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# Cancer Research

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*Précis:* A comprehensive metabolic study of hepatocellular carcinoma defines two novel candidate metabolic biomarkers for this disease.

## MICROENVIRONMENT AND IMMUNOLOGY

- 5003 | **Myeloid-Derived Suppressor Cells as a Vehicle for Tumor-Specific Oncolytic Viral Therapy**

Samuel Eisenstein, Brian A. Coakley, Karen Briley-Saebo, Ge Ma, Hui-ming Chen, Marcia Meseck, Stephen Ward, Celia Divino, Savio Woo, Shu-Hsia Chen, and Ping-Ying Pan

*Précis:* This preclinical study highlights the efficacy of a specific myeloid cell type to serve as a key delivery vehicle for oncolytic viruses that significantly improves tumor killing, prolonging survival and minimizing toxicity.

- 5016 | **TGF- $\beta$  Modulates Ovarian Cancer Invasion by Upregulating CAF-Derived Versican in the Tumor Microenvironment**

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

*Précis:* These findings suggest a central mechanism through which TGF- $\beta$ -targeted therapies may alter the invasive capacity of cancer cells by acting through their microenvironment.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5029 | **Gene Profiling of Canine B-Cell Lymphoma Reveals Germinal Center and Postgerminal Center Subtypes with Different Survival Times, Modeling Human DLBCL**

Kristy L. Richards, Alison A. Motsinger-Reif, Hsiao-Wei Chen, Yuri Fedoriv, Cheng Fan, Dahlia M. Nielsen, George W. Small, Rachael Thomas, Chris Smith, Sandeep S. Dave, Charles M. Perou, Matthew Breen, Luke B. Borst, and Steven E. Suter

*Précis:* This study reveals the remarkable molecular similarity between human and canine forms of a certain type of B-cell lymphoma, overcoming limitations in existing models that have impeded the advancement of etiologic and therapeutic insights.

- 5040 **DDB2: A Novel Regulator of NF- $\kappa$ B and Breast Tumor Invasion**  
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*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.
- 5053 **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, Don X. Nguyen, and David F. Stern  
*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.
- 5066 **Regulation of the Transcriptional Coactivator FHL2 Licenses Activation of the Androgen Receptor in Castrate-Resistant Prostate Cancer**  
Meagan J. McGrath, Lauren C. Binge, Absorn Sriratana, Hong Wang, Paul A. Robinson, David Pook, Clare G. Fedele, Susan Brown, Jennifer M. Dyson, Denny L. Cottle, Belinda S. Cowling, Birunthi Niranjani, Gail P. Risbridger, 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.
- 5080 **Extracellular RNA Liberates Tumor Necrosis Factor- $\alpha$  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.
- 5090 **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.
- 5100 **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.
- 5110 **14-3-3 Proteins Modulate the ETS Transcription Factor ETV1 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.
- 5120 **The DREAM Complex Mediates GIST Cell Quiescence and Is a Novel Therapeutic Target to Enhance Imatinib-Induced Apoptosis**  
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*Précis:* Dissecting the molecular pathways that lead to tumor cell quiescence after targeted therapies leads to novel treatment strategies that potentially can extend survival.
- 5130 **Reprogramming the Chromatin Landscape: Interplay of the Estrogen and Glucocorticoid Receptors at the Genomic Level**  
Tina B. Miranda, Ty C. Voss, Myong-Hee Sung, Songjoon Baek, Sam John, Mary Hawkins, Lars Grøntved, R. Louis Schiltz, and Gordon L. Hager  
*Précis:* These results define an epigenetic mechanism that can explain how the estrogen and glucocorticoid receptors can dictate the binding patterns of other steroid receptors across the genome.

5140 | **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.*

5183 | **RG7116, a Therapeutic Antibody That Binds the Inactive HER3 Receptor and Is Optimized for Immune Effector Activation**

Christian Mirschberger, Christian B. Schiller, Michael Schräml, Nikolaos Dimoudis, Thomas Friess, Christian A. Gerdes, Ulrike Reiff, Valeria Lifke, Gabriele Hoelzlwimmer, 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.*

## PREVENTION AND EPIDEMIOLOGY

5151 | **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.*

5195 | **Inhibitor-Sensitive FGFR2 and FGFR3 Mutations in Lung Squamous Cell Carcinoma**

Rachel G. Liao, Joonil Jung, Jeremy Tchaicha, Matthew D. Wilkerson, Andrey Sivachenko, Ellen M. Beauchamp, Qingsong Liu, Trevor J. Pugh, Chandra Sekhar Pedamallu, D. Neil Hayes, Nathanael S. Gray, Gad Getz, Kwok-Kin Wong, Robert I. Haddad, Matthew Meyerson, and Peter S. Hammerman

**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.*

5163 | **Gleason Grade Progression Is Uncommon**

Kathryn L. Penney, Meir J. Stampfer, Jaquelyn L. Jahn, Jennifer A. Sinnott, Richard Flavin, Jennifer R. Rider, Stephen Finn, Edward Giovannucci, Howard D. Sesso, Massimo Loda, Lorelei A. Mucci, and Michelangelo Fiorentino

**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.*

5206 | **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.*

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5169 | **A Novel Class of Anticancer Compounds Targets the Actin Cytoskeleton in Tumor Cells**



Justine R. Stehn, Nikolas K. Haass, Teresa Bonello, Melissa Desouza, Gregg Kottyan, Herbert Treutlein, Jun Zeng, Paula R.B.B. Nascimento, Vanessa B. Sequeira, Tanya L. Butler, Munif Allanson, Thomas Fath, Timothy A. Hill, Adam McCluskey, Galina Schevzov, Stephen J. Palmer, Edna C. Hardeman, David Winlaw, Vivienne E. Reeve, Ian Dixon, Wolfgang Weninger, Timothy P. Cripe, and Peter W. Gunning

**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.*

5218 | **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.*

5232

**Manganoporphyrins Increase Ascorbate-Induced Cytotoxicity by Enhancing H<sub>2</sub>O<sub>2</sub> Generation**

Malvika Rawal, Samuel R. Schroeder, Brett A. Wagner, Cameron M. Cushing, Jessemmae L. Welsh, Anna M. Button, Juan Du, Zita A. Sibenaller, 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.

5242

**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.

5266

**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.

5277

**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 Svinland, Thorsten Schlomm, 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.

**TUMOR AND STEM CELL BIOLOGY**

5253

**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.

5288

**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.

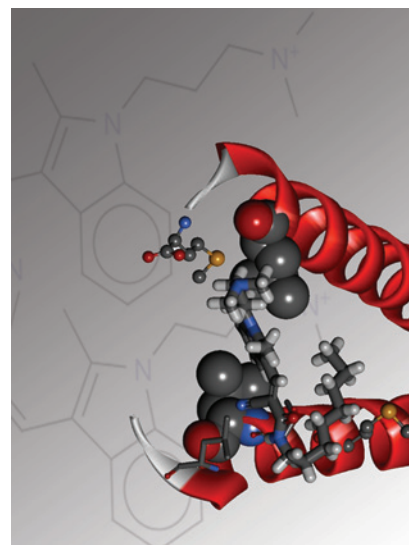
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## ABOUT THE COVER

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.



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