

## BREAKING ADVANCES

- 2915 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 2917 | **Dishonorable Discharge: The Oncogenic Roles of Cleaved E-Cadherin Fragments**  
Justin M. David and Ayyappan K. Rajasekaran
- 2924 | **Targeting of a Conformationally Exposed, Tumor-Specific Epitope of EGFR as a Strategy for Cancer Therapy**  
Hui K. Gan, Antony W. Burgess, Andrew H. A. Clayton, and Andrew M. Scott

## PRIORITY REPORT

- 2931 | **Mice Expressing Activated PI3K Rapidly Develop Advanced Colon Cancer**  
Alyssa A. Leystra, Dustin A. Deming, Christopher D. Zahm, Mohammed Farhoud, Terrah J. Paul Olson, Jamie N. Hadac, Laura A. Nettekoven, Dawn M. Albrecht, Linda Clipson, Ruth Sullivan, Mary Kay Washington, Jose R. Torrealba, Jamey P. Weichert, and Richard B. Halberg
- Précis: Expression of a dominant active form of PI3K in the mouse intestine rapidly induces formation of invasive mucinous adenocarcinomas that are histologically similar to human colon cancer but without engaging the canonical WNT pathway, which is generally thought to be central in this setting.*

## CLINICAL STUDIES

- 2937 | **Gene Immunotherapy of Chronic Lymphocytic Leukemia: A Phase I Study of Intranodally Injected Adenovirus Expressing a Chimeric CD154 Molecule**  
Januario E. Castro, Johanna Melo-Cardenas, Mauricio Urquiza, Juan S. Barajas-Gamboa, Ramin S. Pakbaz, and Thomas J. Kipps
- Précis: Direct injection of immune-stimulatory genes into lymph nodes, where tolerance to tumor antigens occurs, may offer a powerful new kind of immunotherapy for cancer, given the marked clinical activity seen in early trials of this unique strategy to trigger antitumor immunity.*

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2949 | **In Vivo Imaging of Drug-Induced Mitochondrial Outer Membrane Permeabilization at Single-Cell Resolution**  
Sarah Earley, Claudio Vinegoni, Joshua Dunham, Rostic Gorbатов, Paolo Fumene Feruglio, and Ralph Weissleder
- Précis: The ability to visualize and quantify drug-induced apoptosis of human tumor cells in vivo may address questions about how apoptosis is controlled by the tumor microenvironment.*

## MICROENVIRONMENT AND IMMUNOLOGY

- 2957 | **Expression of P2X7 Receptor Increases In Vivo Tumor Growth**  
Elena Adinolfi, Lizzia Raffaghello, Anna Lisa Giuliani, Luigi Cavazzini, Marina Capece, Paola Chiozzi, Giovanna Bianchi, Guido Kroemer, Vito Pistoia, and Francesco Di Virgilio
- Précis: A receptor for extracellular ATP is found to promote tumorigenesis in vivo, providing mechanistic insight into how the biochemical composition of the tumor milieu may support growth and metastasis.*
- 2970 | **Cell-Mediated Autophagy Promotes Cancer Cell Survival**  
William J. Buchser, Thomas C. Laskow, Philip J. Pavlik, Hui-Min Lin, and Michael T. Lotze
- Précis: This study challenges the notion that immune effectors simply destroy targets and instead posits that they are involved in induction of tumor cell autophagy and resistance to anticancer therapy and potentially involved in repair.*
- 2980 | **LIGHT Delivery to Tumors by Mesenchymal Stem Cells Mobilizes an Effective Antitumor Immune Response**  
Weibin Zou, Huilin Zheng, Tong-Chuan He, Jinjia Chang, Yang-Xin Fu, and Weimin Fan
- Précis: Targeted delivery of an immune-stimulating factor in tumors using a stem cell-based vector can stanch immune suppression in the tumor microenvironment and derepress antitumor immunity.*



2990

**Inhibitory Roles of Signal Transducer and Activator of Transcription 3 in Antitumor Immunity during Carcinogen-Induced Lung Tumorigenesis**

Shoichi Ihara, Hiroshi Kida, Hisashi Arase, Lokesh P. Tripathi, Yi-An Chen, Tetsuya Kimura, Mitsuhiro Yoshida, Yozo Kashiwa, Haruhiko Hirata, Reiko Fukamizu, Ruriko Inoue, Kana Hasegawa, Sho Goya, Ryo Takahashi, Toshiyuki Minami, Kazuyuki Tsujino, Mayumi Suzuki, Satoshi Kohmo, Koji Inoue, Izumi Nagatomo, Yoshito Takeda, Takashi Kijima, Kenji Mizuguchi, Isao Tachibana, and Atsushi Kumanogoh

*Précis:* Tissue-specific genetic deletion of STAT3 in lung epithelium decreases susceptibility to lung carcinogenesis and promotes NK cell-mediated antitumor immunity, offering the first strong genetic proof for STAT3 signaling as a cancer therapeutic target for lung cancer treatment.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

3000

**Vav3-Rac1 Signaling Regulates Prostate Cancer Metastasis with Elevated Vav3 Expression Correlating with Prostate Cancer Progression and Posttreatment Recurrence**

Kai-Ti Lin, Jianli Gong, Chien-Feng Li, Te-Hsuan Jang, Wen-Ling Chen, Huei-Jane Chen, and Lu-Hai Wang

*Précis:* Findings highlight a cell adhesion signaling pathway that may contribute centrally to invasive metastasis of prostate cancer.

3010

**Stromal Estrogen Receptor- $\alpha$  Promotes Tumor Growth by Normalizing an Increased Angiogenesis**

Christel Péqueux, Isabelle Raymond-Letron, Silvia Blacher, Frédéric Boudou, Marine Adlanmerini, Marie-José Fouque, Philippe Rochaix, Agnès Noël, Jean-Michel Foidart, Andrée Krust, Pierre Chambon, Laurent Brouchet, Jean-François Arnal, and Françoise Lenfant

*Précis:* Findings reveal that estrogens drive breast tumor growth in part by supporting the ability of endothelial cells in the tumor microenvironment, deepening our understanding of the molecular mechanisms involved in ER-positive tumorigenesis and how ER-positive tumors might be managed.

**PREVENTION AND EPIDEMIOLOGY**

3020

**Postmenopausal Hormone Therapy Is Associated with a Reduced Risk of Colorectal Cancer Lacking CDKN1A Expression**

Jennifer H. Lin, Teppei Morikawa, Andrew T. Chan, Aya Kuchiba, Kaori Shima, Katsuhiko Noshio, Gregory Kirkner, Shumin M. Zhang, JoAnn E. Manson, Edward Giovannucci, Charles S. Fuchs, and Shuji Ogino

*Précis:* A reduction in colorectal cancer risk among U.S. women using postmenopausal hormone therapy may be due to the effect of these medications on a central cell-cycle regulator.

3029

**Adipokines Linking Obesity with Colorectal Cancer Risk in Postmenopausal Women**

Gloria Y.F. Ho, Tao Wang, Marc J. Gunter, Howard D. Strickler, Mary Cushman, Robert C. Kaplan, Sylvia Wassertheil-Smoller, Xiaonan Xue, Swapnil N. Rajpathak, Rowan T. Chlebowski, Mara Z. Vitolins, Philipp E. Scherer, and Thomas E. Rohan

*Précis:* A high level of leptin is an independent risk factor for colorectal cancer, and hyperleptinemia together with hyperinsulinemia may partially explain the association of obesity with colorectal cancer in postmenopausal women.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

3038

**An NQO1 Substrate with Potent Antitumor Activity That Selectively Kills by PARP1-Induced Programmed Necrosis**

Xiumei Huang, Ying Dong, Erik A. Bey, Jessica A. Kilgore, Joseph S. Bair, Long-Shan Li, Malina Patel, Elizabeth I. Parkinson, Yiguang Wang, Noelle S. Williams, Jinming Gao, Paul J. Hergenrother, and David A. Boothman

*Précis:* Therapeutic programmed necrosis can be achieved in tumors using bioactive substrates of the cytosolic NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme that is overexpressed in most solid cancers and can create extensive tumor-selective ROS bursts, damaging tumor cell DNA and rapidly killing cells.

3048

**MEK1/2 Inhibition Elicits Regression of Autochthonous Lung Tumors Induced by KRAS<sup>G12D</sup> or BRAF<sup>V600E</sup>**

Christy L. Trejo, Joseph Juan, Silvestre Vicent, Alejandro Sweet-Cordero, and Martin McMahon

*Précis:* This study uses genetically engineered mouse models of human lung cancer to establish a preclinical proof of concept for MEK inhibitors as broadly effective therapy for lung tumors driven by activated Ras-Raf signaling.

3060 **Novel TOPK Inhibitor HI-TOPK-032 Effectively Suppresses Colon Cancer Growth**

Dong Joon Kim, Yan Li, Kanamata Reddy, Mee-Hyun Lee, Myoung Ok Kim, Yong-Yeon Cho, Sung-Young Lee, Jong-Eun Kim, Ann M. Bode, and Zigang Dong

*Précis: Findings identify a specific inhibitor of a MEK family member that shows effective preclinical efficacy against colorectal cancer, with great potential for improving therapy of this disease.*

3069 **Mcl-1 Phosphorylation Defines ABT-737 Resistance That Can Be Overcome by Increased NOXA Expression in Leukemic B cells**

Suparna Mazumder, Gaurav S. Choudhary, Sayer Al-harbi, and Alexandru Almasan

*Précis: Findings provide insight into acquired resistance mechanisms to the BH3 domain mimetic ABT-737, which is currently being tested in the clinic as navitoclax.*

3091 **Polycomb Protein EZH2 Regulates Tumor Invasion via the Transcriptional Repression of the Metastasis Suppressor RKIP in Breast and Prostate Cancer**

Gang Ren, Stavroula Baritaki, Himangi Marathe, Jingwei Feng, Sungdae Park, Sandy Beach, Peter S. Bazeley, Anwar B. Beshir, Gabriel Fenteany, Rohit Mehra, Stephanie Daignault, Fahd Al-Mulla, Evan Keller, Ben Bonavida, Ivana de la Serna, and Kam C. Yeung

*Précis: This study provides mechanistic insights into a novel metastasis suppressor in breast and prostate cancers, where it is a target of the histone methyltransferase EZH2, known to play an important role in malignant progression.*

3105 **Genetic Ablation of SOX18 Function Suppresses Tumor Lymphangiogenesis and Metastasis of Melanoma in Mice**

Tam Duong, Steven T. Proulx, Paola Luciani, Jean-Christophe Leroux, Michael Detmar, Peter Koopman, and Mathias Francois

*Précis: A molecular switch used during embryonic development to control lymphangiogenesis is switched on during formation of the lymphatic vessels that drain tumors, suggesting new targeted strategies to block the escape of metastases that are often seeded through the lymphatic system.*

## TUMOR AND STEM CELL BIOLOGY

3080 **Uncoupling of PI3K from ErbB3 Impairs Mammary Gland Development but Does Not Impact on ErbB2-Induced Mammary Tumorigenesis**

Hicham Lahlou, Thomas Müller, Virginie Sanguin-Gendreau, Carmen Birchmeier, and William J. Muller

*Précis: In the context of activated HER2-ErbB2 signaling, ErbB3-PI3K coupling is essential for normal mammary gland development but not mammary cancer progression.*

## CORRECTIONS

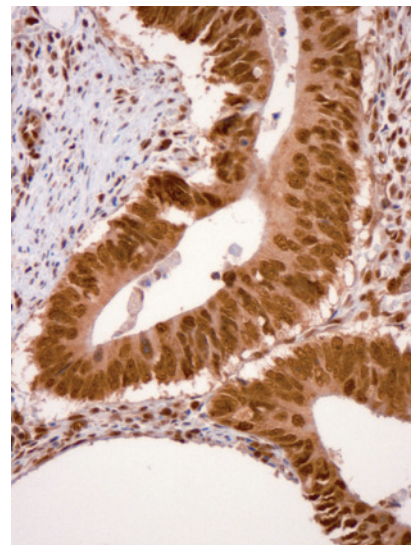
3115 **Correction: Genome-Wide DNA Methylation Profiling of CpG Islands in Breast Cancer Identifies Novel Genes Associated with Tumorigenicity**

3116 **Correction: ARID1A, a Factor That Promotes Formation of SWI/SNF-Mediated Chromatin Remodeling, Is a Tumor Suppressor in Gynecologic Cancers**

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## ABOUT THE COVER

Adenosine 5'-triphosphate (ATP) is a common constituent of the tumor microenvironment where it modulates the anticancer immune response and stimulates tumor cell growth and apoptosis. One of the main cellular receptors mediating these effects is the P2X7 receptor. P2X7 is an ATP-gated plasma membrane ion channel coupled to inflammasome activation, release of inflammatory cytokines, generation of reactive oxygen species, and stimulation of apoptosis. However, paradoxically, Adinolfi and colleagues found that tumorigenesis was accelerated by overexpression of P2X7 in several tumor models, and accordingly, drastically reduced by P2X7 silencing. Adinolfi and colleagues results provide a logical explanation for the intriguing finding that most human malignant tumors overexpress this receptor (a specimen from human differentiated colon cancer stained with an anti-P2X7 polyclonal antibody is shown). For details, see article by Adinolfi et al. on page 2957 of this issue.



# Cancer Research

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