**BREAKING ADVANCES**

399 Highlights from Recent Cancer Literature

**REVIEWS**

401 Urinary Tobacco Smoke–Constituent Biomarkers for Assessing Risk of Lung Cancer

Jian-Min Yuan, Lesley M. Butler, Irina Stepanov, and Stephen S. Hecht

412 ERKs in Cancer: Friends or Foes?

Xavier Deschênes-Simard, Filippos Kottakis, Sylvain Meloche, and Gerardo Ferbeyre

420 Bookmarking Target Genes in Mitosis: A Shared Epigenetic Trait of Phenotypic Transcription Factors and Oncogenes?

Sayyed K. Zaidi, Rodrigo A. Grandy, Cesar Lopez-Camacho, Martin Montecino, Andre J. van Wijnen, Jane B. Lian, Janet L. Stein, and Gary S. Stein

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

426 Bridging Population and Tissue Scale Tumor Dynamics: A New Paradigm for Understanding Differences in Tumor Growth and Metastatic Disease

Jill Gallaher, Aravind Babu, Sylvia Plevritis, and Alexander R.A. Anderson

Précis: Vascular response is a primary cause of the differences in rates of tumor growth and metastatic disease in two of the most common cancers.

**MICROENVIRONMENT AND IMMUNOLOGY**

436 CCL2/CCR2-Dependent Recruitment of Functional Antigen-Presenting Cells into Tumors upon Chemotherapy

Yuting Ma, Stephen R. Mattarollo, Sandy Adjemian, Heng Yang, Laretitia Aymeric, Dalil Hannani, João Paulo Portela Catani, Helene Duret, Michele W.L. Teng, Oliver Kepp, Yidan Wang, Antonella Sistigu, Joachim L. Schultze, Gautier Stoll, Lorenzo Galluzzi, Laurence Zitvogel, Mark J. Smyth, and Guido Kroemer

Précis: These findings illustrate the importance of CCL2/CCR2 signaling pathways for immunogenic chemotherapeutics to elicit their antitumor effects, suggesting risks that CCL2/CCR2 targeting strategies being tested clinically may actually worsen clinical outcomes in cancer patients.

446 Immune Chaperone gp96 Drives the Contributions of Macrophages to Inflammatory Colon Tumorigenesis

Crystal Morales, Saleh Rachidi, Feng Hong, Shaoli Sun, Xinshou Ouyang, Caroline Wallace, Yongliang Zhang, Elizabeth Garret-Mayer, Jennifer Wu, Bei Liu, and Zihai Li

Précis: By using a macrophage-specific gene knockout mouse, this important study reveals how tumor-associated macrophages not only orchestrate local inflammation but also cell mutagenesis to drive the development of colon cancer.

460 MUC1 in Macrophage: Contributions to Cigarette Smoke–Induced Lung Cancer

Xiuling Xu, Mabel T. Padilla, Bilan Li, Alexandra Wells, Kousuke Kato, Carmen Tellez, Steven A. Belinsky, Kwang Chul Kim, and Yong Lin

Précis: These results shed light on the mechanisms of inflammation-associated lung carcinogenesis, showing how cigarette smoke promotes contributions from lung macrophages in the tissue microenvironment to promote lung cancer.

471 Defective TGF-β Signaling in Bone Marrow–Derived Cells Prevents Hedgehog-Induced Skin Tumors

Qipeng Fan, Dongsheng Gu, Hailan Liu, Ling Yang, Xiaoli Zhang, Mervin C. Yoder, Mark H. Kaplan, and Jingwu Xie

Précis: Dysregulation of the Hedgehog pathway in cancer cells drives the formation of a supportive microenvironment, by stimulating a core mechanism of support for the development of myeloid-derived suppressor cells.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

484 Cyclophilin B Supports Myc and Mutant p53-Dependent Survival of Glioblastoma Multiforme Cells

Jae Won Choi, Mark A. Schroeder, Jann N. Sarkaria, and Richard J. Bram

Précis: These results define the protein chaperone cyclophilin B as a promising molecular target for treatment of glioblastoma multiforme, with immediate clinical implications for repositioning the approved drug cyclosporin as a potential therapeutic to treat this aggressive malignancy.
Circadian Regulation of mTOR by the Ubiquitin Pathway in Renal Cell Carcinoma
Hiroyuki Okazaki, Naoya Matsunaga, Takashi Fujioka, Fumiyasu Okazaki, Yui Akagawa, Yunyu Tsurudome, Mayumi Ono, Michihiko Kukwa, Satoru Koyanagi, and Shigehiro Ohdo

Precis: This important study shows how a pivot cell growth regulator is controlled by circadian clock systems, with significant therapeutic implications.

MDR1 Synonymous Polymorphisms Alter Transporter Specificity and Protein Stability in a Stable Epithelial Monolayer
King Leung Fung, James Pan, Shinobu Ohnuma, Paul E. Lund, Jessica N. Pixley, Chava Kimchi-Sarfaty, Suresh V. Ambudkar, and Michael M. Gottesman

Precis: Synonymous "silent" polymorphisms in the multiple drug resistance gene can nonetheless alter the function of the gene product and drive chemotherapeutic resistance.

Table of Contents
TUMOR AND STEM CELL BIOLOGY

609  FGFR1–WNT–TGF-β Signaling in Prostate Cancer Mouse Models Recapitulates Human Reactive Stroma
Julienne L. Carstens, Payam Shahi, Susan Van Tsang, Billie Smith, Chad J. Creighton, Yiqun Zhang, Amber Seamans, Mamatha Seshammagari, Indira Vedula, Jonathan M. Levitt, Michael M. Ittmann, David R. Rowley, and David M. Spencer

Précis: Targeting the reactive stroma in aggressive prostate adenocarcinoma may generate a two-pronged attack that is more efficacious, by attacking cancer cells as well as the critical stromal tissue driving their outgrowth.

621  PPARα Activation Can Help Prevent and Treat Non–Small Cell Lung Cancer
Nataliya Skrypnyk, Xiwu Chen, Wen Hu, Yan Su, Stacey Mont, Shilin Yang, Mahesha Gangadhariah, Shouzuo Wei, John R. Falck, Jawahar Lal Jat, Roy Zent, Jorge H. Capdevila, and Ambra Pozzi

Précis: This important study provides a preclinical proof-of-concept for administering clinically approved PPARα agonists to treat lung cancer, with immediate implications to reposition an existing drug treatment that is well tolerated and may be highly efficacious in this setting.

LETTERS TO THE EDITOR

632  Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors—Letter
David C. Binder and Hans Schreiber

633  Dual Blockade of PD-1 and CTLA-4 Combined with Tumor Vaccine Effectively Restores T-Cell Rejection Function in Tumors—Response
Jai Kumar Duraiswamy, Gordon J. Freeman, and George Coukos

635  Editors’ Viewpoint—Response
Mario P. Colombo and George C. Prendergast

CORRECTIONS

636  Correction: A Single-Nucleotide Substitution Mutator Phenotype Revealed by Exome Sequencing of Human Colon Adenomas

637  Correction: Neuropilin-2 Is Upregulated in Lung Cancer Cells during TGF-β1–Induced Epithelial–Mesenchymal Transition

ABOUT THE COVER

Anthracycline-based chemotherapy promotes the recruitment of CD11c+(green) CD86+(red) dendritic cells in close proximity to Caspase 3a+(magenta) dying tumor cells. This process relies on “eat me” signal ATP and CCL2/CCR2 chemotactic axis. For details, see the article by Ma and colleagues on page 436 of this issue.