# Contents

**November 15, 2013 • Volume 73 • Number 22**

## BREAKING ADVANCES

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### Highlights from Recent Cancer Literature

Sheema Khan, Ansarullah, Deepak Kumar, Meena Jaggi, and Subbash C. Chauhan

## REVIEWS

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### Targeting microRNAs in Pancreatic Cancer: Microplayers in the Big Game

Sheema Khan, Ansarullah, Deepak Kumar, Meena Jaggi, and Subbash C. Chauhan

### Cancerous Inhibitor of Protein Phosphatase 2A, an Emerging Human Oncoprotein and a Potential Cancer Therapy Target

Anchit Khanna, John E. Pimanda, and Jukka Westermarck

### miRNA Dysregulation in Breast Cancer

Laoghaise Mulrane, Sharon F. McGee, William M. Gallagher, and Darran P. O'Connor

## INTEGRATED SYSTEMS AND TECHNOLOGIES

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### A DNA Methylation Prognostic Signature of Glioblastoma: Identification of NPTX2-PTEN-NF-κB Nexus

Sudhanshu Shukla, Irene Rosita Pia Patric, Sivaarumugam Thinararjan, Sojaya Srinivasan, Baisakhi Mondal, Alangar S. Hegde, Bangalore A. Chandramouli, Vani Santosh, Arimappamagan Arivazhagan, and Kumaravel Somasundaram

**Précis:** This study of global DNA methylation in the most deadly form of brain cancer reveals a simple prognostic marker, with potential implications for treatment.

## MICROENVIRONMENT AND IMMUNOLOGY

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### Parathyroid Hormone–Related Protein Drives a CD11b+Gr1−Cell–Mediated Positive Feedback Loop to Support Prostate Cancer Growth

Serk In Park, Changki Lee, W. David Sadler, Amy J. Koh, Jacqueline Jones, Jung Won Seo, Fabiana N. Soki, Sun Wook Cho, Stephanie D. Daignault, and Laurie K. McCauley

**Précis:** A cancer cell-secreted bone regulatory factor promoting hypercalcemia has a pivotal role in recruiting a class of immune-suppressor cells that drive tumor angiogenesis and progression.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

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### Soluble Carcinoembryonic Antigen Activates Endothelial Cells and Tumor Angiogenesis

Kira H. Bramswig, Marina Poettler, Matthias Unsel, Friedrich Wrba, Pavel Uhrin, Wolfgang Zimmermann, Christoph C. Ziehlinski, and Gerald W. Prager

**Précis:** These findings define a functional role in tumor angiogenesis for a serum biomarker used widely in the oncology clinic to monitor the growth of many cancers.

### Adjuvants That Improve the Ratio of Antigen-Specific Effector to Regulatory T Cells Enhance Tumor Immunity

Rachel Perret, Sophie R. Sierra, Natalia K. Botelho, Stéphanie Cognac, Alena Donda, and Pedro Romero

**Précis:** These findings may improve the design of effective cancer vaccines by advancing understanding of the interactions of different vaccine components and immune cell types.

### Enhancement of Antitumor Immunity in Lung Cancer by Targeting Myeloid-Derived Suppressor Cell Pathways

Anandi Sawant, Cara C. Schafer, Tong Huan Jin, Jaroslaw Zmijewski, Hubert M. Tse, Justin Roth, Zhihuan Sun, Gene P. Siegal, Victor J. Thannickal, Stefan C. Grant, Selvarangan Ponnazhagan, and Jessy S. Deshane

**Précis:** This study identifies a novel therapeutic strategy to overcome tumoral immunosuppression in lung cancer, opening new routes to trigger regression and prevent relapses in this disease.

### Genetic and Pharmacologic Inhibition of mTORC1 Promotes EMT by a TGF-β–Independent Mechanism

Ivan Mikaelian, Mounihad Malek, Rudy Gadel, Jean Viallet, Amandine Garcia, Anaïs Girard-Gaguepain, Cédric Hesling, Germain Gillet, Philippe Gonzalo, Ruth Rimokh, and Marc Billaud

**Précis:** This important study raises concerns about using mTORC1 inhibitors for clinical management of cancer, given that they not only impair tumor immunity but also even promote EMT in epithelial cells, perhaps explaining the progressive pulmonary fibrosis associated with therapeutic use of mTOR inhibitors.
Hallmarks of Aromatase Inhibitor Drug Resistance Revealed by Epigenetic Profiling in Breast Cancer

Précis: Personalized breast cancer treatment might be achieved within the clinical setting by profiling DNA binding sites for transcription factors and epigenetic marks, suggesting that a similar strategy can be applied in other types of cancer.

The Transcription Factor IRF8 Counteracts BCR-ABL to Rescue Dendritic Cell Development in Chronic Myelogenous Leukemia
Tomoya Watanabe, Chie Hotta, Shin-ichi Koizumi, Kazuho Miyashita, Jun Nakabayashi, Daisuke Kurotaki, Go R. Sato, Michio Yamamoto, Masatoshi Nakazawa, Hiroyuki Fujita, Rika Sakai, Shin Fujisawa, Akira Nishiyama, Zenro Ikezawa, Michiko Aihara, Yoshiaki Ishigatsubo, and Tomohiko Tamura

Précis: These findings suggest that the transcription factor IRF8 may offer an attractive target for the development of next-generation therapies for chronic myeloid leukemia.

Intestinal GUCY2C Prevents TGF-β Secretion Coordinating Desmoplasia and Hyperproliferation in Colorectal Cancer
Ahmara V. Gibbons, Jieru E. Lin, Gilbert W. Kim, Glen F. Marszalowicz, Peng Li, Brian A. Stoecker, Erik S. Blomain, Satish Rattan, Adam E. Snook, Stephanie Schulz, and Scott A. Waldman

Précis: A tumor suppressor that coordinates EMT homeostasis acts in part through paracrine circuits that oppose tumor desmoplasia and progression.

CIP2A Modulates Cell-Cycle Progression in Human Cancer Cells by Regulating the Stability and Activity of Plk1
Jae-Sung Kim, Eun Ju Kim, Jeong Su Oh, In-Chul Park, and Sang-Gu Hwang

Précis: These results establish a new function for an oncogenic inhibitor of the protein phosphatase PP2A in facilitating the stability of a critical mitotic kinase for cell cycle transit and tumorigenesis.

Loss of TBK1 Induces Epithelial–Mesenchymal Transition in the Breast Cancer Cells by ERα Downregulation
Kyung-Min Yang, YunShin Jung, Jeong-Mi Lee, WonJoo Kim, Jin Ki Cho, Joon Jeong, and Seong-Jin Kim

Précis: A new regulator of estrogen receptor-α expression in breast cancer influences EMT, with prognostic and therapeutic relevance.

Maintenance of Androgen Receptor Inactivation by S-Nitrosylation
Yu Qin, Anindya Dey, Hamsa Thyayele Purayil, and Yehia Daaka

Précis: This article reveals a new regulatory mechanism for the androgen receptor in prostate cancer, with immediate prospects for sequential targeting of its different domains to extend therapeutic efficacy in patients with advanced disease.

Cytoplasmic Irradiation Results in Mitochondrial Dysfunction and DRP1-Dependent Mitochondrial Fission
Bo Zhang, Mercy M. Davidson, Hongning Zhou, Chunxin Wang, Winsome F. Walker, and Tom K. Hei

Précis: This study offers a mechanistic explanation for how ionizing radiation causes genotoxic damage, helping address long-standing gaps in knowledge concerning its extranuclear effects.

CD95L Cell Surface Cleavage Triggers a Prometastatic Signaling Pathway in Triple-Negative Breast Cancer
Marine Malleter, Sébastien Tauzin, Alban Bessede, Rémy Castellano, Armelle Goubard, Florence Godey, Jean Levêque, Pascal Jézéquel, Loic Campion, Mario Campone, Thomas Ducret, Gaëtan MacGrogan, Laure Debure, Yves Collette, Pierre Vacher, and Patrick Legembre

Précis: These findings elucidate the mechanistic basis for a metastatic function of CD95L that is connected to cell migration, opening a new direction in understanding its contributions to carcinogenesis.

CDK1 Phosphorylation of YAP Promotes Mitotic Defects and Cell Motility and Is Essential for Neoplastic Transformation
Shuping Yang, Lin Zhang, Miao Liu, Rong Chong, Shi-Jian Ding, Yuanhong Chen, and Jixin Dong

Précis: These results show how a pivotal effector of the Hippo pathway mediates its mitotic effects critical for oncogenesis.
Personalizing the Treatment of Pediatric Medulloblastoma: Polo-like Kinase 1 as a Molecular Target in High-Risk Children


Precis: These findings suggest repositioning inhibitors of a critical mitotic kinase, currently in clinical testing, to treat a deadly pediatric tumor.

Crizotinib Inhibits Metabolic Inactivation of Gemcitabine in c-Met–driven Pancreatic Carcinoma

Amir Avan, Viola Caretti, Niccola Funel, Elena Galvani, Mina Maftouh, Richard J. Honeywell, Tonny Lagerweij, Olaf van Tellingen, Daniela Campani, Dieter Fuchs, Henk M. Verheul, Gerrit-Jan Schuurhuis, Ugo Boggi, Godefritus J. Peters, Thomas Wurdinger, and Elisa Giovannetti

Precis: A new set of imageable orthotopic models of human pancreatic cancer, which better recapitulates the tumors of origin, points to c-Met as a key therapeutic target for clinical evaluation in this disease.

Chk1 Targeting Reactivates PP2A Tumor Suppressor Activity in Cancer Cells


Precis: These findings provide explanatory power for single-agent antitumor activity of a new generation of Chk1 inhibitors that mediate blockade of MYC and survival in cancer cells.
RNAi-Mediated Silencing of Myc Transcription Inhibits Stem-like Cell Maintenance and Tumorigenicity in Prostate Cancer

Gianluca Civenni, Anastasia Malek, Domenico Albino, Ramon García-Escudero, Sara Napoli, Stefano Di Marco, Sandra Pinton, Manuela Sarti, Giuseppina M. Carbone, and Carlo V. Catapano

Précis: This important study offers a preclinical proof of concept to target Myc function in cancer stem-like cells as a general strategy to attack most if not all human cancers.

MyoD Is a Tumor Suppressor Gene in Medulloblastoma

Joyoti Dey, Adrian M. Dubuc, Kyle D. Pedro, Derek Thirstrup, Brig Mecham, Paul A. Northcott, Xiaochong Wu, David Shih, Stephen J. Tapscott, Michael LeBlanc, Michael D. Taylor, and James M. Olson

Précis: A central muscle differentiation factor is for the first time shown to be expressed during development of the cerebellum and to function there as a tumor suppressor.

Retraction: p53 Regulates Cellular Resistance to Complement Lysis through Enhanced Expression of CD59

Retraction: Modulation of CD59 Expression by Restrictive Silencer Factor–Derived Peptides in Cancer Immunotherapy for Neuroblastoma

ABOUT THE COVER

Diaphanous-related formins create new and/or stabilize microfilament and microtubule structures that support polarized cell adhesion, migration, and division. GTP-bound Rho proteins activate these formins by direct binding. The molecular mechanism of Rho activation is through steric disruption of intramolecular interactions between Dia-inhibitory (DID) and Dia-autoregulatory (DAD) domains. Screening for compounds that block DID-DAD binding led to the discovery of intramimics, which are small molecules that interfere with autoinhibition, resulting in activation of cellular formins. Using immunofluorescence to detect detyrosinated microtubules (a trait of stabilized microtubules), this image illustrates microtubules stabilized by intramimic exposure. For details on the mechanism and pharmacologic impairment of tumor growth, see article by Lash and colleagues on page 6793.