**BREAKING ADVANCES**

3191 Highlights from Recent Cancer Literature

**REVIEWS**

3193 The **MET** Oncogene in Glioblastoma Stem Cells: Implications as a Diagnostic Marker and a Therapeutic Target
Carla Boccaccio and Paolo M. Comoglio

3200 Vesicle Trafficking and RNA Transfer Add Complexity and Connectivity to Cell–Cell Communication
Charles T. Roberts Jr and Peter Kurre

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

3206 Application of Raman Spectroscopy to Identify Microcalcifications and Underlying Breast Lesions at Stereotactic Core Needle Biopsy
Ishan Barman, Narahara Chari Dingari, Anushree Saha, Sasha McGee, Luis H. Galindo, Wendy Liu, Donna Plecha, Nina Klein, Ramachandra Rao Dasari, and Maryann Fitzmaurice

**Molecular and Cellular Pathobiology**

3235 Hypoxia Triggers Hedgehog-Mediated Tumor–Stromal Interactions in Pancreatic Cancer

3248 Single Copies of Mutant KRAS and Mutant PIK3CA Cooperate in Immortalized Human Epithelial Cells to Induce Tumor Formation

**MICROENVIRONMENT AND IMMUNOLOGY**

3225 The Endogenous Tryptophan Metabolite and NAD+ Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress
Felix Sahm, Iris Oezen, Christiane A. Opitz, Bernhard Radlwimmer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemin, Wolfgang Wick, and Michael Platten

**Contents**

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**Prevention and Epidemiology**

**3306** Colorectal Cancer Risk Associated with Hormone Use Varies by Expression of Estrogen Receptor-β

Anja Rudolph, Csaba Toth, Michael Hoffmeister, Wilfried Roth, Esther Herpel, Peter Schirrmacher, Hermann Brenner, and Jenny Chang-Claude

**Précis:** Expression of estrogen receptor β, the predominant estrogen receptor in colon tissue, appears to be involved in the reduction of colorectal cancer risk that may arise with use of oral contraceptives or menopausal hormone therapy.

**3325** Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer

Irina V. Kovtun, John C. Cherille, Stephen J. Murphy, Sarah H. Johnson, Shahnam Zarei, Farhad Kosari, William R. Sukov, R. Jeffrey Karnes, and George Vasmatzis

**Précis:** This work has important clinical implications because it demonstrates that changes associated with aggressive tumor behavior can be identified prior to the morphologic changes characteristic of aggressive prostate cancer.

**3328** Collagen Prolyl Hydroxylases Are Essential for Breast Cancer Metastasis

Daniele M. Gilkes, Pallavi Chaturvedi, Saumendra Bajpai, Carmen C. Wong, Hong Wei, Stephen Pitcairn, Maimon E. Hubbi, Denis Wirtz, and Gregg L. Semenza

**Précis:** Although collagen prolyl hydroxylases have been implicated broadly in cancer pathophysiology, their precise contributions have not been well understood, an important gap in knowledge addressed by this study.

**3329** Interleukin-1β Promotes Skeletal Colonization and Progression of Metastatic Prostate Cancer Cells with Neuroendocrine Features

Qingxin Liu, Mike R. Russell, Kristina Shahriri, Daniela L. Jernigan, Mercedes I. Lioni, Fernando U. Garcia, and Alessandro Fatatis

**Précis:** The identification of IL-1β as an important mediator of metastasis in prostate cancer should prompt immediate testing of anti-IL-1β strategies to treat advanced disease.

**Therapeutics, Targets, and Chemical Biology**

**3316** Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGF2, Is Mediated by Neurophilin 1

Ling Zhang, Graham C. Parry, and Eugene G. Levin

**Précis:** Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.

**3326** DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer

Jianzhong Cao, Yongmei Song, Nan Bi, Jie Shen, Wenyang Liu, Jing Fan, Guogui Sun, Tong Tong, Jie He, Yuankai Shi, Xin Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Lu, Lei Lv, Hui Deng, Jing Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

**Précis:** These findings identify a little-studied microRNA the epigenetic downregulation of which strongly affects clinical outcomes and malignant cell behaviors in small-cell lung cancer.

**3336** PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains

Sarah Picand, David Da Costa, Angeliki Thanasopoulou, Panagis Filipakopoulos, Paul V. Fish, Martin Philpott, Oleg Fedorov, Paul Brennan, Mark E. Bunnage, Dafydd R. Owen, James E. Bradner, Philippe Taniere, Brendan O’Sullivan, Susanne Müller, Juerg Schwaller, Tatjana Stankovic, and Stefan Knapp

**Précis:** This study suggests that it may be possible to target an important transcriptional regulatory domain that has been implicated in a broad number of aggressive blood cancers, as a generalizable therapeutic approach.

**3347** Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake

Marlous Arjaans, Thijs H. Oude Munnink, Sjouke F. Oosting, Anton G.T. Terwisscha van Scheltinga, Jourik A. Gietema, Erik T. Garbacik, Juerg Schwaller, Tatjana Stankovic, and Elisabeth G.E. de Vries

**Précis:** Bevacizumab treatment decreases tumor uptake of antibodies by vessel normalization, and this should be taken into account in the design of clinical trials that combine bevacizumab with other antibodies.
Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis

Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1

Regulation of FANCD2 by the mTOR Pathway Contributes to the Resistance of Cancer Cells to DNA Double-Strand Breaks

CIP4 Controls CCL19-Driven Cell Steering and Chemotaxis in Chronic Lymphocytic Leukemia

Simultaneous Targeting of Tumor Antigens and the Tumor Vasculature Using T Lymphocyte Transfer Synergize to Induce Regression of Established Tumors in Mice

miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL-6–Mediated Paracrine Effects in Head and Neck Cancer

Hedgehog Signaling Alters Reliance on EGF Receptor Signaling and Mediates Anti-EGFR Therapeutic Resistance in Head and Neck Cancer

Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations

Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence

Precise: By providing deeper insights into the pharmacodynamic requirements for the cytotoxic effects of the paradigm kinase inhibitor imatinib, this study may more broadly assist the development of maximally effective kinase inhibitors for cancer treatment.

Precise: This study offers proof of principle for using antiangiogenic drugs to enhance the efficacy of adoptive T-cell therapies for cancer treatment.

Precise: This study offers important new mechanistic insights into how leukemia cells migrate, with potentially important implications for understanding how to block invasive growth by these cells.

Precise: This mechanistically extensive study reveals a core pathway of support for cancer stem-like cells in head and neck squamous carcinomas, with implications for new treatment strategies in this setting.

Precise: A virus that infects a large proportion of brain tumors in a mouse model.

Precise: This study provides a rationale to improve the efficacy of AKT inhibitors for cancer therapy.

Precise: This study provides the basis for the sensitization of cancer cells to DNA damaging agents by targeting the mTOR pathway and gives insight into potential strategies that may enhance therapeutic activity or reduce sequelae from high-dose therapies, particularly in children.
Dual Role of the Antioxidant Enzyme Peroxiredoxin 6 in Skin Carcinogenesis
Frank Rolfs, Marcel Huber, Florian Gruber, Friederike Böhm, Herbert J. Pfister, Valery N. Bochkov, Erwin Tschachler, Reinhard Dummer, Daniel Hohl, Matthias Schäfer, and Sabine Werner
Précis: Antioxidant functions do not contribute exclusively to tumor suppression, as widely believed, but can also promote tumor development depending on the stage of the disease.

Growth of Triple-Negative Breast Cancer Cells Relies upon Coordinate Autocrine Expression of the Proinflammatory Cytokines IL-6 and IL-8
Précis: Findings offer a preclinical proof of principle to improve therapy of triple-negative breast cancer, a particularly aggressive disease subtype lacking effective mechanism-based interventions.

ABOUT THE COVER
In gliomas, constitutive metabolism of the essential amino acid tryptophan leads to the accumulation of the tryptophan metabolite quinolinic acid. Quinolinic acid is used by tumor cells to generate NAD⁺, thus contributing to the resistance towards radiotherapy and chemotherapy by replenishing depleted intracellular NAD pools. Using Western blot analyses and immunohistochemistry, it was found that the key enzyme leading to accumulation of quinolinic acid, 3-hydroxyanthranilate oxygenate (3-HAO), is expressed by tumor-infiltrating monocytes. Thus, infiltrating monocytes contribute to resistance to cytotoxic therapies in malignant gliomas. For details, see article by Sahm and colleagues on page 3225.