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238 Quantitative Fluorescence Microscopy Measures Vascular Pore Size in Primary and Metastatic Brain Tumors
Rajendar K. Mittapalli, Chris E. Adkins, Kaci. A. Bohn, Afroz S. Mohammad, Julie A. Lockman, and Paul R. Lockman
Précis: In vivo fluorescent imaging calculates chemotherapeutic permeability into tumors in the brain and details a new hypothesis on how monoclonal antibodies work in brain metastases of breast cancer.

247 Label-Free Raman Spectroscopy Detects Stromal Adaptations in Premetastatic Lungs Primed by Breast Cancer
Santosh Kumar Paidi, Asif Rizwan, Chao Zheng, Menglin Cheng, Kristine Glunde, and Ishan Barman
Précis: This imaging study elucidates stromal adaptations in premetastatic lung sites, enabling an objective recognition of tumor metastatic potential.

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268 Lysyl Oxidase Is a Strong Determinant of Tumor Cell Colonization in Bone
Caroline Reynaud, Laura Ferreras, Paola Di Mauro, Casina Kan, Martine Croset, Edith Bonnelye, Floriane Pez, Clémence Thomas, Géraldine Aimond, Antoine E. Karmoul, Marie Brevet, and Philippe Clézardin
Précis: These findings reveal a targetable mechanism that could be exploited to block metastasis of colorectal cancer to bone, an essentially untreatable form of the disease.

279 Macrophage-Secreted TNFα and TGFβ1 Influence Migration Speed and Persistence of Cancer Cells in 3D Tissue Culture via Independent Pathways
Ran Li, Jess D. Hebert, Tara A. Lee, Hao Xing, Alexandra Boussommer-Calleja, Richard O. Hynes, Douglas A. Lauffenburger, and Roger D. Kamm
Précis: These findings identify independent cooperating pathways through which macrophages control the speed and persistence of cancer cell migration in 3D tissue microenvironments.

303 MIF-Induced Stromal PKCβ2/IL8 Is Essential in Human Acute Myeloid Leukemia
Précis: In identifying the bidirectional MIF/IL8 survival mechanism between AML cells and bone marrow-derived mesenchymal stromal cells, this study provides a rationale to therapeutically target this protumoral feedback loop.
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**MOLECULAR AND CELLULAR PATHOBIOLOGY**

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401 Menin and Daxx Interact to Suppress Neuroendocrine Tumors through Epigenetic Control of the Membrane Metallo-Endopeptidase
Zijie Feng, Lei Wang, Yanmei Sun, Zongzhe Jiang, John Domsic, Chiyang An, Bowen Xing, Jingjing Tian, Xiuqiang Liu, David C. Metz, Xiaolu Yang, Ronen Marmorstein, Xiaosong Ma, and Xianxin Hua
Précis: This study suggesting new insights into tumor suppressor interplay in epigenetic regulation of neuroendocrine tumors may impact decisions about their therapy.

412 Polycomb-Mediated Disruption of an Androgen Receptor Feedback Loop Drives Castration-Resistant Prostate Cancer
Ka-wing Fong, Jonathan C. Zhao, Jung Kim, Shangze Li, Yeqing A. Yang, Bing Song, Laure Rittie, Ming Hu, Ximing Yang, Bernard Perbal, and Jindan Yu
Précis: These provocative results identify an intracellular function of a matricellular protein in directing cytosolic regulation of androgen receptor signaling and prostate cancer progression.

423 Integrative Comparison of mRNA Expression Patterns in Breast Cancers from Caucasian and Asian Americans with Implications for Precision Medicine
Yanxia Shi, Albert Steppi, Ye Cao, Jianan Wang, Max M. He, Liren Li, and Jinfeng Zhang
Précis: Genetic associations identified in this study may enable a more focused study of genotypic differences that can explain the disparity in BRCA1 incidence and mortality rates between Asian and Caucasian patient populations in the U.S.

434 Plk4 Promotes Cancer Invasion and Metastasis through Arp2/3 Complex Regulation of the Actin Cytoskeleton
Karineh Kazazian, Christopher Go, Hannah Wu, Olga Brashavitskaya, Roland Xu, James W. Dennis, Anne-Claude Gingras, and Carol J. Swallow
Précis: These findings reveal a novel role for Plk4 in promoting cancer invasion and metastasis through regulation of Arp2/3-mediated actin cytoskeletal rearrangement, thus validating Plk4 as a viable therapeutic target in cancer treatment.

448 Chemopreventive Effects of ROS Targeting in a Murine Model of BRCA1-Deficient Breast Cancer
Mo Li, Qian Chen, and Xiaochun Yu
Précis: This potentially seminal study suggests an answer to the long-standing question of why germline BRCA1 mutations cause tissue-specific tumors, with immediate implications for evaluating suitable antioxidant modalities as a strategy to mitigate the risks of familial breast cancer increased by BRCA1 mutation.

459 Quantification of Pathway Cross-talk Reveals Novel Synergistic Drug Combinations for Breast Cancer
Samira Jaeger, Ana Igca, Rodrigo Arroyo, Victor Alcalde, Begoña Canovas, Modesto Orozco, Angel R. Nebreda, and Patrick Aloy
Précis: This study uses a computational approach to discover synergistic combinations between targeted drugs to treat breast cancer, with the capability of providing broad-spectrum utility across several cancer types.

470 Transcriptional Selectivity of Epigenetic Therapy in Cancer
Takahiro Sato, Matteo Cesaroni, Woonbok Chung, Shoghap Panjarian, Anthony Tran, Jozef Madzo, Yasuyuki Okamoto, Hanghang Zhang, Xiaowei Chen, Jaroslav Jelinek, and Jean-Pierre J. Issa
Précis: In providing a comprehensive analysis of the specificity of epigenetic therapy in cancer, this study shows how combined targeting of DNA and histone methylation may offer an improved efficacy of this type of therapy for cancer treatment.

482 EpCAM Inhibition Sensitizes Chemoresistant Leukemia to Immune Surveillance
Xiaohu Zheng, Xiaolei Fan, Binqing Fu, Meijuan Zheng, Aimei Zhang, Kai Zhong, Jialai Yan, Rui Sun, Zhigang Tian, and Haiming Wei
Précis: This study shows how another cancer cell-targeting strategy actually mediates its efficacy by modulating the immune system, a growing theme in targeted drug development.

494 Aurora A and NF-κB Survival Pathway Drive Chemoresistance in Acute Myeloid Leukemia via the TRAF-Interacting Protein TIFA
Tong-You Wade Wei, Pei-Yu Wu, Ting-Jung Wu, Hsin-An Hou, Wen-Chien Chou, Chieh-Lin Jerry Teng, Chih-Ru Lin, Jo-Mei Maureen Chen, Ting-Yang Lin, Hsiang-Chun Su, Chia-Chi Flora Huang, Chang-Tze Ricky Yu, Shih-Lan Hsu, Hwei-Fang Tien, and Ming-Daw Tsai
Précis: These findings show how a survival signaling pathway mediated by a key mitotic regulator can be targeted to enhance the chemosensitivity of deadly leukemias.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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Précis: These findings show how a survival signaling pathway mediated by a key mitotic regulator can be targeted to enhance the chemosensitivity of deadly leukemias.
Genomic Profiling of a Large Set of Diverse Pediatric Cancers Identifies Known and Novel Mutations across Tumor Spectra

Précis: Analysis of an aggregate genomic dataset for pediatric tumors may illuminate novel therapeutic targets, validate oncogenic mechanisms, guide treatment decisions, and design appropriate clinical trials for children with cancer.

Biphasic Rapamycin Effects in Lymphoma and Carcinoma Treatment
Yang Liu, Srilakshmi Pandeswara, Vinh Dao, Alvaro Padrón, Justin M. Drerup, Shunhua Lao, Aijie Liu, Vincent Hurez, and Tyler J. Curiel

Précis: These findings show how novel low-dose administration of mTOR inhibitors can effectively cooperate with, rather than antagonize immunotherapy, resuscitating interest in mTOR-targeting therapies, which have otherwise been mainly disappointing in clinical trials.

Circadian Clock Gene Bmal1 Inhibits Tumorigenesis and Increases Paclitaxel Sensitivity in Tongue Squamous Cell Carcinoma
Qingming Tang, Bo Cheng, Mengru Xie, Yatao Chen, Jiajia Zhao, Xin Zhou, and Lili Chen

Précis: By identifying a novel tumor suppressor gene that sensitizes cancer cells to paclitaxel, this study may have implications for timed chronotherapy of head and neck cancer, where this drug is used.

Breast Cancer Resistance to Antiestrogens Is Enhanced by Increased ER Degradation and ERBB2 Expression
Tomohiro Shibata, Kosuke Watari, Hiroto Izumi, Akihiko Kawahara, Satoshi Hattori, Chibiro Fukuminu, Yuichi Murakami, Ryuji Takahashi, Ifhi Toh, Ken-ichi Ito, Shigehiro Ohdo, Maki Tanaka, Masayoshi Kage, Michihiko Kuwano, and Mayumi Ono

Précis: These findings unravel a novel mechanism of resistance to antiestrogen drugs in ER+ breast cancer cells, with potential prognostic and therapeutic implications.

A Novel Spectroscopically Determined Pharmacodynamic Biomarker for Skin Toxicity in Cancer Patients Treated with Targeted Agents

Précis: This study describes a noninvasive imaging technique to rapidly assess skin toxicity caused by diverse cancer treatments, addressing a common type of side effect experienced by patients receiving cancer therapy.

Systematic Drug Screening Identifies Tractable Targeted Combination Therapies in Triple-Negative Breast Cancer

Précis: Through a guided screen of FDA-approved and investigational drugs, this study suggests new treatments for aggressive triple-negative breast cancers that can be immediately translated to clinical trials.

SPINK6 Promotes Metastasis of Nasopharyngeal Carcinoma via Binding and Activation of Epithelial Growth Factor Receptor
Li-Sheng Zheng, Jun-Ping Yang, Yun Cao, Li-Xia Peng, Rui Sun, Ping Xie, Meng-Yao Wang, Dong-Fang Meng, Dong-Hua Luo, Xiong Zou, Ming-Yuan Chen, Hai-Qiang Mai, Ling Guo, Xiang Guo, Jian-Yong Shao, Bi-Jun Huang, Wei Zhang, and Chao-Nan Qian

Précis: These findings identify a novel EGFR ligand and candidate prognostic marker for metastasis in nasopharyngeal carcinoma.
ABOUT THE COVER

Epithelial cell adhesion molecule (EpCAM) is frequently overexpressed in patients with myeloid leukemia, but not in normal donors. Therefore, EpCAM has the potential to serve as an effective therapeutic target in leukemia. In a myeloid leukemia xenograft model, the mice were treated with anti-EpCAM antibody or IgG for 3 weeks. Immunofluorescence staining for intratumor apoptotic leukemia cells (TUNEL positive, green) was increased in tumors treated with anti-EpCAM antibody. Nuclei were stained with DAPI (blue). For details, see article by Zheng and colleagues on page 482.