## BREAKING ADVANCES

### Highlights from Recent Cancer Literature

5847

## REVIEWS

### Why Your Preferred Targeted Drugs May Become Unaffordable

Martine J. Piccart

5849

### The Emerging Role of Immunosurveillance in Dictating Metastatic Spread in Breast Cancer

Clare Y. Slaney, Jai Rautela, and Belinda S. Parker

5852

## PERSPECTIVE

### The CpG Island Methylator Phenotype: What's in a Name?

Laura A.E. Hughes, Veerle Melotte, Joachim de Schrijver, Michiel de Maat, Vincent T.H.R.M. Smit, Judith V.A.M.G. Bovée, Pim J. French, Piet A. van den Brandt, Leo J. Schouten, Tim de Meyer, Wim van Crietkine, Nita Ahuja, James G. Herman, Matty P. Weijenberg, and Manon van Engeland

5858

## MICROENVIRONMENT AND IMMUNOLOGY

### Cetuximab Attenuates Its Cytotoxic and Radiosensitizing Potential by Inducing Fibronectin Biosynthesis

Iris Eke, Katja Storch, Mechthild Krause, and Nils Cordes

5869

### Complementary Populations of Human Adipose CD34\(^+\) Progenitor Cells Promote Growth, Angiogenesis, and Metastasis of Breast Cancer

Stefania Orecchioni, Giuliana Gregato, Ines Martin-Padura, Francesca Reggiani, Paola Braidoti, Patrizia Mancuso, Angelica Calleri, Jessica Quarna, Paola Marighetti, Chiara Aldeni, Giancarlo Pruneri, Stefano Martella, Andrea Manconi, Jean-Yves Petit, Mario Rietjens, and Francesco Bertolini

5880

## MOLECULAR AND CELLULAR PATHOBIOLOGY

### Dysregulated Hematopoiesis Caused by Mammary Cancer Is Associated with Epigenetic Changes and Hox Gene Expression in Hematopoietic Cells

Alexander Sio, Manreet K. Chehal, Kevin Tsai, Xueling Fan, Morgan E. Roberts, Brad H. Nelson, Jolanta Grembecka, Tomasz Cierpicki, Danielle L. Krebs, and Kenneth W. Harder

5892

**Précis:** These findings provide insight into how tumor-secreted factors profoundly disturb hematopoiesis, for example by causing myeloproliferative-like disease (leukemoid reaction), anemia, and disrupted bone marrow stem compartments.

### Adenomatous Polyps Are Driven by Microbe-Instigated Focal Inflammation and Are Controlled by IL-10–Producing T Cells

Kristen L. Dennis, Yunwei Wang, Nichole R. Blatner, Shuya Wang, Abdulrahman Saadalla, Erin Trudeau, Axel Roers, Casey T. Weaver, James J. Lee, Jack A. Gilbert, Eugene B. Chang, and Khoshayarsharza Khazaie

5905

**Précis:** IL-10 provided by T cells in the colon is critical to control bacterial-driven inflammation and polyp growth, providing a rationale for this cytokine as a candidate target for immunotherapy in colon cancer.

### Constitutive β-Catenin Activation Induces Male-Specific Tumorigenesis in the Bladder Urothelium

Congxing Lin, Yan Yin, Kristina Stemler, Peter Humphrey, Adam S. Kibel, Indira U. Mysorekar, and Liang Ma

5914

**Précis:** Investigations in a preclinical model of bladder cancer suggest that males have a predilection for this disease due to a synergy between the β-catenin and androgen receptor signaling pathways.

### FGFR4 Promotes Stromal-Induced Epithelial-to-Mesenchymal Transition in Colorectal Cancer

Rui Liu, Jingyi Li, Ke Xin, Tao Zhang, Yunlong Lei, Yi Chen, Lu Zhang, Kai Huang, Kui Wang, Hong Wu, Min Wu, Edouard C. Nice, Canhui Huang, and Yuquan Wei

5926

**Précis:** An FGFR receptor is found to be pivotal for the process by which the tumor stromal microenvironment triggers conversion of epithelial cancer cells to mesenchymal phenotypes that are more invasive and metastatic.
Downregulation of microRNA-515-5p by the Estrogen Receptor Modulates Sphingosine Kinase 1 and Breast Cancer Cell Proliferation

Precis: This study links the estrogen receptor and a microRNA implicated in breast cancer risk to a key lipid kinase that is essential for maintaining continuous cell proliferation in breast cancer.

Nm23-H1 Binds to Gelsolin and Inactivates Its Actin-Severing Capacity to Promote Tumor Cell Motility and Metastasis
Natascia Marino, Jean-Claude Marshall, Joshua W. Collins, Ming Zhou, Yongzhen Qian, Timothy Veenstra, and Patricia S. Steeg

Precis: A protein with protean and somewhat confusing functions in cancer is found to limit the metastasis in breast cancer by blocking the action of an actin-severing protein in breast cancer cells.

Cyclin D1-Dependent Induction of Luminal Inflammatory Breast Tumors by Activated Notch3
Hua Ling, Jean-Rene Sylvestre, and Paul Jolicoeur

Precis: Activated forms of Notch3 may preferentially induce expansion of luminal progenitor cells in the mammary gland that can contribute to inflammatory breast cancer, a particularly aggressive and poorly managed disease.

Notch1 Is Required for Kras-Induced Lung Adenocarcinoma and Controls Tumor Cell Survival via p53
Silvia Licciglui, Jacqueline L. Avila, Linda Hanlon, Scott Troutman, Matteo Cesaroni, Smitha Kota, Brian Keith, M. Celeste Simon, Ellen Puré, Fred Radtke, Anthony J. Capobianco, and Joseph L. Kissil

Precis: These findings define a novel role for the Notch1 receptor in lung cancer, offering a molecular basis for observations related to patient prognosis and reinforcing the notion that Notch1 is a worthy therapeutic target in this setting.

Indirubin Derivative 6BIO Suppresses Metastasis
Simone Braig, Christine A. Kressirer, Johanna Liebl, Fabian Bischoff, Stefan Zahler, Laurent Meijer, and Angelika M. Vollmar

Precis: These findings highlight the antimetastatic activity of a compound that blocks multiple kinase pathways involved in metastasis, supporting a concept termed "polypharmacology" in developing drugs to attack this most deadly aspect of cancer.

Combination of Antibody That Inhibits Ligand-Independent HER3 Dimerization and a p110α Inhibitor Potently Blocks PI3K Signaling and Growth of HER2+ Breast Cancers

Precis: These preclinical findings suggest a strategy to effectively manage HER2-overexpressing cancers that have progressed on the HER2-targeted drug trastuzumab, addressing a key clinical challenge.
An Antibody That Locks HER3 in the Inactive Conformation Inhibits Tumor Growth Driven by HER2 or Neuregulin

Précis: HER3 is a member of the EGFR family that mediates oncogenic functions of other family members, thereby offering a target that can more generally shut down signaling by this common cancer cell system.

Double Minute Chromosomes in Glioblastoma Multiforme Are Revealed by Precise Reconstruction of Oncogenic Amplicons
J. Zachary Sanborn, Sofie R. Salama, Mia Grifford, Cameron W. Brennan, Tom Mikkelsen, Suresh Jhanwar, Sol Katzman, Lynda Chin, and David Haussler

Précis: Oncogenic amplicons, a feature of many glioblastomas, were precisely reconstructed by high-throughput sequencing data, a process that could be useful for diagnosis and monitoring of disease.

MicroRNA-218 Inhibits Glioma Invasion, Migration, Proliferation, and Cancer Stem-like Cell Self-Renewal by Targeting the Polycomb Group Gene Bmi1
Yanyang Tu, Xingchun Gao, Gang Li, Hualin Fu, Daxiang Cui, Hui Liu, Weilin Jin, and Yongsheng Zhang

Précis: A tumor-suppressive microRNA acts by regulating a central transcriptional corepressor molecule implicated in glioblastoma, from which insights into its downstream targets in stem cell populations have emerged recently.

FOXO Transcription Factors Control E2F1 Transcriptional Specificity and Apoptotic Function
Igor Shats, Michael L. Gatsa, Beiyu Liu, Steven P. Angus, Lingchong You, and Joseph R. Nevins

Précis: This investigation into apoptosis mechanisms suggests a rationale to combine HDAC and PI3K inhibitors as a broad-acting strategy to attack numerous types of human cancer.

ERG Is a Critical Regulator of Wnt/LEF1 Signaling in Prostate Cancer
Longtao Wu, Jonathan C. Zhao, Jung Kim, Hong-Jian Jin, Cun-Yu Wang, and Jindan Yu

Précis: This study provides a mechanistic rationale to use Wnt pathway inhibitors to treat prostate cancers that harbor a characteristic TMPRSS2-ERG genetic fusion.

Obesity Promotes Breast Cancer by CCL2-Mediated Macrophage Recruitment and Angiogenesis
Lisa M. Arendt, Jessica McCready, Patricia J. Keller, Dana D. Baker, Stephen P. Naber, Victoria Seewaldt, and Charlotte Kuperwasser

Précis: These findings developed in a novel humanized breast cancer model reveal a mechanistic role for adipocytes and macrophages that may act at early times to promote breast cancer development in obese individuals, with implications for both prevention and treatment.

Correction: A Novel Class of Anticancer Compounds Targets the Actin Cytoskeleton in Tumor Cells

Correction: Constitutive HER2 Signaling Promotes Breast Cancer Metastasis through Cellular Senescence

Correction: PTK6 Activation at the Membrane Regulates Epithelial–Mesenchymal Transition in Prostate Cancer
ABOUT THE COVER

Tumor cells evolve by interacting with the local microenvironment. In this study, an FGF receptor (FGFR4) is found to be pivotal for the process by which the tumor stromal microenvironment triggers conversion of epithelial cancer cells to mesenchymal phenotypes that are more invasive and metastatic. Tumor-associated fibroblasts-mediated FGFR4 activation is strongly related to a high risk of tumor metastasis and poor patient outcome, suggesting novel therapeutic opportunities for the treatment of colorectal cancer. For details, see article by Liu and colleagues on page 5926.