements in immunocompetent mice can be resolved by systemic delivery of hNSC-derived EVs involving a mechanism dependent on expression of miR-124.
- 4278** **A Proof of Concept for Biomarker-Guided Targeted Therapy against Ovarian Cancer Based on Patient-Derived Tumor Xenografts**  
Adam C. Palmer, Deborah Plana, Hui Gao, Joshua M. Korn, Guizhi Yang, John Green, Xiamei Zhang, Roberto Velazquez, Margaret E. McLaughlin, David A. Ruddy, Colleen Kowal, Julie Muszynski, Caroline Bullock, Stacy Rivera, Daniel P. Rakiec, GiNell Elliott, Paul Fordjour, Ronald Meyer, Alice Loo, Esther Kurth, Jeffrey A. Engelman, Hans Bitter, William R. Sellers, Juliet A. Williams, and Peter K. Sorger  
This study exploits a panel of patient-derived xenografts to demonstrate that most ovarian tumors can be matched to effective biomarker-guided treatments.

## CONVERGENCE AND TECHNOLOGIES

- 4288** **A Tissue-Engineered 3D Microvessel Model Reveals the Dynamics of Mosaic Vessel Formation in Breast Cancer**  
Vanesa L. Silvestri, Elodie Henriot, Raleigh M. Linville, Andrew D. Wong, Peter C. Searson, and Andrew J. Ewald  
A tissue-engineered microdevice that recapitulates the tumor-vascular microenvironment enables real-time imaging of the cellular mechanisms of mosaic vessel formation and vascular defect generation.

## CORRECTION

- 4302** **Correction: ARID1A Hypermethylation Disrupts Transcriptional Homeostasis to Promote Squamous Cell Carcinoma Progression**  
Qingyu Luo, Xiaowei Wu, Wan Chang, Pengfei Zhao, Xiaolin Zhu, Hongyan Chen, Yabing Nan, Aiping Luo, Xuantong Zhou, Dan Su, Wenjie Jiao, and Zhihua Liu

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## ABOUT THE COVER

Tumor vessels exhibit a wide range of structural and functional defects, which can influence the mechanism by which tumor cells enter the circulation. Due to the challenges associated with observing the dynamics of tumor-vessel interactions deep within tumors in real-time, Silvestri and colleagues developed a 3D tissue-engineered model where primary mammary tumor organoids are cocultured with a functional microvessel. Using fluorescence imaging, it was found that tumor organoids most frequently integrate within the endothelium through gaps in the basement membrane exposing tumor cells to microvessel flow. Other types of interactions observed were vessel constriction and vessel displacement. For details, see article by Silvestri and colleagues on page 4288.

