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

**INTEGRATED SYSTEMS AND TECHNOLOGIES**
- Application of Raman Spectroscopy to Identify Microcalcifications and Underlying Breast Lesions at Stereotactic Core Needle Biopsy
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  - 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.
- Manganese-Enhanced MRI Reveals Early-Phase Radiation-Induced Cell Alterations *In Vivo*
  - Shigeyoshi 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**
- The Endogenous Tryptophan Metabolite and NAD⁺ Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress
  - Felix Sahm, Iris Oezen, Christiane A. Opitz, Bernhard Radlhammer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemain, 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**
- 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.
- 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.
Dachshund Binds p53 to Block the Growth of Lung Adenocarcinoma Cells
Ke Chen, Kongming Wu, Xiaoxin Cai, Wei Zhang, Jie Zhou, Jing Wang, Adam Ertel, Zhiping Li, Hallgeir Rui, Andrew Quong, Michael P. Lisanti, Aydin Tozeren, Ceylan Tanes, Sankar Addya, Michael Gormley, Chenguang Wang, Steven B. McMahon, and Richard G. Pestell

Precis: This report identifies a modifier of EGFR signaling and stem cell function as an important new regulator of p53 in the most common type of lung cancer.

Lineage Relationship of Gleason Patterns in Gleason Score 7 Prostate Cancer
Irina V. Kovtun, John C. Cherille, Stephen J. Murphy, Sarah H. Johnson, Shabnam Zarei, Farhad Kosari, William R. Sukov, R. Jeffrey Karnes, and George Vasmatzis

Precis: 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.

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

Precis: 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.

Interleukin-1β Promotes Skeletal Colonization and Progression of Metastatic Prostate Cancer Cells with Neuroendocrine Features
Qingxin Liu, Mike R. Russell, Kristina Shahriri, Danielle L. Jernigan, Mercedes I. Lioni, Fernando U. Garcia, and Alessandro Fatatis

Precis: 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.

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 Schirmacher, Hermann Brenner, and Jenny Chang-Claude

Precis: 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.

Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGFR2, Is Mediated by Neurophilin 1
Ling Zhang, Graham C. Parry, and Eugene G. Levin

Precis: 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, Guogui Sun, Tong Tong, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Luo, Lei Lv, Hui Deng, Jing Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

Precis: 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.

PF1-1, 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, Tatianna Stankovic, and Stefan Knapp

Precis: 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
Marlous Arjaans, Thijs H. Oude Munnink, Sjoouke F. Oosting, Anton G.T. Terwisscha van Scheltinga, Jourik A. Gietema, Erik T. Garbacik, Stefan Knapp, Sara Picaud, David Da Costa, and Elisabeth G.E. de Vries

Precis: 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 EGF Receptor Signaling and Mediates Anti-EGFR Therapeutic Resistance in Head and Neck Cancer


**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.

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


**Précis:** 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.

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

Gema Malet-Engra, Julien Vauid, 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 important implications for understanding how to block invasive growth by these cells.

### Regulation of FANC D2 by the mTOR Pathway Contributes to the Resistance of Cancer Cells to DNA Double-Strand Breaks

Changxian Shen, Duane Oswald, Doris Phelpes, Hakan Cam, Christopher E. Pelloski, 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, Wenxue Wang, and Andrew S. Kraft

**Précis:** This study provides the basis for the efficacy of AKT inhibitors for cancer therapy.
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.