BREAKING ADVANCES

5847 Highlights from Recent Cancer Literature

REVIEWS

5849 Why Your Preferred Targeted Drugs May Become Unaffordable
Martine J. Piccart

5852 The Emerging Role of Immunosurveillance in Dictating Metastatic Spread in Breast Cancer
Clare Y. Slaney, Jai Rautela, and Belinda S. Parker

PERSPECTIVE

5858 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. Smul, Judith V.M.G. Bovée, Pim J. French, Piet A. van den Brandt, Leo J. Schouten, Tim de Meyer, Wim van Criekinge, Nita Ahuja, James G. Herman, Matty P. Weijenberg, and Manon van Engeland

MICROENVIRONMENT AND IMMUNOLOGY

5869 Cetuximab Attenuates Its Cytotoxic and Radiosensitizing Potential by Inducing Fibronectin Biosynthesis
Iris Eke, Katja Storch, Mechthild Krause, and Nils Cordes
Précis: These findings show how an EGF receptor antibody used widely in the clinic actually induces a self-attenuating mechanism of drug resistance by stimulating cell-ECM interactions that block therapeutic efficacy.

5880 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 Braidotti, Patrizia Mancuso, Angelica Calleri, Jessica Quarna, Paolo Marighetti, Chiara Aldeni, Giancarlo Pruneri, Stefano Martella, Andrea Manconi, Jean-Yves Petit, Mario Rietjens, and Francesco Bertolini
Précis: Along with those from another study in this issue, these findings suggest one explanation for how obesity may promote the progression and metastatic spread of breast cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

5914 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
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.

5926 FGFR4 Promotes Stroma-Induced Epithelial-to-Mesenchymal Transition in Colorectal Cancer
Rui Liu, Jingyi Li, Ke Xie, Tao Zhang, Yunlong Lei, Yi Chen, Lu Zhang, Kai Huang, Kui Wang, Hong Wu, Min Wu, Edouard C. Nice, Canhua Huang, and Yuquan Wei
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, Youzhen 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 Licciulli, 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.

Chemoprevention of Prostate Cancer by D,L-Sulforaphane Is Augmented by Pharmacological Inhibition of Autophagy
Avani R. Vyas, Eun-Ryeong Hahm, Julie A. Arlotti, Simon Watkins, Donna Beer Stoltz, Dhimant Desai, Shantu Amin, and Shvendra V. Singh

Precis: Autophagic inhibitors may leverage the chemoprevention of prostate cancer, perhaps also delaying the progression of early, noninvasive lesions to more advanced cancers, addressing an important clinical challenge.

Telomere Length in Peripheral Blood Lymphocytes Contributes to the Development of HPV-Associated Oropharyngeal Carcinoma
Yang Zhang, Erich M. Sturgis, Kristina R. Dahlstrom, Juyi Wen, Hongliang Liu, Qingyi Wei, Guojun Li, and Zhensheng Liu

Precis: Individuals with HPV16 exposure plus shorter telomere lengths in their blood lymphocytes may have a higher risk of developing oral cancers, compared with those with either HPV16 exposure or shorter telomere lengths alone.

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 P13K Signaling and Growth of HER2+ Breast Cancers
Joan T. Garrett, Cammie R. Sutton, Richard Kurupi, Carl UlI Bialucha, Seth A. Etenberg, Scott D. Collins, Qing Sheng, Jerry Wallweber, Lisa DeFazio-Eli, and Carlos L. Arteaga

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

Precis: 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.

6036 TUMOR AND STEM CELL BIOLOGY
Double Minute Chromosomes in Glioblastoma Multiforme Are Revealed by Precise Reconstruction of Oncogenic Amplicons
J. Zachary Sanborn, Sofie R. Salama, Mia Griffor, Cameron W. Brennan, Tom Mikkelsen, Suresh Jhanwar, Sol Katzman, Lynda Chin, and David Haussler

Precis: Oncogenic amplicons, a feature of many glioblastomas, were precisely reconstructed by high-throughout 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

Precis: 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. Gatza, Beiyu Liu, Steven P. Angus, Lingchong You, and Joseph R. Nevins

Precis: 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.

6046 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

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

6056 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

Precis: 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.

CORRECTIONS

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

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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.