## Breaking Insights

**Highlights from Recent Cancer Literature**

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## Reviews

**The Tumor Microenvironment Innately Modulates Cancer Progression**
Dominique C. Hinshaw and Lalita A. Shevde

**Chemotherapy-Induced Metastasis: Molecular Mechanisms, Clinical Manifestations, Therapeutic Interventions**
George S. Karagiannis, John S. Condeelis, and Maja H. Oktay

## Cancer Research Highlights

**Monitoring Oxygenation Levels Deep in the Tumor Core: Noninvasive Imaging of Hypoxia, Now in Real-Time 3D**
Alexander L. Klibanov and Song Hu

**Unsuspected Protumorigenic Signaling Role for the Oncometabolite GABA in Advanced Prostate Cancer**
Renea A. Taylor and Matthew J. Watt

## Controversy and Consensus

**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

**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

**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

**Chemotherapy-Induced Distal Enhancers Drive Transcriptional Programs to Maintain the Chemoresistant State in Ovarian Cancer**

**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-Qin Zhou, Li Lin, Lu-Lu Zhang, Jia-Wei Li, Xiao-Dan Huang, Rui-Qi Liu, Fu-Ping Chen, Xiao-Jun He, Jia Kou, Jian Zhang, Xin Wen, Ying-Qin Li, Jun Ma, Na Liu, and Ying Sun

## Genome and Epigenome

**Chemotherapy-Induced Distal Enhancers Drive Transcriptional Programs to Maintain the Chemoresistant State in Ovarian Cancer**

**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.

**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-Qin Zhou, Li Lin, Lu-Lu Zhang, Jia-Wei Li, Xiao-Dan Huang, Rui-Qi Liu, Fu-Ping 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.
Radiolabeled Oligonucleotides Targeting the RNA Subunit of Telomerase Inhibit Telomerase and Induce DNA Damage in Telomerase-Positive Cancer Cells

**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.

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

**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.

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

**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.

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

**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.

IL6 Promotes a STAT3-PRL3 Feedforward Loop via SHP2 Repression in Multiple Myeloma

**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.

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

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

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

**Significance:** These findings validate the importance of TLR4 signaling in reprogramming normal myeloid cells into functional myeloid-derived suppressor cells.
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, Yue-Hong Wang, Sheng-Nan Jia, Guo-Ping Ding, 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.

CONVERGENCE AND TECHNOLOGIES

Volumetric Optoacoustic Imaging Unveils High-Resolution Patterns of Acute and Cyclic Hypoxia in a Murine Model of Breast Cancer
Avihai Ron, Xosé Luis 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.

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 Miquin 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.

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.
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.