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Kathleen H. Goss and Michelle M. Le Beau

#### REVIEW

**2138** Cancer Cell Dormancy in Novel Mouse Models for Reversible Pancreatic Cancer: A Lingering Challenge in the Development of Targeted Therapies

Wan-Chi Lin, Nirakar Rajbhandari, and Kay-Uwe Wagner

#### PRIORITY REPORT

**2144** A Specific STAT3-Binding Peptide Exerts Antiproliferative Effects and Antitumor Activity by Inhibiting STAT3 Phosphorylation and Signaling

Daejin Kim, In-Hyun Lee, Sunghyun Kim, Minsuk Choi, Hyungjun Kim, Sukyung Ahn, Phei Er Saw, Hyungsu Jeon, Yumi Lee, and Sangyong Jon

**Précis:** These results offer preclinical proof of concept for a novel type of bioactive STAT3 inhibitor that may be tractable for clinical development, addressing a long-standing challenge to target the broad array of cancers harboring constitutively activated STAT3.

#### CLINICAL STUDIES

**2152** Detection of Brain Tumor Cells in the Peripheral Blood by a Telomerase Promoter-Based Assay

Kelly M. MacArthur, Gary D. Kao, Sanjay Chandrasekaran, Michelle Alonso-Basanta, Christina Chapman, Robert A. Lustig, E. Paul Wileyro, Stephen M. Hahn, and Jay F. Dorsey

**Précis:** This study suggests how the ubiquity of telomerase activation in tumor cells might be exploited as a generalized strategy to detect circulating tumor cells in cancer patients as a tool to monitor therapeutic response and disease relapse.

#### INTEGRATED SYSTEMS AND TECHNOLOGIES

**2160** Novel Methylated Biomarkers and a Robust Assay to Detect Circulating Tumor DNA in Metastatic Breast Cancer

Mary Jo Fackler, Zoila Lopez Bujanda, Christopher Umbricht, Wei Wen Teo, Soonweng Cho, Zhe Zhang, Kala Visvanathan, Stacie Jeter, Pedram Argani, Chenguang Wang, Jaclyn P. Lyman, Marina de Brot, James N. Ingle, Judy Boughey, Kandace McGuire, Tari A. King, Lisa A. Carey, Leslie Coppe, Antonio C. Wolff, and Saraswati Sukumar

**Précis:** This report describes a multiplexed PCR method for detecting circulating methylated DNA in the serum of patients with metastatic breast cancer, offering >90% sensitivity and specificity to detect disease.

#### MICROENVIRONMENT AND IMMUNOLOGY

**2171** Immunosurveillance by Antiangiogenesis: Tumor Growth Arrest by T Cell–Derived Thrombospondin-1

Keri L. Schadler, Erika J. Crosby, Alice Yao Zhou, Dong Ha Bhang, Lior Braunstein, Kwan Hyuck Baek, Danielle Crawford, Alison Crawford, Jill Angelosanto, E. John Wherry, and Sandra Ryeeom

**Précis:** Tumorigenesis can be blocked by an antiangiogenic process triggered by acute viral infection, suggesting a novel and simple immunologic approach to stimulate an endogenous antiangiogenic therapy for cancer.

**2182** p53 and NF-κB Coregulate Proinflammatory Gene Responses in Human Macrophages

Julie M. Lowe, Daniel Menendez, Pierre R. Busnel, Maria Shatz, Erin L. Kirk, Melissa A. Troester, Stavros Garantziotis, Michael B. Fessler, and Michael A. Resnick

**Précis:** These findings implicate macrophage p53 in conditioning the immune microenvironment of tumors, and they suggest how p53-activating chemotherapeutics can attack tumor cells lacking p53 function.

**2193** RAE1 Ligands for the NKG2D Receptor Are Regulated by STING-Dependent DNA Sensor Pathways in Lymphoma

Adeline R. Lam, Nina Le Bert, Samantha S.W. Ho, Ru J. Shen, Melissa L.F. Tang, Gordon M. Xiong, J. Ludovic Croxford, Christine X. Koo, Ken J. Ishii, Shizuo Akira, David H. Raulet, and Stephan Gasser

**Précis:** This study reveals how the DNA damage response activated in cancer cells leads to upregulation of ligands that are recognized by natural killer cells, allowing an important early mechanism of tumor immunosurveillance that must be overcome during tumorigenesis.
High Numbers of Differentiated Effector CD4 T Cells Are Found in Patients with Cancer and Correlate with Clinical Response after Neoadjuvant Therapy of Breast Cancer

Isabelle Péguellet, Maud Milder, Delphine Louis, Anne Vincent-Salomon, Thierry Dorval, Sophie Piperno-Neumann, Suzy M. Scholl, and Olivier Lantz

**Précis:** Effector CD4 T cells increase in the blood of cancer patients, and this increase correlates with response to neoadjuvant chemotherapy, implicating CD4 T cells in tumor regression.

Foxp3+ T Cells Inhibit Antitumor Immune Memory Modulated by mTOR Inhibition

Yanping Wang, Tim Sparwasser, Robert Figlin, and Hyung L. Kim

**Précis:** These findings offer a preclinical proof of concept for the combinatorial efficacy of mTOR inhibition with depletion of T regulatory cells, which enhances antitumor immune memory.

Autocrine Motility Factor Modulates EGF-Mediated Invasion Signaling

Dhong Hyo Kho, Tianpeng Zhang, Vitaly Balan, Yi Wang, Seung-Wook Ha, Youming Xie, and Avraham Raz

**Précis:** These findings show how a cytokine secreted in the tumor microenvironment modulates EGF-induced invasion and heightens acquired drug resistance.

Vemurafenib Cooperates with HPV to Promote Initiation of Cutaneous Tumors

Matthew Holdershield, Edward Lorenzana, Ben Weisburn, Lisa Lomovasky, Lise Boussemart, Ludovic Lacroix, Gorana Tomasic, Michel Favre, Stephan Vagner, Caroline Robert, Majid Ghoddusi, Dylan Daniel, Nancy Pryer, Frank McCormick, and Darrin Stuart

**Précis:** RAF inhibitors used to treat melanoma patients paradoxically activate MAPK signaling, which this report shows will cooperate with HPV infections in the skin to promote formation of squamous cancers and other skin lesions as a side effect of drug treatment.

E3 Ubiquitin Ligase HOIP Attenuates Apoptotic Cell Death Induced by Cisplatin


**Précis:** These results identify a candidate therapeutic target for the development of combinatorial chemotherapies to potentiate the efficacy of platinum-based anticancer drugs, a mainstay of the medical oncology clinic.

RSF1 Is a Positive Regulator of NF-κB-Induced Gene Expression Required for Ovarian Cancer Chemoresistance

Yeong-In Yang, Ji-Hye Ahn, Kyung-Tae Lee, Je-Ming Shih, and Jung-Hye Choi

**Précis:** This study identifies a mechanistic basis to understand chemoresistance in ovarian cancer, with implications for improving treatment of late stages of this disease.

Androgen Receptor Splice Variants Determine Taxane Sensitivity in Prostate Cancer

Maria Thadani-Mulero, Luigi Portella, Shihua Sun, Matthew Sung, Alexandre Matov, Robert L. Vessella, Eva Corey, David M. Nanus, Stephen R. Plymate, and Pariskevi Giannakakou

**Précis:** This important work suggests that different androgen receptor variants that accumulate in advanced prostate cancer cells utilize distinct pathways of nuclear import that affect the efficacy of taxane treatment, suggesting a strategy for individualized treatment that might improve clinical outcomes.

Identification of a Tumor-Suppressive Human-Specific MicroRNA within the FHIT Tumor-Suppressor Gene

Baicheng Hu, Xiaomin Ying, Jian Wang, Jittima Piriyapongsa, I. King Jordan, Jipo Sheng, Fang Yu, Po Zhao, Yizhuo Li, Hongyan Wang, Wook Loon Ng, Shuofeng Hu, Xiang Wang, Chenguang Wang, Xiaofei Zheng, Wuju Li, Walter J. Curran, and Ya Wang

**Précis:** These findings illustrate the importance of a relatively small but unique class of human-specific microRNAs in tumor suppression, with possible implications in how to interpret in human cancer the action of the tumor suppressor FHIT, within which a new member of this microRNA class was found.

IGF-I Regulates Redox Status in Breast Cancer Cells by Activating the Amino Acid Transport Molecule xC−

Yuzhe Yang and Douglas Yee

**Précis:** These findings suggest that targeting a cell surface amino acid transporter may heighten the therapeutic efficacy of anti-IGF1 receptor inhibitors, which may be broadly useful in treating various solid tumors.
A Systems Biology Approach Identifies Effective Tumor–Stroma Common Targets for Oral Squamous Cell Carcinoma

Wenxia Meng, Yun Wu, Xin He, Chuanxia Liu, Qinghong Gao, Lin Ge, Lanyan Wu, Ying Liu, Yaqing Guo, Xiaoyu Li, Yurong Liu, Sixiu Chen, Xianli Kong, Zhi Liang, and Hongmei Zhou

**Précis:** This study suggests a concept aimed at identifying drug targets that would be beneficial to attack in cancer cells and adjacent stromal cells simultaneously, offering a discovery framework for future drug combination strategies.

HO-3867, a Safe STAT3 Inhibitor, Is Selectively Cytotoxic to Ovarian Cancer


**Précis:** The orally active compound described may offer a long awaited translational opportunity to target STAT3 in the large number of cancer patients in whom STAT3 upregulation not only drives tumor cell growth but also immune escape, as an appealing tool for immunochemotherapy.

Context-Selective Death of Acute Myeloid Leukemia Cells Triggered by the Novel Hybrid Retinoid-HDAC Inhibitor MC2392

Floriana De Bellis, Vincenzo Carafa, Mariarosaria Conte, Dante Rotili, Francesca Petraglia, Filomena Matarese, Kees-Jan Françojs, Julien Ablain, Sergio Valente, Remy Castellano, Armelle Goubard, Yves Collette, Amit Mandoli, Joost H.A. Martens, Hendrik G. Stunnenberg, and Lucia Altucci

**Précis:** These findings offer preclinical evidence that targeting multiple signaling pathways with a single hybrid drug is a feasible and attractive paradigm for new cancer therapies.

Loss of NF1 in Cutaneous Melanoma Is Associated with RAS Activation and MEK Dependence

Moriah H. Nissan, Christine A. Pratilas, Alexis M. Jones, Ricardo Ramirez, Helen Won, Cailian Liu, Shakuntala Tiwari, Li Kong, Aparnithi J. Hanrahan, Zhan Yao, Taha Merghoub, Antoni Ribas, Paul B. Chapman, Rona Yaeger, Barry S. Taylor, Nikolaus Schultz, Michael F. Berger, Neal Rosen, and David B. Solit

**Précis:** The mechanistic consequences of NF1 loss in melanoma have clinical impact not only for treatment of melanoma, but also for neurofibromatosis type 1 and other cancers in which NF1 is altered.

Identification of FoxR2 as an Oncogene in Medulloblastoma

Hideto Koso, Asano Tsuhako, Eli Lyons, Jerrold M. Ward, Alistair G. Rust, David J. Adams, Nancy A. Jenkins, Neal G. Copeland, and Sumiko Watanabe

**Précis:** A transposon screen for medulloblastoma cancer genes identifies new genes that regulate SHH signaling and proliferation of granule neuron precursors.

Cofilin Drives Cell-Invasive and Metastatic Responses to TGF-β in Prostate Cancer

Joanne Collazo, Beibei Zhu, Spencer Larkin, Sarah K. Martin, Hong Pu, Craig Horbinski, Shahriar Koochekpour, and Natasha Kyripanou

**Précis:** An F-actin severing protein that is required for cytoskeletal reorganization, filopodia formation, and cell migration is found to be critical for metastasis, with potential implications on how to disrupt this central feature of cancer progression.

Correction: A Transgenic Mouse Model for Early Prostate Metastasis to Lymph Nodes
ABOUT THE COVER

Androgen receptor (AR) nuclear accumulation and transcriptional activity is critical for prostate cancer growth in hormone-naïve and castration resistant disease (CRPC). The taxanes, microtubule-stabilizing drugs, are widely used in the treatment of CRPC. The dynein motor protein to efficiently traffic AR to the nucleus utilizes microtubule dynamics. Taxane treatment interferes with this process and sequesters AR in the cytoplasm. AR splice variants are often expressed in CRPC and confer resistance to androgen deprivation therapies. Using confocal microscopy of prostate cancer cells expressing ARv567 (green) and the dynein accessory protein dynamin (red) whose expression inhibits dynein-cargo binding, we show that ARv567 variant, similar to the AR wt, utilizes dynein motor protein and microtubules to efficiently translocate to the nucleus. For details, see article by Thadani-Mulero and colleagues on page 2270.