**BREAKING ADVANCES**

6437 Highlights from Recent Cancer Literature

**CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES**

6439 A Milestone Review on How Macrophages Affect Tumor Growth
Christophe Caux, Rodrigo Nalio Ramos, George C. Prendergast, Nathalie Bendriss-Vermare, and Christine Ménétrier-Caux

6443 The Moment that KRAS Mutation Started to Evolve into Precision Medicine in Metastatic Colorectal Cancer
Toshikazu Ushijima and Takayuki Yoshino

**REVIEWS**

6445 Allogeneic Stem Cell Transplantation: A Historical and Scientific Overview
Anurag K. Singh and Joseph P. McGuirk

6452 Eph Receptor Tyrosine Kinases in Tumor Immunity
Eileen Shiuan and Jin Chen

**PERSPECTIVE**

6458 Serine Synthesis Helps Hypoxic Cancer Stem Cells Regulate Redox
Debangshu Samanta and Gregg L. Semenza

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

6463 In Vivo Imaging of Tumor Metabolism and Acidosis by Combining PET and MRI-CEST pH Imaging
Dario L. Longo, Antonietta Bartoli, Lorena Consolino, Paola Bardini, Francesca Arena, Markus Schwaiger, and Silvio Aime

**MICROENVIRONMENT AND IMMUNOLOGY**

6471 FGF2 from Marrow Microenvironment Promotes Resistance to FLT3 Inhibitors in Acute Myeloid Leukemia
Elie Traer, Jacqueline Martinez, Nathalie Javidi-Sharifi, Anupriya Agarwal, Jennifer Dunlap, Isabel English, Tibor Kovacsics, Jeffrey W. Tyner, Melissa Wong, and Brian J. Druker

Précis: These results support a strategy of early combination therapy in AML to target survival signals from the bone marrow microenvironment, in particular the growth factor FGF2.

6483 CCR2 Influences T Regulatory Cell Migration to Tumors and Serves as a Biomarker of Cyclophosphamide Sensitivity
Pierre-Louis Loyher, Juliette Rochefort, Camille Baudesson de Chanville, Pauline Hamon, Géraldine Lescaille, Chloé Bertolus, Maude Guillot-Delost, Matthew F. Krummel, François M. Lemoine, Christophe Combadiere, and Alexandre Boissonnas

Précis: The CCL2/CCR2 chemokine axis not only attracts myeloid cells to tumors, but also a subset of CCR2+ Treg cells implicated in immune suppression, possibly helping explain the beneficial effects of low-dose cyclophosphamide in some patients.

6495 Spatial Proximity to Fibroblasts Impacts Molecular Features and Therapeutic Sensitivity of Breast Cancer Cells Influencing Clinical Outcomes
Andriy Marusyk, Doris P. Tabassum, Michalina Janiszewska, Andrew E. Place, Anne Trinh, Andrii I. Rozhok, Saumyadipta Pyne, Jennifer L. Guerriero, Shaokun Shu, Muhammad Ekram, Alexander Ilbikin, Daniel P. Cahill, Yuri Nikolsky, Timothy A. Chan, Mothaffar F. Rimawi, Susan Hilsenbeck, Rachel Schiff, Kent C. Osborne, Antony Letai, and Kornelia Polyak

Précis: Stromal fibroblasts have profound effects on breast cancer cells, which impact therapeutic responses and clinical outcomes in patients.
MOLECULAR AND CELLULAR PATHOBIOLOGY

6507 Dual Roles for CXCL4 Chemokines and CXCR3 in Angiogenesis and Invasion of Pancreatic Cancer
Cathy Quemener, Jessica Baud, Kevin Boyé, Alexandre Dubrac, Clotilde Billrottet, Fabienne Soulet, Florence Darlot, Laurent Dumartin, Marie Sire, Renaud Grepin, Thomas Daubon, Fabienne Rayne, Harald Wodrich, Anne Couvelard, Raphael Pineau, Martin Schilling, Hervé Prats, and Andreas Bikfalvi

Précis: These findings identify the little studied chemokine CXCL4L1 as a nodal point in the development and progression of pancreatic cancer, with potential biomarker and therapeutic implications in this disease.

6520 Aberrant JMJD3 Expression Upregulates Slug to Promote Migration, Invasion, and Stem Cell–Like Behaviors in Hepatocellular Carcinoma
Bo Tang, Guangying Qi, Fang Tang, Shengguang Yuan, Zhenran Wang, Xingsi Liang, Bo Li, Shuiping Yu, Jie Liu, Qi Huang, Yangchao Wei, Run Zhai, Biao Lei, Hongping Yu, Stephen Tomlinson, and Songqing He

Précis: These results establish the chromatin-modifying protein JMJD3 as a critical driver of stem cell–like and metastatic behaviors in liver cancer, with implications for prognosis and treatment.

6533 Protective Role for TWEAK/Fn14 in Regulating Acute Intestinal Inflammation and Colitis-Associated Tumorigenesis
Luca Di Martino, Maneesh Dave, Paola Menghini, Wei Xin, Kristen O. Arseneau, Theresa T. Pizarro, and Fabio Cominelli

Précis: A TNF family member and its receptor have a protective role against colitis-associated tumor development, offering a novel chemopreventive target in patients with intestinal inflammation.

6543 IGFBP2 Activates the NF-κB Pathway to Drive Epithelial–Mesenchymal Transition and Invasive Character in Pancreatic Ductal Adenocarcinoma
Song Gao, Yan Sun, Xuebin Zhang, Limei Hu, Yuexin Liu, Corrine Yingxuan Chua, Lynette M. Phillips, He Ren, Jason B. Fleming, Huamin Wang, Paul J. Chiao, Jilun Hao, and Wei Zhang

Précis: This study identifies an antibody-tractable target, which is overexpressed in human pancreatic adenocarcinomas and is sufficient to confer the characteristically aggressive clinical features of this cancer, with important therapeutic implications.

6555 BRD4 Regulates Breast Cancer Dissemination through Jagged1/Notch1 Signaling
Guillaume Andrieu, Anna H. Tran, Katherine J. Strissel, and Gerald V. Denis

Précis: The bromodomain transcription factor BRD4 is critical not only for migration and invasion of triple-negative breast cancer through jagged1/Notch1 signaling, but also as an inflammatory effector molecule in the tumor microenvironment.

6568 Molecular Evolution Patterns in Metastatic Lymph Nodes Reflect the Differential Treatment Response of Advanced Primary Lung Cancer
Sang-Won Um, Je-Gun Joung, Hyun Lee, Hojoong Kim, Ryu-Tae Kim, Jinha Park, D. Neil Hayes, and Woong-Yang Park

Précis: These results argue that multiple biopsies and sequencing strategies from different regions of a tumor are needed to accurately understand the landscape of genetic alterations in an advanced primary lung cancer as a precursor to decision making about which targeted therapies to prescribe a patient.

6588 Cardiolipins Are Biomarkers of Mitochondria-Rich Thyroid Oncocytic Tumors
Jialing Zhang, Wendong Yu, Seung Woo Ryu, John Lin, Gerardo Buentello, Robert Tilshbhirani, James Suliburk, and Livia S. Eberlin

Précis: These findings suggest cardiolipins as new candidate therapeutic targets for oncogenic malignancies, a class of tumors characterized by excessive eosinophilic, granular cytoplasm due to an aberrant accumulation of mitochondria.
PREVENTION AND EPIDEMIOLOGY

6607 Chronic Stress Facilitates Lung Tumorigenesis by Promoting Exocytosis of IGF2 in Lung Epithelial Cells
Hyun-Ji Jang, Hye-Jin Boo, Ho Jin Lee, Hye-Young Min, and Ho-Young Lee
Précis: These important results identify an actionable mechanism to limit the effects of chronic stress on lung tumorigenesis, offering a chemopreventative strategy that could be immediately evaluated in clinic.

6643 Hybrid Manganese Dioxide Nanoparticles Potentiate Radiation Therapy by Modulating Tumor Hypoxia
Azhar Z. Abbasi, Claudia R. Gordijo, Mohammad Ali Amini, Azusa Maeda, Andrew M. Rauth, Ralph S. DaCosta, and Xiao Yu Wu
Précis: These findings offer a preclinical proof of concept for the use of hybrid manganese nanoparticle formulations as effective adjuvants to improve the antitumor efficacy of radiotherapy.

6657 Lurbinecetin Inactivates the Ewing Sarcoma Oncoprotein EWS-FLI1 by Redistributing It within the Nucleus
Matt L. Harlow, Nichole Maloney, Joseph Roland, Maria Jose Guillen Navarro, Matthew K. Easton, Susan M. Kitchen-Goosen, Elissa A. Boguslawski, Zachary B. Madaj, Ben K. Johnson, Megan J. Bowman, Maurizio D’Incalci, Mary E. Winn, Lisa Turner, Galen Hostetter, Carlos Maria Galmartin, Pablo M. Aviles, and Patrick J. Grohar
Précis: This study reports the mechanistic and preclinical efficacy of a disease-specific therapy to target EWS-FLI1, the transcription factor that drives Ewing sarcoma.

6669 Comparative Analysis of Bispecific Antibody and Streptavidin-Targeted Radioimmunotherapy for B-cell Cancers
Précis: This report describes the preclinical development of a novel bispecific antibody that enhances the tolerability and efficacy of pretargeted radioimmunotherapy.

6680 Mutant IDH1 Expression Drives TERT Promoter Reactivation as Part of the Cellular Transformation Process
Précis: These results presented here show that while IDH1 mutation in brain tumors does not create or select for ATRX or TERT promoter mutations, it can indirectly reactivate TERT and, in doing so, contributes to astrocyte immortalization and transformation.
### Pharmacological Inhibition of Centrosome Clustering by Slingshot-Mediated Cofilin Activation and Actin Cortex Destabilization

Gleb Konotop, Elena Bausch, Tomoaki Nagai, Andrey Tuchinovich, Natalia Becker, Axell Bennet, Michael Boutros, Kensaku Mizuno, Alwin Krämer, and Marc Steffen Raab

*Précis: This study demonstrates that drug-induced cofilin activation selectively eradicates tumor cells by inhibition of centrosome clustering, mediated by cortical actin cytoskeleton destabilization.*

### UGT2B17 Expedites Progression of Castration-Resistant Prostate Cancers by Promoting Ligand-Independent AR Signaling

Haolong Li, Ning Xie, Ruiqi Chen, Mélanie Verreault, Ladan Fazli, Martin E. Gleave, Olivier Barbier, and Xuesen Dong

*Précis: These findings reveal a novel function for an enzyme that enhances androgen-independent signaling and mitosis in prostate cancer cells.*

### TPL2 Is an Oncogenic Driver in Keratocanthoma and Squamous Cell Carcinoma


*Précis: This study provides a pivotal genetic foundation and preclinical model for mechanism-based studies of two types of skin carcinoma and its treatment.*

### v-Src Oncogene Induces Trop2 Proteolytic Activation via Cyclin D1

Xiaoming Ju, Xuannaio Jiao, Adam Ertel, Mathew C. Casimiro, Gabriele Di Sante, Shengqiong Deng, Zhiping Li, Agnese Di Rocco, Tingting Zhan, Adam Hawkins, Tanya Stoyanova, Sebastiano Ando, Alessandro Fatatis, Michael P. Lisanti,Leonard G. Comelli, Lucia R. Languino, and Richard G. Pestell

*Précis: These findings show how cyclin D1 acts as a central transducer of the signals generated by Src family kinases, which are activated in most prostate cancers.*

### SOX9 Elevation Acts with Canonical WNT Signaling to Drive Gastric Cancer Progression

Juliana Carvalho Santos, Estelania Carrasco-Garcia, Mikel García-Puga, Paula Aldaz, Milagrosa Montes, Maria Fernandez-Reyes, Caroline Candida de Oliveira, Charles H Lawrie, Marcos J. Araúzo-Bravo, Marcelo Lima Ribeiro, and Ander Matheu

*Précis: These findings establish the significance of SOX9 in mediating the pathogenic effects of H. pylori infection on gastric cancer and its heterogeneity, with implications for targeting WNT-SOX9 signaling as a rational therapeutic strategy.*

### Recurrent Loss of STING Signaling in Melanoma Correlates with Susceptibility to Viral Oncolysis

Tianli Xia, Hiroyasu Konno, and Glen N. Barber

*Précis: This study suggests STING pathway competency as a predictive marker for susceptibility to cancer cell lysis by oncolytic viruses, including HSV1, which in a recombinant form, is being developed in clinic as a cancer therapeutic agent.*
ABOUT THE COVER

Centrosome amplification is frequently found in both solid tumors and hematological malignancies. Experimentally, supernumerary centrosomes can be induced by overexpression of polo-like kinase 4 (PLK4), the principal regulator of centriole replication. The image depicts a large human osteosarcoma cell, which harbors numerous spindle poles as a consequence of exogenous PLK4 overexpression. In early prophase, chromatin condensation is accompanied by the separation of centrosomes and recruitment of the mitotic kinesin Eg5 (green) to spindle poles and proximal asters. For details, see article by Konotop and colleagues on page 6690.