

BREAKING INSIGHTS

- 4555** Highlights from Recent Cancer Literature

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- 4557** **The Tumor Microenvironment Innately Modulates Cancer Progression**
Dominique C. Hinshaw and Lalita A. Shevde
- 4567** **Chemotherapy-Induced Metastasis: Molecular Mechanisms, Clinical Manifestations, Therapeutic Interventions**
George S. Karagiannis, John S. Condeelis, and Maja H. Oktay

CANCER RESEARCH HIGHLIGHTS

- 4577** **Monitoring Oxygenation Levels Deep in the Tumor Core: Noninvasive Imaging of Hypoxia, Now in Real-Time 3D**
Alexander L. Klibanov and Song Hu
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- 4580** **Unsuspected Protumorigenic Signaling Role for the Oncometabolite GABA in Advanced Prostate Cancer**
Renea A. Taylor and Matthew J. Watt
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CONTROVERSY AND CONSENSUS

- 4582** **Studying Cancer Evolution and Therapeutic Responses in Different Organs: The Pros and Cons of a Broad Focus**
Catherine Pham-Danis and James DeGregori

PRIORITY REPORT

- 4585** **Selective Targeting of Myoblast Fusogenic Signaling and Differentiation-Arrest Antagonizes Rhabdomyosarcoma Cells**
Valerie A. Granados, Usha Avimeni-Vadlamudi, Pooja Dalal, Samuel R. Scarborough, Kathleen A. Galindo, Priya Mahajan, and Rene L. Galindo
Significance: EGFR and its downstream signaling mediator AKT1 play a role in the fusion and differentiation processes of rhabdomyosarcoma cells, representing a therapeutic vulnerability of rhabdomyosarcoma.

GENOME AND EPIGENOME

- 4592** **Analysis of Over 140,000 European Descendants Identifies Genetically Predicted Blood Protein Biomarkers Associated with Prostate Cancer Risk**
Lang Wu, Xiang Shu, Jiandong Bao, Xingyi Guo; the PRACTICAL, CRUK, BPC3, CAPS, PEGASUS Consortia, Zsofia Kote-Jarai, Christopher A. Haiman, Rosalind A. Eeles, and Wei Zheng
Significance: Integration of genomics and proteomics data identifies biomarkers associated with prostate cancer risk.
- 4599** **Chemotherapy-Induced Distal Enhancers Drive Transcriptional Programs to Maintain the Chemoresistant State in Ovarian Cancer**
Stephen Shang, Jiekun Yang, Amir A. Jazaeri, Alexander James Duval, Turan Tufan, Natasha Lopes Fischer, Mouadh Benamar, Fadila Guessous, Inyoung Lee, Robert M. Campbell, Philip J. Ebert, Tarek Abbas, Charles N. Landen, Analisa Difeo, Peter C. Scacheri, and Mazhar Adli
Significance: Integrative genome-wide epigenomic and transcriptomic analyses of platinum-sensitive and -resistant ovarian lines identify key distal regulatory regions and associated master regulator transcription factors that can be targeted by small-molecule epigenetic inhibitors.
- 4612** **Long Noncoding RNA FAM225A Promotes Nasopharyngeal Carcinoma Tumorigenesis and Metastasis by Acting as ceRNA to Sponge miR-590-3p/miR-1275 and Upregulate ITGB3**
Zi-Qi Zheng, Zhi-Xuan Li, Guan-Qun Zhou, Li Lin, Lu-Lu Zhang, Jia-Wei Lv, Xiao-Dan Huang, Rui-Qi Liu, FoPing Chen, Xiao-Jun He, Jia Kou, Jian Zhang, Xin Wen, Ying-Qin Li, Jun Ma, Na Liu, and Ying Sun
Significance: These findings demonstrate the clinical significance of the lncRNA FAM225A in nasopharyngeal carcinoma (NPC) and the regulatory mechanism involved in NPC development and progression, providing a novel prognostic indicator and promising therapeutic target.

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METABOLISM AND CHEMICAL BIOLOGY

- 4627** Radiolabeled Oligonucleotides Targeting the RNA Subunit of Telomerase Inhibit Telomerase and Induce DNA Damage in Telomerase-Positive Cancer Cells



Mark R. Jackson, Bas M. Bavelaar, Philip A. Waghorn, Martin R. Gill, Afaf H. El-Sagheer, Tom Brown, Madalena Tarsounas, and Katherine A. Vallis

Significance: These findings present a novel radiolabeled oligonucleotide for targeting telomerase-positive cancer cells that exhibits dual activity by simultaneously inhibiting telomerase and promoting radiation-induced genomic DNA damage.

- 4638** Glutamate Decarboxylase 65 Signals through the Androgen Receptor to Promote Castration Resistance in Prostate Cancer

Yi Gao, Lu Chen, ZunGuo Du, WenChao Gao, ZhengMing Wu, XiuJuan Liu, Hai Huang, DanFeng Xu, and QingQuan Li

See related commentary, p. 4580

Significance: This study reports metabolic alterations that could be responsible for the development of CRPC and identifies the GABA-producing enzyme GAD65 as a potential new therapeutic target.

MOLECULAR CELL BIOLOGY

- 4650** Cell-Cycle-Dependent Phosphorylation of PRPS1 Fuels Nucleotide Synthesis and Promotes Tumorigenesis

Xiaoqian Jing, Xiong-jun Wang, Tao Zhang, Wencheng Zhu, Yi Fang, Haoxuan Wu, Xinyu Liu, Ding Ma, Xiaopin Ji, Yimei Jiang, Kun Liu, Xianze Chen, Yi Shi, Yaqi Zhang, Minmin Shi, Weihua Qiu, and Ren Zhao

Significance: These findings show that the enzymatic activity of PRPS1 is crucial for cell-cycle regulation and suggest PRPS1 phosphorylation at S103 as a direct therapeutic target and diagnostic biomarker for colorectal cancer.

- 4665** Targeting Mechanoresponsive Proteins in Pancreatic Cancer: 4-Hydroxyacetophenone Blocks Dissemination and Invasion by Activating MYH14

Alexandra Surcel, Eric S. Schifffhauer, Dustin G. Thomas, Qingfeng Zhu, Kathleen T. DiNapoli, Maik Herbig, Oliver Otto, Hoku West-Foyle, Angela Jacobi, Martin Kräter, Katarzyna Plak, Jochen Guck, Elizabeth M. Jaffee, Pablo A. Iglesias, Robert A. Anders, and Douglas N. Robinson

Significance: This study demonstrates that mechanoresponsive proteins become upregulated with pancreatic cancer progression and that this system of proteins can be pharmacologically targeted to inhibit the metastatic potential of pancreatic cancer cells.

- 4679** IL6 Promotes a STAT3-PRL3 Feedforward Loop via SHP2 Repression in Multiple Myeloma
Phyllis S.Y. Chong, Jianbiao Zhou, Julia S.L. Lim, Yan Ting Hee, Jing-Yuan Chooi, Tae-Hoon Chung, Zea Tuan Tan, Qi Zeng, Daniel D. Waller, Michael Sebag, and Wee-Joo Chng

Significance: IL6 promotes STAT3-dependent transcriptional upregulation of PRL-3, which in turn rephosphorylates STAT3 and aberrantly activates STAT3 target genes, leading to bortezomib resistance in multiple myeloma.

- 4689** Metastasis Suppressors NME1 and NME2 Promote Dynamin 2 Oligomerization and Regulate Tumor Cell Endocytosis, Motility, and Metastasis

Imran Khan, Brunilde Gril, and Patricia S. Steeg

Significance: NME1 suppresses metastasis via changes in tumor endocytosis and motility, mediated by dynamin (DNM2) GTPase activity.

- 4703** Gene Editing of $\alpha 6$ Integrin Inhibits Muscle Invasive Networks and Increases Cell-Cell Biophysical Properties in Prostate Cancer

Cynthia S. Rubenstein, Jaime M.C. Gard, Mengdie Wang, Julie E. McGrath, Nadia Ingabire, James P. Hinton, Kendra D. Marr, Skyler J. Simpson, Raymond B. Nagle, Cindy K. Miranti, Noel A. Warfel, Joe G.N. Garcia, Hina Arif-Tiwari, and Anne E. Cress

Significance: This study shows an innovative strategy to block prostate cancer metastasis and invasion in the muscle through gene editing of a specific $\alpha 6$ integrin extracellular region.

TUMOR BIOLOGY AND IMMUNOLOGY

- 4715** Melanoma Extracellular Vesicles Generate Immunosuppressive Myeloid Cells by Upregulating PD-L1 via TLR4 Signaling

Viktor Fleming, Xiaoying Hu, Céline Weller, Rebekka Weber, Christopher Groth, Zeno Riester, Laura Hüser, Qian Sun, Vasyil Nagibin, Carsten Kirschning, Vincenzo Bronte, Jochen Utikal, Peter Altevogt, and Viktor Umansky

Significance: These findings validate the importance of TLR4 signaling in reprogramming normal myeloid cells into functional myeloid-derived suppressor cells.

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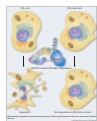
4729 SET Domain–Containing Protein 4 Epigenetically Controls Breast Cancer Stem Cell Quiescence

Sen Ye, Yan-Fu Ding, Wen-Huan Jia, Xiao-Li Liu, Jing-Yi Feng, Qian Zhu, Sun-Li Cai, Yao-Shun Yang, Qian-Yun Lu, Xue-Ting Huang, Jin-Shu Yang, Sheng-Nan Jia, Guo-Ping Ding, Yue-Hong Wang, Jiao-Jiao Zhou, Yi-Ding Chen, and Wei-Jun Yang

Significance: These findings advance our knowledge on the epigenetic determinants of quiescence in cancer stem cell populations and pave the way for future pharmacologic developments aimed at targeting drug-resistant quiescent stem cells.

TRANSLATIONAL SCIENCE

4744 Targeting BCR-ABL1 in Chronic Myeloid Leukemia by PROTAC-Mediated Targeted Protein Degradation



George M. Burslem, Anna Reister Schultz, Daniel P. Bondeson, Christopher A. Eide, Samantha L. Savage Stevens, Brian J. Druker, and Craig M. Crews

Significance: Small-molecule–induced degradation of BCR-ABL1 in CML provides an advantage over inhibition and provides insights into CML stem cell biology.

4754 Therapeutic Targeting of Aldolase A Interactions Inhibits Lung Cancer Metastasis and Prolongs Survival

Yu-Chan Chang, Jean Chiou, Yi-Fang Yang, Chia-Yi Su, Yuan-Feng Lin, Chia-Ning Yang, Pei-Jung Lu, Ming-Shyan Huang, Chih-Jen Yang, and Michael Hsiao

Significance: This study demonstrates the role of aldolase A and its interaction with γ -actin in the metastasis of non–small cell lung cancer and that blocking this interaction could be an effective cancer treatment.

CONVERGENCE AND TECHNOLOGIES

4767 Volumetric Optoacoustic Imaging Unveils High-Resolution Patterns of Acute and Cyclic Hypoxia in a Murine Model of Breast Cancer



Avihai Ron, Xosé Luís Deán-Ben, Sven Gottschalk, and Daniel Razansky

See related commentary, p. 4577

Significance: vMSOT provides quantitative measures of volumetric hypoxic fraction and cyclic hypoxia in a label-free and noninvasive manner, providing new readouts to aid tumor staging and treatment decisions.

4776 Time-Resolved MRI Assessment of Convection-Enhanced Delivery by Targeted and Nontargeted Nanoparticles in a Human Glioblastoma Mouse Model

Zachary R. Stephen, Peter A. Chiarelli, Richard A. Revia, Kui Wang, Forrest Kievit, Chris Dayringer, Mike Jeon, Richard Ellenbogen, and Miqin Zhang

Significance: MRI is used to monitor convection-enhanced delivery in real time using a nanoparticle-based contrast agent, and glioma-specific targeting significantly improves the volume of distribution in tumors.

4787 A Near-Infrared Phosphorescent Nanoprobe Enables Quantitative, Longitudinal Imaging of Tumor Hypoxia Dynamics during Radiotherapy

Xianchuang Zheng, Liyang Cui, Min Chen, Luis A. Soto, Edward E. Graves, and Jianghong Rao

Significance: This study presents a novel nanoagent for the visualization and quantification of tumor hypoxia.

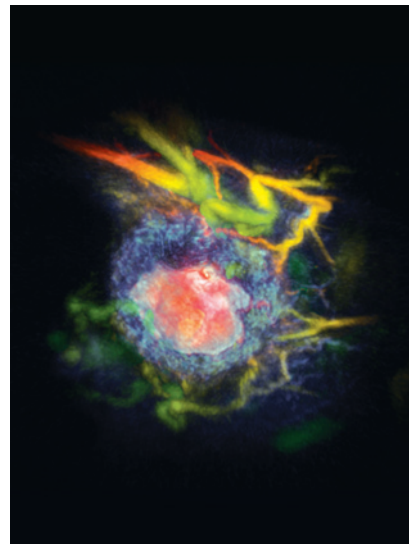
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ABOUT THE COVER

Breast cancer xenograft imaged *in vivo* by volumetric multispectral optoacoustic tomography (vMSOT). Fine vasculature patterns in the superficial epidermal layer are visible along with the larger feeding vessels and the necrotic core. The unique spectral differentiation capacity of vMSOT grants label-free measures of the blood oxygenation at high resolution across the entire tumor volume, while hypoxic fraction and cyclic hypoxia can further be dynamically quantified during oxygen challenge. For details, see article by Ron and colleagues on page 4767.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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