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BREAKING ADVANCES

- 2133 **Highlights from Recent Cancer Literature**

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- 2135 **Janet Davison Rowley: In Memoriam (1925–2013)**
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 Wileyto, 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 Cope, 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 Ryeom
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- κ B Coregulate Proinflammatory Gene Responses in Human Macrophages**
Julie M. Lowe, Daniel Menendez, Pierre R. Bushel, 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, Yu 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, enabling an important early mechanism of tumor immunosurveillance that must be overcome during tumorigenesis.

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- 2204 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 Péguillet, 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.

- 2217 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.

- 2229 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 2238 Vemurafenib Cooperates with HPV to Promote Initiation of Cutaneous Tumors**
Matthew Holderfield, Edward Lorenzana, Ben Weisburd, Lisa Lomovasky, Lise Boussemart, Ludovic Lacroix, Gorana Tomasic, Michel Favre, Stephan Vagner, Caroline Robert, Majid Ghodduzi, 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.

- 2246 E3 Ubiquitin Ligase HOIP Attenuates Apoptotic Cell Death Induced by Cisplatin**
Craig MacKay, Eilis Carroll, Adel F.M. Ibrahim, Amit Garg, Gareth J. Inman, Ronald T. Hay, and Arno F. Alpi

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.

- 2258 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, Ie-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.

- 2270 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 Paraskevi 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.

- 2283 Identification of a Tumor-Suppressive Human-Specific MicroRNA within the FHIT Tumor-Suppressor Gene**
Baocheng Hu, Xiaomin Ying, Jian Wang, Jittima Piriyaopongsa, I. King Jordan, Jipo Sheng, Fang Yu, Po Zhao, Yazhuo Li, Hongyan Wang, Wooi Loon Ng, Shuofeng Hu, Xiang Wang, Chenguang Wang, Xiaofei Zheng, Wujun 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.


THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2295 IGF-1 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.

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- 2306** **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, Yiqing Guo, Xiaoyu Li, Yurong Liu, Sixiu Chen, Xiangli 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.
- 2316** **HO-3867, a Safe STAT3 Inhibitor, Is Selectively Cytotoxic to Ovarian Cancer**
Kellie S. Rath, Shan K. Naidu, Pushpa Lata, Hemant K. Bid, Brian K. Rivera, Georgia A. McCann, Brent J. Tierney, Adam C. ElNaggar, Veronica Bravo, Gustavo Leone, Peter Houghton, Kálmán Hideg, Periannan Kuppusamy, David E. Cohn, and Karuppaiyah Selvendiran
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.
- 2328** **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 François, Julien Ablain, Sergio Valente, Remy Castellano, Armelle Goubard, Yves Collette, Amit Mandoli, Joost H.A. Martens, Hugues de Thé, Angela Nebbioso, Antonello Mai, 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.

- 2340** **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, Aphrothiti 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.

TUMOR AND STEM CELL BIOLOGY

- 2351** **Identification of FoxR2 as an Oncogene in Medulloblastoma**
Hideto Koso, Asano Tshako, 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.
- 2362** **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 Kyprianou
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

- 2374** **Correction: A Transgenic Mouse Model for Early Prostate Metastasis to Lymph Nodes**

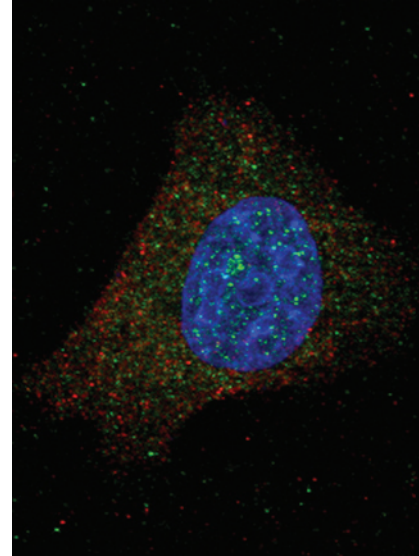
 AC icon indicates Author Choice

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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 dynamitin (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.



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