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

Precis: These findings illustrate a powerful noninvasive spectroscopic approach to detect microcalcifications and other cancer-associated lesions that offers real-time feedback to radiologists during biopsy procedures and thus could reduce nondiagnostic and false-negative biopsies.

3216 Manganese-Enhanced MRI Reveals Early-Phase Radiation-Induced Cell Alterations In Vivo
Shigeo Saito, Sumitaka Hasegawa, Aiko Sekita, Rumiana Bakalova, Takako Furukawa, Kenya Murase, Tsumeo Saga, and Ichio Aoki

Precis: This study reports a noninvasive method to monitor cell-cycle alterations in tumors based on manganese uptake and MRI offering a potentially useful tool for longitudinal studies to optimize radiotherapy.

MICROENVIRONMENT AND IMMUNOLOGY

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

Precis: A downstream catabolite of the tryptophan degradation pathway of IDO- and TDO-dependent immune escape, which is elevated in the majority of human cancers, is found to be a key element in their therapeutic resistance, with implications to improve treatment.

MOLECULAR AND CELLULAR PATHOBIOLOGY

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

Precis: These findings provide evidence for a novel molecular mechanism that explains the high levels of hypoxia and desmoplasia that contribute to therapy resistance in pancreatic cancer.

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

Precis: These findings suggest a paradigm that helps to explain how a single mutant KRAS allele can cooperate with mutant PIK3CA to impart a transformed phenotype.
### Prevention and Epidemiology

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

Anja Rudolph, Csaba Toth, Michael Hofmeister, Wilfried Roth, Esther Herpel, Peter Schirrmecher, 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.

#### Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer


**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.

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

Qingxin Liu, Mike R. Russell, Kristina Shahriari, Daniela L. Jernigan, Mercedes I. Lioni, 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.

### Therapeutics, Targets, and Chemical Biology

#### Inhibition of Tumor Cell Migration by LID22-4, 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.

#### 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, Guoqiu Sun, Tong Tong, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinhua He, Hongyu Zhang, Kelong Ma, Xiaoying Luo, Lei Ly, 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.

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

Sarah Picard, David Da Costa, Angeliki Thanasopoulou, Panagis Filippakopoulos, 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.

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


**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


**Précis:** 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.

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

Dhanalakshmi Chinnasamy, Eric Tran, Zhiya Yu, Richard A. Morgan, Nicholas P. Restifo, and Steven A. Rosenberg

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

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


**Précis:** Preclinical results show that resistance to the widely used EGFR targeting drug cetuximab, which occurs widely in the clinic, can be prevented by administration of inhibitors of the hedgehog pathway, which appears to be emerging as a major factor in cancer drug resistance more broadly.

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

Changxian Shen, Duane Oswald, Doris Phelps, Hakan Cam, Christopher E. Pessloki, Qishen Pang, and Peter J. Houghton

**Précis:** 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.

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

Bo Cen, Sandeep Mahajan, Wenzxue Wang, and Andrew S. Kraft

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

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

Gema Malet-Engra, Julien Vauud, Loïc Ysebaert, Manon Farcé, Fanny Lafouresse, Guy Laurent, Frédérique Gaits-Iacovoni, Giorgio Scita, and Loïc Dupré

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

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

Cheng-Chia Yu, Lo-Lin Tsai, Mong-Lien Wang, Chuan-Hang Yu, Wen-Liang Lo, Yun-Ching Chang, Guang-Yuh Chiou, Ming-Tung Chou, and Shih-Hwa Chiou

**Précis:** 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.

Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations

Richard L. Price, Jeun Song, Katherine Bingmer, Tae Hyong Kim, Ji-Young Yi, Michal O. Nowicki, Xiaokui Mo, Todd Hollon, Eric Murran, Christopher Alvarez-Breckenridge, Seledad Fernandez, Balveen Kaur, Andreana Rivera, Michael Oglesbee, Charles Cook, E. Antonio Chiocca, and Chang-Hyuk Kwon

**Précis:** A virus that infects a large proportion of humans is linked for the first time to formation of brain tumors in a mouse model.

Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence

Hang Cui, Yahui Kong, Mei Xu, and Hong Zhang

**Précis:** These findings offer a novel mechanism to enhance our understanding of the tumor-suppressive function of Notch signaling in cancer, with implications in many solid tumor settings.
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.