## Contents

**August 15, 2013 • Volume 73 • Number 16**

### BREAKING ADVANCES

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4963</td>
<td>Highlights from Recent Cancer Literature</td>
<td></td>
</tr>
</tbody>
</table>

### REVIEWS

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4965</td>
<td>Targeting the Tumor Microenvironment: From Understanding Pathways to Effective Clinical Trials</td>
<td>Hua Fang and Yves A. DeClerck</td>
</tr>
<tr>
<td>4978</td>
<td>p63 Sharp1, and HIFs: Master Regulators of Metastasis in Triple-Negative Breast Cancer</td>
<td>Stefano Piccolo, Elena Enzo, and Marco Montagner</td>
</tr>
</tbody>
</table>

### PERSPECTIVE

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4982</td>
<td>Early B-Cell Differentiation in Merkel Cell Carcinomas: Clues to Cellular Ancestry</td>
<td>Axel zur Hausen, Dorit Rennspiess, Veronique Winnepenninckx, Ernst-Jan Speel, and Anna Kordelia Kurz</td>
</tr>
</tbody>
</table>

### MEETING REPORT

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>

### INTEGRATED SYSTEMS AND TECHNOLOGIES

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4992</td>
<td>Metabolic Characterization of Hepatocellular Carcinoma Using Nontargeted Tissue Metabolomics</td>
<td>Qiang Huang, Yexiong Tan, Peiyuan Yin, Guozhu Ye, Peng Gao, Xin Lu, Hongyang Wang, and Guowang Xu</td>
</tr>
</tbody>
</table>

### MICROENVIRONMENT AND IMMUNOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003</td>
<td>Myeloid-Derived Suppressor Cells as a Vehicle for Tumor-Specific Oncolytic Viral Therapy</td>
<td>Samuel Eisenstein, Brian A. Coakley, Karen BRiley-Sarbo, Ge Ma, Hui-ming Chen, Marcia Meseck, Stephen Ward, Celia Divino, Savio Woo, Shu-Hsia Chen, and Ping-Ying Pan</td>
</tr>
<tr>
<td>5016</td>
<td>TGF-β Modulates Ovarian Cancer Invasion by Upregulating CAF-Derived Versican in the Tumor Microenvironment</td>
<td>Tsz-Lun Yeung, Cecilia S. Leung, Kwong-Kwok Wong, Goli Samimi, Melissa S. Thompson, Jinsong Liu, Tarrik M. Zaid, Sue Ghosh, Michael J. Birrer, and Samuel C. Mok</td>
</tr>
</tbody>
</table>

### MOLECULAR AND CELLULAR PATHOBIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
</table>
Extracellular RNA Liberates Tumor Necrosis Factor-α to Promote Tumor Cell Trafficking and Progression

Extracellular RNA Liberates Tumor Necrosis Factor-α to Promote Tumor Cell Trafficking and Progression

Silvia Fischer, Sabine Gesierich, Barbara Griemert, Anne Schänzer, Till Acker, Hellmut G. Augustin, Anna-Karin Olsson, and Klaus T. Preissner

Précis: These findings establish crucial functions for extracellular RNA released from tumor cells in driving invasion and progression, and suggest in vivo applications for RNase1 as a provocative therapeutic approach.

Critical Tumor Suppressor Function Mediated by Epithelial Mig-6 in Endometrial Cancer

Tae Hoon Kim, Dong-Kee Lee, Sung-Nam Cho, Grant D. Orvis, Richard R. Behringer, John P. Lydon, Bon Jeong Ku, Adrienne S. McCampbell, Russell R. Broaddus, and Jae-Wook Jeong

Précis: This study provides insights into how progesterone prevents endometrial cancer, a long-standing question for which mechanistic knowledge might advance thinking about how to use this hormone in treatment.

Acquired Expression of NFATc1 Downregulates E-Cadherin and Promotes Cancer Cell Invasion

Tsukasa Oikawa, Atsuko Nakamura, Nobuyuki Onishi, Taketo Yamada, Koichi Matsuo, and Hideyuki Saya

Précis: Carcinoma cells that switch on expression of an important hematopoietic transcription factor acquire new capacities for invasive movement and growth.

14-3-3 Proteins Modulate the ETS Transcription Factor ET1 in Prostate Cancer

Sangphil Oh, Sook Shin, Stan A. Lightfoot, and Ralf Janknecht

Précis: This article provides mechanistic insight into the pathophysiology of multiple tumors, including prostate cancer and melanomas.

The DREAM Complex Mediates GIST Cell Quiescence and Is a Novel Therapeutic Target to Enhance Imatinib-Induced Apoptosis


Précis: A DNA repair protein that also participates in the control of cell cycle and transcription is found to exert profound effects on the invasive behavior of breast cancer cells, defining a new function for this protein and suggesting further investigations into its potential as a prognostic factor and therapeutic target.

DDB2: A Novel Regulator of NF-κB and Breast Tumor Invasion

Marie Ennen, Renni Klootz, Nadège Touche, Sonia Ledrappier, Lionel Domenjoud, Joseph Abecassis, François Plénat, and Philippe Becue

Précis: This study identifies DDB2 as a novel regulator of NF-κB and breast tumor invasion. This DNA repair protein also participates in the control of cell cycle and transcription, suggesting that it may play a role in the invasive behavior of breast cancer cells.

EGF Receptor Activates MET through MAPK to Enhance Non–Small Cell Lung Carcinoma Invasion and Brain Metastasis

Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, Minghui Zhao, Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, and Minnu Thomas

Précis: These results show how EGFR-MET signaling is critical for aggressive behavior in lung adenocarcinomas and rationalize its continued investigation as a therapeutic target in NSCLC, whether tumors harbor wild-type or mutant EGFR at early stages of progression.

Regulation of the Transcriptional Coactivator FHL2 Licenses Activation of the Androgen Receptor in Castrate-Resistant Prostate Cancer

Meagan J. McGrath, Lauren C. Binge, Abhorsn Siratana, Hong Wang, Paul A. Robinson, David Pook, Clare G. Fedele, Susan Brown, Jennifer M. Dyson, Denny L. Cottle, Belinda S. Cowling, Birunthi Niranjana, Gail P. Rishbridger, and Christina A. Mitchell

Précis: This potentially seminal paper not only provides insights into how the androgen receptor is activated in advanced prostate cancer but also offers broader import because the mechanism discovered may affect other oncogenic transcription factors that drive different human cancers.

14-3-3 Proteins Modulate the ETS Transcription Factor ET1 in Prostate Cancer

Sangphil Oh, Sook Shin, Stan A. Lightfoot, and Ralf Janknecht

Précis: This article provides mechanistic insight into the pathophysiology of multiple tumors, including prostate cancer and melanomas.

The DREAM Complex Mediates GIST Cell Quiescence and Is a Novel Therapeutic Target to Enhance Imatinib-Induced Apoptosis


Précis: A DNA repair protein that also participates in the control of cell cycle and transcription is found to exert profound effects on the invasive behavior of breast cancer cells, defining a new function for this protein and suggesting further investigations into its potential as a prognostic factor and therapeutic target.

DDB2: A Novel Regulator of NF-κB and Breast Tumor Invasion

Marie Ennen, Renni Klootz, Nadège Touche, Sonia Ledrappier, Lionel Domenjoud, Joseph Abecassis, François Plénat, and Philippe Becue

Précis: This study identifies DDB2 as a novel regulator of NF-κB and breast tumor invasion. This DNA repair protein also participates in the control of cell cycle and transcription, suggesting that it may play a role in the invasive behavior of breast cancer cells.

EGF Receptor Activates MET through MAPK to Enhance Non–Small Cell Lung Carcinoma Invasion and Brain Metastasis

Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, Minghui Zhao, Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, and Minnu Thomas

Précis: These results show how EGFR-MET signaling is critical for aggressive behavior in lung adenocarcinomas and rationalize its continued investigation as a therapeutic target in NSCLC, whether tumors harbor wild-type or mutant EGFR at early stages of progression.

Regulation of the Transcriptional Coactivator FHL2 Licenses Activation of the Androgen Receptor in Castrate-Resistant Prostate Cancer

Meagan J. McGrath, Lauren C. Binge, Abhorsn Siratana, Hong Wang, Paul A. Robinson, David Pook, Clare G. Fedele, Susan Brown, Jennifer M. Dyson, Denny L. Cottle, Belinda S. Cowling, Birunthi Niranjana, Gail P. Rishbridger, and Christina A. Mitchell

Précis: This potentially seminal paper not only provides insights into how the androgen receptor is activated in advanced prostate cancer but also offers broader import because the mechanism discovered may affect other oncogenic transcription factors that drive different human cancers.

14-3-3 Proteins Modulate the ETS Transcription Factor ET1 in Prostate Cancer

Sangphil Oh, Sook Shin, Stan A. Lightfoot, and Ralf Janknecht

Précis: This article provides mechanistic insight into the pathophysiology of multiple tumors, including prostate cancer and melanomas.

The DREAM Complex Mediates GIST Cell Quiescence and Is a Novel Therapeutic Target to Enhance Imatinib-Induced Apoptosis


Précis: A DNA repair protein that also participates in the control of cell cycle and transcription is found to exert profound effects on the invasive behavior of breast cancer cells, defining a new function for this protein and suggesting further investigations into its potential as a prognostic factor and therapeutic target.

DDB2: A Novel Regulator of NF-κB and Breast Tumor Invasion

Marie Ennen, Renni Klootz, Nadège Touche, Sonia Ledrappier, Lionel Domenjoud, Joseph Abecassis, François Plénat, and Philippe Becue

Précis: This study identifies DDB2 as a novel regulator of NF-κB and breast tumor invasion. This DNA repair protein also participates in the control of cell cycle and transcription, suggesting that it may play a role in the invasive behavior of breast cancer cells.

EGF Receptor Activates MET through MAPK to Enhance Non–Small Cell Lung Carcinoma Invasion and Brain Metastasis

Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, Minghui Zhao, Jerrica L. Breindel, Jonathan W. Haskins, Elizabeth P. Cowell, and Minnu Thomas

Précis: These results show how EGFR-MET signaling is critical for aggressive behavior in lung adenocarcinomas and rationalize its continued investigation as a therapeutic target in NSCLC, whether tumors harbor wild-type or mutant EGFR at early stages of progression.

Regulation of the Transcriptional Coactivator FHL2 Licenses Activation of the Androgen Receptor in Castrate-Resistant Prostate Cancer

Meagan J. McGrath, Lauren C. Binge, Abhorsn Siratana, Hong Wang, Paul A. Robinson, David Pook, Clare G. Fedele, Susan Brown, Jennifer M. Dyson, Denny L. Cottle, Belinda S. Cowling, Birunthi Niranjana, Gail P. Rishbridger, and Christina A. Mitchell

Précis: This potentially seminal paper not only provides insights into how the androgen receptor is activated in advanced prostate cancer but also offers broader import because the mechanism discovered may affect other oncogenic transcription factors that drive different human cancers.
RHPN2 Drives Mesenchymal Transformation in Malignant Glioma by Triggering RhoA Activation
Carla Danussi, Uri David Akavia, Francesco Niola, Andreja Jovic, Anna Lasorella, Dana Pe’er, and Antonio Iavarone

**Précis:** These results identify a key genetic module promoting the most aggressive cancer phenotype in glioblastoma patients, leading to the worst outcomes.

---

**PREVENTION AND EPIDEMIOLOGY**

A Sequence Polymorphism in miR-608 Predicts Recurrence after Radiotherapy for Nasopharyngeal Carcinoma
Jian Zheng, Jieqiong Deng, Mang Xiao, Lei Yang, Liyuan Zhang, Yonghe You, Min Hu, Na Li, Hongchun Wu, Wei Li, Jiachun Lu, and Yifeng Zhou

**Précis:** A single-nucleotide polymorphism in a microRNA that affects chromatid break repair can predict clinical outcomes after radiotherapy in nasopharyngeal cancer, with potentially broader implications for other DNA damaging cancer therapies.

---

Gleason Grade Progression Is Uncommon

**Précis:** These findings suggest that prostate tumor grade may be established early in tumorigenesis, with one implication being that patients newly diagnosed with early-stage and lower-grade disease may feel more comfortable on an active surveillance protocol.

---

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

A Novel Class of Anticancer Compounds Targets the Actin Cytoskeleton in Tumor Cells

**Précis:** This study offers a preclinical proof of concept for small molecules that target the actin cytoskeleton of cancer cells as an efficacious treatment strategy.

---

RG7116, a Therapeutic Antibody That Binds the Inactive HER3 Receptor and Is Optimized for Immune Effector Activation
Christian Mirschberger, Christian B. Schiller, Michael Schräml, Nikolas Dimoudis, Thomas Friess, Christian A. Gerdes, Ulrike Reiff, Valeria Lilke, Gabriele Hoelzlswimmer, Irene Kolm, Karl-Peter Hopfner, Gerhard Niederfellner, and Birgit Bossenmaier

**Précis:** As a central integrator of the EGF family receptor system in cancer, HER3 offers an appealing therapeutic target in many types of human cancer.

---

Inhibitor-Sensitive FGFR2 and FGFR3 Mutations in Lung Squamous Cell Carcinoma

**Précis:** These findings provide a rationale to target certain lung or head and neck squamous cell carcinomas with FGFR inhibitors that are currently in clinical trials, possibly identifying patient populations that may benefit the most.

---

Cotargeting Androgen Receptor and Clusterin Delays Castrate-Resistant Prostate Cancer Progression by Inhibiting Adaptive Stress Response and AR Stability
Hiroaki Matsumoto, Yoshiaki Yamamoto, Masaki Shiota, Hidetoshi Kuruma, Eliana Beraldi, Hideyasu Matsuyama, Amina Zoubeidi, and Martin Gleave

**Précis:** This study offers a mechanism-based strategy to leverage the therapeutic effects of androgen receptor antagonists in advanced prostate cancer, which remains a deadly scourge.

---

mTOR Signaling Feedback Modulates Mammary Epithelial Differentiation and Restrains Invasion Downstream of PTEN Loss
Susmita Ghosh, Lidenys Varela, Akshay Sood, Ben Ho Park, and Tamara L. Lotan

**Précis:** This report suggests additional new cautions regarding the use of mTOR inhibitors for cancer treatment, contributing to ongoing controversies about their potential utility.
Manganoporphyrins Increase Ascorbate-Induced Cytotoxicity by Enhancing H₂O₂ Generation

Malvika Rawal, Samuel R. Schroeder, Brett A. Wagner, Cameron M. Cushing, Jessemae L. Welsh, Anna M. Button, Juan Du, Zita A. Sibennaller, Garry R. Buettner, and Joseph J. Cullen

Précis: A class of porphyrins being developed as superoxide dismutase mimics have the potential to safely leverage the anticancer effects of pharmacologic ascorbate therapy.

Intratumoral Modeling of Gefitinib Pharmacokinetics and Pharmacodynamics in an Orthotopic Mouse Model of Glioblastoma

Jyoti Sharma, Hua Lv, and James M. Gallo

Précis: The major issue of heterogeneity in solid tumors, having been characterized yet again by deep sequencing studies, dramatically affects intratumoral drug activities, for which better models are needed to enhance our understanding.

Potassium Channel KCNA1 Modulates Oncogene-Induced Senescence and Transformation

Hélène Lallet-Daher, Clotilde Wiel, Delphine Gitenay, Naveenan Navaratnam, Arnaud Augert, Benjamin Le Calvé, Stéphanie Verbeke, David Carling, Sébastien Aubert, David Vindrieux, and David Bernard

Précis: This study identifies a novel tumor suppressor pathway that restricts oncogenesis by triggering premature senescence.

CTEN Prolongs Signaling by EGFR through Reducing Its Ligand-Induced Degradation

Shiao-Ya Hong, Yi-Ping Shih, Tianhong Li, Kermit L. Carraway III, and Su Hao Lo

Précis: The most effective therapeutic targeting of EGFR for cancer therapy will likely be based in part on an understanding of the epigenetic conditions that contribute to its effective stabilization.

O-GlcNAc Transferase Integrates Metabolic Pathways to Regulate the Stability of c-MYC in Human Prostate Cancer Cells

Harri M. Itkonen, Sarah Minner, Ingrid J. Guldvik, Mareike Julia Sandmann, Maria Christina Tsourlakis, Viktor Berge, Aud Svindland, Thorsten Schomm, and Ian G. Mills

Précis: Targeting a protein glycosylation pathway that is dysregulated by metabolic flux in cancer cells blocks MYC and inhibits cancer cell proliferation, possibly offering a broad-based anticancer strategy.

JAK-STAT Blockade Inhibits Tumor Initiation and Clonogenic Recovery of Prostate Cancer Stem-like Cells

Paula Kroon, Paul A. Berry, Michael J. Stower, Greta Rodrigues, Vincent M. Mann, Matthew Simms, Deepak Bhasin, Somsundaram Chettiar, Chenglong Li, Pui-Kai Li, Norman J. Maitland, and Anne T. Collins

Précis: The most primitive cells in prostate cancer require STAT3 for survival, further rationalizing this molecule as a therapeutic target to treat advanced prostate cancer.
ABOUT THE COVER

The actin cytoskeleton, due to its role in many processes involved in cellular transformation, has long been a sought after anticancer target, yet attempts to develop such compounds have been hampered by unacceptable toxicity. By targeting the other core polymer system of the microfilaments, tropomyosin, it is possible to discriminate between actin filaments required for sarcomeric function and those required for tumor growth. In silico modeling shows the predicted association of the first in class anti-tropomyosin compound, TR100, with the C-terminus of a cancer-associated tropomyosin, Tm5NM1. The interaction between Tm5NM1 and TR100 results in disruption of actin filament organization and death of tumor cells, both in vitro and in vivo. For details, see article by Stehn and colleagues on page 5169.