# Table of Contents

## BREAKING ADVANCES

**2763** Highlights from Recent Cancer Literature

## REVIEWS

**2765** Antiangiogenic VEGF-Ax: A New Participant in Tumor Angiogenesis  
Sandeepa M. Eswarappa and Paul L. Fox  

**2770** Tackling Crizotinib Resistance: The Pathway from Drug Discovery to the Pediatric Clinic  
Elizabeth R. Tucker, Laura S. Danielson, Paolo Innocenti, and Louis Chesler

## MICROENVIRONMENT AND IMMUNOLOGY

**2775** Breast Cancer Cell–Derived GM-CSF Licenses Regulatory Th2 Induction by Plasmacytoid Predendritic Cells in Aggressive Disease Subtypes  
Cristina Ghirelli, Fabien Reyal, Marine Jeanmougin, Raphael Zollinger, Philiémon Sirven, Paula Michea, Christophe Caux, Nathalie Bendriss-Vermare, Marie-Hélène Donnadieu, Martial Caly, Virginie Fourchotte, Anne Vincent-Salomon, Brigitte Sigal-Zaffran, Xavier Sastre-Garau, and Vassili Sounelis  
Précis: This study describes a mechanism through which an aggressive breast cancer activates pDC to promote a regulatory Th2 response, with implications for therapeutic targeting of a tumor-immune axis of growing recognition in its significance to malignancy.

**2780** NOS Inhibition Modulates Immune Polarization and Improves Radiation-Induced Tumor Growth Delay  
Précis: This work describes a novel and clinically feasible strategy to facilitate the safe delivery of systemic viral anticancer therapies by using clinically available β3 integrin inhibitors to control the problematic inflammatory side effects induced by these effective anticancer agents.

**2785** Tumor-Promoting Desmoplasia Is Disrupted by Depleting FAP-Expressing Stromal Cells  
Précis: This report identifies a stromal cell population expressing fibroblast activation protein (FAP), which is required for the desmoplastic response seen in many human carcinomas, also showing how FAP-expressing cells promote tumor growth via immune suppression and immune-independent remodeling of the stromal microenvironment.

**2790** Pharmacological Inhibition of β3 Integrin Reduces the Inflammatory Toxicities Caused by Oncolytic Adenovirus without Compromising Anticancer Activity  
Ashley Browne, Laura A. Tookman, Carin K. Ingemarsdotter, Russell D. Bouwman, Katrina Pirlo, Yaohe Wang, Iain A. McNeish, and Michelle Lockley  
Précis: This study describes a novel and clinically feasible strategy to facilitate the safe delivery of systemic viral anticancer therapies by using clinically available β3 integrin inhibitors to control the problematic inflammatory side effects induced by these effective anticancer agents.

**2795** Definition of Prostaglandin E2–EP2 Signals in the Colon Tumor Microenvironment That Amplify Inflammation and Tumor Growth  
Xiaojun Ma, Tomohiro Aoki, Tatsuaki Tsuruyama, and Shuh Narumiya  
Précis: These findings show how prostaglandin signaling in neutrophils and cancer-associated fibroblasts in the colorectal tumor microenvironment shape its inflammatory character, providing a mechanistic rationale to use EP2 antagonists as an alternative to aspirin for chemoprevention.

**2800** Tumor-Promoting Desmoplasia Is Disrupted by Depleting FAP-Expressing Stromal Cells  
Précis: This report identifies a stromal cell population expressing fibroblast activation protein (FAP), which is required for the desmoplastic response seen in many human carcinomas, also showing how FAP-expressing cells promote tumor growth via immune suppression and immune-independent remodeling of the stromal microenvironment.

**2805** Pharmacological Inhibition of β3 Integrin Reduces the Inflammatory Toxicities Caused by Oncolytic Adenovirus without Compromising Anticancer Activity  
Ashley Browne, Laura A. Tookman, Carin K. Ingemarsdotter, Russell D. Bouwman, Katrina Pirlo, Yaohe Wang, Iain A. McNeish, and Michelle Lockley  
Précis: This work describes a novel and clinically feasible strategy to facilitate the safe delivery of systemic viral anticancer therapies by using clinically available β3 integrin inhibitors to control the problematic inflammatory side effects induced by these effective anticancer agents.

**2810** Definition of Prostaglandin E2–EP2 Signals in the Colon Tumor Microenvironment That Amplify Inflammation and Tumor Growth  
Xiaojun Ma, Tomohiro Aoki, Tatsuaki Tsuruyama, and Shuh Narumiya  
Précis: These findings show how prostaglandin signaling in neutrophils and cancer-associated fibroblasts in the colorectal tumor microenvironment shape its inflammatory character, providing a mechanistic rationale to use EP2 antagonists as an alternative to aspirin for chemoprevention.
MOLECULAR AND CELLULAR PATHOBIOLOGY

2833  TET2 Mutations Affect Non-CpG Island DNA Methylation at Enhancers and Transcription Factor–Binding Sites in Chronic Myelomonocytic Leukemia
Jumpei Yamazaki, Jaroslav Jelinek, Yue Lu, Matteo Cesaroni, Jozef Madzo, Frank Neumann, Rong He, Rodolphe Taby, Aparna Vasanthakumar, Trisha Macrae, Kelly R. Osmar, Hagop M. Kantarjian, Shoudan Liang, Marcos R. Estecio, Lucy A. Godley, and Jean-Pierre J. Issa
Précis: Results show how mutations in a leukemia-associated gene act epigenetically by influencing the DNA methylation of hematopoietic-specific enhancers that affect leukemia development.

PREVENTION AND EPIDEMIOLOGY

2844  Mitochondrial DNA Copy Number in Peripheral Blood Cells and Risk of Developing Breast Cancer
Alina Lemnrua, Mark N. Brook, Olivia Fletcher, Penny Coulson, Katarzyna Tomczyk, Michael Jones, Alan Ashworth, Anthony Swedlow, Nick Orr, andMontserrat Garcia-Closas
Précis: The use of miDNA copy number measured in blood samples prior to diagnosis is associated with elevated risk of developing breast cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2851  Enhanced MET Translation and Signaling Sustains K-Ras–Driven Proliferation under Ancestral-Independent Growth Conditions
Saori Fujita-Sato, Jacqueline Galeas, Morgan Truitt, Cameron Pitt, Anatoly Iriisman, Sourav Bandopadhyay, Davide Ruggiero, and Frank McCormick
Précis: These results suggest that to drive malignant cell growth K-Ras requires the activity of the Met receptor kinase, a therapeutic target already being explored in the clinic, with implications in addressing the long-standing challenge of how to attack K-Ras–driven human tumors.

2886  Vacuolar-ATPase Inhibition Blocks Iron Metabolism to Mediate Therapeutic Effects in Breast Cancer
Lina S. Schneider, Karin von Schwarzenberg, Thorsten Lehn, Melanie Urlich, Rebekka Kubisch-Dohmen, Johanna Liebl, Dirk Trauner, Dirk Menche, and Angelika M. Vollmar
Précis: Inhibition of a vacuolar ATPase that functions as an ion pump in maintaining cellular metabolic pathways in cancer appears to selectively disturb iron metabolic pathways, thereby blocking tumor growth.

2897  KRAS Genomic Status Predicts the Sensitivity of Ovarian Cancer Cells to Decitabine
Michelle L. Stewart, Pablo Tamayo, Andrew J. Wilson, Stephanie Wang, Yun Min Chang, Jong W. Kim, Dineo Khabele, Alykhan F. Shamji, and Stuart L. Schreiber
Précis: These findings define a mechanistic basis and a biomarker to predict the sensitivity of ovarian cancer cells to a cytosine DNA methytransferase inhibitor, with potentially generalizable applications.

2907  Targeting Pancreatic Cancer Metastasis by Inhibition of Vav1, a Driver of Tumor Cell Invasion
Précis: These findings offer a preclinical rationale for repositioning the well-established drug azathioprine to inhibit metastasis of deadly pancreatic cancers.
Evidence Suggesting That Discontinuous Dosing of ALK Kinase Inhibitors May Prolong Control of ALK+ Tumors


Précis: This important study shows how kinase upregulation in cancer cells can foster resistance to a kinase inhibitory drug, but that this upregulation also sensitizes cells to kinase-mediated toxicities that can be exploited by altering the drug dosing schedule, as a strategy to defeat the drug resistance.

Noninvasive Imaging of Tumor PD-L1 Expression Using Radiolabeled Anti–PD-L1 Antibodies

Sandra Heskamp, Willemijn Hobo, Janneke D.M. Molkenboer-Kuenen, Daniel Olive, Wim J.G. Oyen, Harry Dolstra, and Otto C. Boerman

Précis: PD-L1 expression in tumors is important for PD-1/PD-L1–based therapeutics and can be monitored noninvasively using SPECT/CT imaging, which may more readily enable patient selection for trials of this type of antibody-based immune checkpoint therapy.

Genetic Identification of SEMA3F as an Antilymphangiogenic Metastasis Suppressor Gene in Head and Neck Squamous Carcinoma

Colleen L. Doçi, Constantinos M. Mikelis, Michael S. Lionakis, Alfredo A. Molinolo, and J. Silvio Gutkind

Précis: By focusing on recurrent 3p21 deletions in head and neck cancers, this study identifies a novel metastasis suppressor gene that offers an appealing prognostic biomarker and therapeutic target in this setting.

Androgen-Induced TMPRSS2 Activates Matriptase and Promotes Extracellular Matrix Degradation, Prostate Cancer Cell Invasion, Tumor Growth, and Metastasis

Chun-Jung Ko, Cheng-Chung Huang, Hsin-Ying Lin, Chun-Pai Juan, Shao-Wei Lan, Hsin-Yi Shyu, Shang-Ru Wu, Pei-Wen Hsiao, Hsiang-Po Huang, Chia-Tung Shun, and Ming-Shyue Lee

Précis: This important study shows how the serine protease TMPRSS2 promotes the growth, invasion, and metastasis of prostate cancer cells via activation of the matrix protease matriptase, with implications that targeting these two proteases may offer new options to treat advanced prostate cancer.

ABOUT THE COVER

In normal epithelial cells, there is a balance of pro- and antiangiogenic and lymphangiogenic factors maintaining proper tissue homeostasis. During malignant transformation, early loss of one such factor, the lymphatic endothelial cell inhibitor SEMA3F, is necessary to enable pathologic lymphangiogenesis. As the squamous cell carcinoma cells develop a more aggressive phenotype, acquired expression of surface receptors like neuropilin 2 (NRP2), a receptor typically expressed at high levels on lymphatic endothelial cells, further facilitate tumor vascularity, expansion, and metastatic spread. Thus, expression of SEMA3F may function in both an autocrine and paracrine fashion through NRP2 to inhibit tumor growth, lymphatic invasion, and metastasis. For details, see article by Doçi and colleagues on page 2937.
Cancer Research


75 (14)


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/75/14

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.