Highlights from Recent Cancer Literature

Targeting the Tumor Microenvironment: From Understanding Pathways to Effective Clinical Trials
Hua Fang and Yves A. DeClerck

p63, Sharp1, and HIFs: Master Regulators of Metastasis in Triple-Negative Breast Cancer
Stefano Piccolo, Elena Enzo, and Marco Montagner

Early B-Cell Differentiation in Merkel Cell Carcinomas: Clues to Cellular Ancestry
Axel zur Hausen, Dorit Rennspiess, Veronique Winnepenninckx, Ernst-Jan Speel, and Anna Kordelia Kurz

The 19th Annual Prostate Cancer Foundation Scientific Retreat: Meeting Report
Guneet Walia, Kenneth J. Pienta, Jonathan W. Simons, and Howard R. Soule

Metabolic Characterization of Hepatocellular Carcinoma Using Nontargeted Tissue Metabolomics
Qiang Huang, Yexiong Tan, Peiyuan Yin, Guozhu Ye, Peng Gao, Xin Lu, Hongyang Wang, and Guowang Xu

Myeloid-Derived Suppressor Cells as a Vehicle for Tumor-Specific Oncolytic Viral Therapy
Samuel Eisenstein, Brian A. Coinkey, Karen Briley-Sarbas, Ge Ma, Hui-ming Chen, Marcia Meseck, Stephen Ward, Celia Divino, Savio Woo, Shu-Hsia Chen, and Ping-Ying Pan

Precis: 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.

TGF-β Modulates Ovarian Cancer Invasion by Upregulating CAF-Derived 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

Precis: These findings suggest a central mechanism through which TGF-β-targeted therapies may alter the invasive capacity of cancer cells by acting through their microenvironment.

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 Fedoriw, 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

Precis: 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.
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 D. 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 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.

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

Sergei Boichuk, Joshua A. Parry, Kathleen R. Makielki, Larisa Litovchick, Juliane L. Baron, James P. Zewe, Agnieszka Wozniak, Keith R. Mehalek, Julianne L. Baron, Ty C. Voss, Myong-Hee Sung, Tina Miranda, Serhiy Dzhelil, and Anette Duensing

Précis: Dissecting the molecular pathways that lead to tumor cell quiescence after targeted therapies leads to novel treatment strategies that potentially can extend survival.

Reprogramming the Chromatin Landscape: Interplay of the Estrogen and Glucocorticoid Receptors at the Genomic Level

Tina Miranda, Ty C. Yoss, Myong-Hee Sung, Songjooon Bark, Sam John, Mary Hawkins, Lars Granvold, R. Louis Schiltz, and Gordon L. Hager

Précis: This article provides mechanistic insight into how the estrogen and glucocorticoid receptors can dictate the binding patterns of other steroid receptors across the genome.
**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.

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**5163**

**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.

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**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**5169**

**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.

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**5183**

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

Christian Mirschberger, Christian B. Schiller, Michael Schraml, Nikolaos Dimoudis, Thomas Friess, Christian A. Gerdes, Ulrike Reiff, Valeria Lifke, Gabriele Hoelzlzimmer, 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.
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. 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.

Intramural 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 Svinland, 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.

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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.