# Cancer Research
## 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 Bendriess-Vemare, Marie-Hélène Donnadieu, Martial Caly, Virginie Fourchotte, Anne Vincent-Salomon, Brigitte Sigal-Zafrani, Xavier Sastre-Garau, and Vassili Soumelis

**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.

2788  NOS Inhibition Modulates Immune Polarization and Improves Radiation-Induced Tumor Growth Delay

**Précis:** NOS inhibition has long been studied in cancer to limited impact, but these new preclinical results show how inhibiting NOS in patients after they undergo radiotherapy can relieve immune escape in the tumor microenvironment and greatly improve treatment responses.

2800  Tumor-Promoting Desmoplasia Is Disrupted by Depleting FAP-Expressing Stromal Cells

**Précis:** This report identifies a stromal cell population expressing the 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.

2811  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.

2822  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.
### TUMOR AND STEM CELL BIOLOGY

**2916** Evidence Suggesting That Discontinuous Dosing of ALK Kinase Inhibitors May Prolong Control of ALK<sup>+</sup> 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.

---

**2928** Noninvasive Imaging of Tumor PD-L1 Expression Using Radiolabeled Anti–PD-L1 Antibodies

Sandia 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.

---

**2937** 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.

---

**2949** 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.