BREAKING INSIGHTS

1 Highlights from Recent Cancer Literature

CANCER RESEARCH HIGHLIGHTS

3 Type I Protein Arginine Methyltransferases Overexpression Promotes Transformation and Potentiates Her2/Neu–Driven Tumorigenesis
Zachary L. Watson and Benjamin G. Bitler
See related article, p. 21

5 Time for a “Plan B” in Peritoneal Metastatic Disease
Claudio Tripodo
See related article, p. 159

GENOME AND EPIGENOME

7 Multiregion Sequencing Reveals the Genetic Heterogeneity and Evolutionary History of Osteosarcoma and Matched Pulmonary Metastases
Di Wang, Xiaohui Niu, Zhijie Wang, Cheng-Li Song, Zhen Huang, Ke-Neng Chen, Jiachen Xue, Jun Zhao, Yu Wang, Minglei Zhao, X. Sunney Xie, Xiaozheng Kang, Yanhua Tian, X. Sunney Xie, Xiaozheng Kang, Yanhua Tian, Liangliang Cai, Jie-Fei Han, Tongtong An, Yu Sun, Shugeng Gao, Jun Zhao, Jianming Ying, Luhua Wang, Jie He, and Jie Wang
Significance: High-throughput sequencing of primary and metastatic osteosarcoma provides new insights into the diagnosis of and potential clinical therapeutic strategies for pulmonary metastasis.

21 Mouse Models of Overexpression Reveal Distinct Oncogenic Roles for Different Type I Protein Arginine Methyltransferases
Jianqiang Bao, Alessandra Di Lorenzo, Kevin Lin, Yue Lu, Yi Zhong, Manu M. Sebastian, William J. Muller, Yanzhong Yang, and Mark T. Bedford
Significance: These findings establish Cre-activated mouse models of three different arginine methyltransferases, PRMT1, CARM1, and PRMT6, which are overexpressed in human cancers, providing a valuable tool for the study of PRMT function in tumorigenesis.
See related commentary, p. 3

MOLECULAR CELL BIOLOGY

33 TGFβ-Activated USP27X Deubiquitinase Regulates Cell Migration and Chemoresistance via Stabilization of Snail1
Guillem Lambies, Martina Miceli, Catalina Martinez-Guillamon, Rubén Olivera-Salgado, Raúl Peña, Carolina-Paola Frias, Irene Calderón, Boyko S. Atanassov, Sharon Y. R. Dent, Joaquín Arribas, Antonio García de Herreros, and Víctor M. Díaz
Significance: These findings show that inhibition of USP27X destabilizes Snail1 to impair EMT and renders tumor cells sensitive to chemotherapy, thus opening new strategies for the inhibition of Snail1 expression and its protumoral actions.

47 CXADR-Mediated Formation of an AKT Inhibitory Signalosome at Tight Junctions Controls Epithelial–Mesenchymal Plasticity in Breast Cancer
Azadeh Nilchian, Joel Johansson, Aram Ghalali, Sandra T. Asanin, Ana Santiago, Oskar Rosencrantz, Kerstin Sollerbrant, C. Theresa Vincent, Malin Sund, Ulla Stenius, and Jonas Fuxe
Significance: The tight junction protein CXADR controls epithelial-mesenchymal plasticity in breast cancer by stabilizing the AKT regulators PTEN and PHLPP2.

61 Mammary Precancerous Stem and Non-Stem Cells Evolve into Cancers of Distinct Subtypes
Wen Bu, Zhenyu Liu, Weiyu Jiang, Chandandeep Nagi, Shixia Huang, Dean P. Edwards, Eunji Jo, Qianxue Mo, Chad J. Creighton, Susan G. Hilsenbeck, Andrew D. Leavitt, Michael T. Lewis, Stephen T. C. Wong, and Yi Li
Significance: This work uses a novel mouse mammary gland cancer model to show that tumors initiated from different precancerous mammary epithelial cells are distinct.

72 Aberrant Activation of β-Catenin Signaling Drives Glioma Tumorigenesis via USP1-Mediated Stabilization of EZH2
Li Ma, Kangyu Lin, Guoqiang Chang, Yiwen Chen, Chen Yue, Qing Guo, Sichong Zhang, Zhiliang Jia, Tony T. Huang, Aidong Zhou, and Suyun Huang
Significance: These findings identify the β-catenin-USP1-EZH2 signaling axis as a critical mechanism for glioma tumorigenesis that may serve as a new therapeutic target in glioblastoma.
86 Histone Demethylase KDM4B Promotes DNA Damage by Activating Long Interspersed Nuclear Element-1
Ying Xiang, Kai Yan, Qian Zheng, Haiqiang Ke, Jie Cheng, Wenjun Xiong, Xin Shi, Lei Wei, Min Zhao, Fei Yang, Ping Wang, Xing Lu, Li Fu, Xuemei Lu, and Feng Li

**Significance:** The histone demethylase KDM4B promotes tumorigenesis by inducing retrotransposition and DNA damage.

99 Temozolomide Induces Senescence and Repression of DNA Repair Pathways in Glioblastoma Cells via Activation of ATR–CHK1, p21, and NF-κB
Dorthe Aasland, Laura Götzinger, Laura Hauck, Nancy Berte, Jessica Meyer, Melanie Effenberger, Simon Schneider, Emelie E. Reuber, Wynand P. Roos, Maja T. Tomicic, Bernd Kaina, and Markus Christmann

**Significance:** These findings reveal a mechanism by which the anticancer drug temozolomide induces senescence and downregulation of DNA repair pathways in glioma cells.

114 Loss of the BCR-FGFR1 GEF Domain Suppresses RHOA Activation and Enhances B-Lymphomagenesis in Mice
Tianxiang Hu, Yating Chong, Sumin Lu, Haiyan Qin, Mingqiang Ren, Natasha M. Savage, Chang-Sheng Chang, and John K Cowell

**Significance:** RHOA activation is a critical event in the progression of BCR–FGFR1–driven leukemogenesis in stem cell leukemia and lymphoma syndrome and is regulated by the BCR GEF domain.

125 Inhibition of Thioredoxin/Thioredoxin Reductase Induces Synthetic Lethality in Lung Cancers with Compromised Glutathione Homeostasis
Xiang Yan, Xiaoashan Zhang, Li Wang, Ran Zhang, Xingxian Pu, Shuhong Wu, Lei Li, Pan Tong, Jing Wang, Qing H. Meng, Vanessa B. Jensen, Luc Girard, John D. M. Minna, Jack A. Roth, Stephen G. Swisher, John V. Heymach, and Bingliang Fang

**Significance:** These findings demonstrate that lung cancers with compromised expression of enzymes required for glutathione homeostasis, including reduced GSR gene expression, may be targeted by thioredoxin/thioredoxin reductase inhibitors.

133 PIN1 Maintains Redox Balance via the c-Myc/NRF2 Axis to Counteract Kras-Induced Mitochondrial Respiratory Injury in Pancreatic Cancer Cells
Chen Liang, Si Shi, Mingyang Liu, Yi Qin, Qingcai Meng, Jie Hua, Shunrong Ji, Yuqing Zhang, Jingsuan Yang, Jin Xu, Quanzing Ni, Min Li, and Xianjun Yu

**Significance:** This study suggests that antioxidants protect Kras-mutant pancreatic cancer cells from oxidative injury, which may contribute to development of a targeted therapeutic strategy for Kras-driven PDAC by impairing redox homeostasis.

**TUMOR BIOLOGY AND IMMUNOLOGY**

146 M2 Macrophage-Derived Exosomes Promote Cell Migration and Invasion in Colon Cancer
Jingqin Lan, Li Sun, Feng Xu, Lu Liu, Yuqing Hu, Da Song, Zhenlin Hou, Wei Wu, Xueling Luo, Jing Wang, Xiangli Yuan, Junbo Hu, and Guihua Wang

**Significance:** These findings report a functional role for miRNA-containing exosomes derived from M2 macrophages in regulating migration and invasion of colorectal cancer cells.

159 Activation of B-1 Cells Promotes Tumor Cell Killing in the Peritoneal Cavity
Marcela A. Haro, Allison M. Dyevoich, James P. Phipps, and Karen M. Haas

**Significance:** This work identifies a critical antitumor role for innate-like B cells localized within the peritoneal cavity and demonstrates a novel strategy to activate their tumor-killing potential.

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171 Treatment-Induced Tumor Cell Apoptosis and Secondary Necrosis Drive Tumor Progression in the Residual Tumor Microenvironment through MerTK and IDO1
Thomas A. Werfel, David I. Ellion, Bushra Rahman, Donna J. Hicks, Violeta Sanchez, Paula I. Gonzales-Ericsson, Melissa J. Nixon, Janaal L. James, Justin M. Balko, Peggy A. Scherle, Holly K. Koblisch, and Rebecca S. Cook

**Significance:** These findings show in a model of Her2+ breast cancer that necrosis secondary to impaired effector cell activation activates IDO1 to drive immunosuppression and tumor progression.
183 miR-146a Controls Immune Response in the Melanoma Microenvironment

Significance: These findings identify a microRNA-based mechanism by which melanoma cells escape the immune system, providing a new therapeutic strategy to improve the current management of patients with melanoma.

196 Adipokines Deregulate Cellular Communication via Epigenetic Repression of Gap Junction Loci in Obese Endometrial Cancer

Significance: Studies reveal that adipose-derived stem cells in endometrial cancer pathogenesis influence epigenetic repression of gap junction loci, which suggests targeting of gap junction activity as a preventive strategy for obesity-associated endometrial cancer.

209 Activation of PP2A and Inhibition of mTOR Synergistically Reduce MYC Signaling and Decrease Tumor Growth in Pancreatic Ductal Adenocarcinoma

Significance: These findings present a combinatorial strategy targeting serine/threonine protein phosphatase PP2A and mTOR in PDA, a cancer for which there are currently no targeted therapeutic options.

220 Measurement of Plasma Cell-Free Mitochondrial Tumor DNA Improves Detection of Glioblastoma in Patient-Derived Orthotropic Xenograft Models
Richard Mair, Florent Moulire, Christopher G. Smith, Dineika Chandrananda, Davina Gale, Francesco Marass, Dana W.Y. Tsui, Charles E. Massie, Alan J. Wright, Collin Watts, Nitzan Rosenfeld, and Kevin M. Brindle

Significance: These findings show that detection of tumor mitochondrial DNA is more sensitive than circulating tumor DNA analysis to detect and monitor tumor burden in patient-derived orthotropic xenografts of glioblastoma.

231 Genetic Variants of VEGFA and FLT4 Are Determinants of Survival in Renal Cell Carcinoma Patients Treated with Sorafenib


242 Hyperpolarized MRI Visualizes Warburg Effects and Predicts Treatment Response to mTOR Inhibitors in Patient-Derived ccRCC Xenograft Models

Significance: These findings demonstrate hyperpolarized 13C[1-12C]pyruvate MRI as a tool for accurately assessing the clinical success of mTOR inhibition in patients with ccRCC.

251 MDM2-Recruiting PROTAC Offers Superior, Synergistic Antiproliferative Activity via Simultaneous Degradation of BRD4 and Stabilization of p53
John Hines, Schan Lartigue, Hanqing Dong, Yimin Qian, and Craig M. Crews

Significance: These findings present the first BRD4-targeting MDM2-based PROTAC that possesses potent, distinct, and synergistic biological activities associated with both ends of this heterobifunctional molecule.

263 A Gene Expression Classifier from Whole Blood Distinguishes Benign from Malignant Lung Nodules Detected by Low-Dose CT
Andrew V. Kossenkov, Rehan Qureshi, Noor B. Dawany, Jayamanna Wickramasinghe, Qin Liu, R. Sonali Majumdar, Celia Chang, Sandy Widura, Trisha Kumar, Wen-Hwai Horng, Eric Konnistro, Gerard Criner, Jun-Chieh J. Tsay, Harvey Pass, Sai Vendamari, Anil Vachani, Thomas Bauer, Brian Nam, William N. Rom, Michael K. Showe, and Louise C. Showe

Significance: These findings describe a minimally invasive and clinically practical pulmonary nodule classifier that has good diagnostic ability at distinguishing benign from malignant pulmonary nodules.
A Collaborative Analysis of Individual Participant Data from 19 Prospective Studies Assesses Circulating Vitamin D and Prostate Cancer Risk


Significance: This international collaboration comprises the largest prospective study on blood vitamin D and prostate cancer risk and shows no association with aggressive disease but some evidence of a higher risk of nonaggressive disease.