## BREAKING ADVANCES

1647  
**Highlights from Recent Cancer Literature**

## REVIEW

1649  
**Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy**  
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

## MEETING REPORT

1658  
**Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential**  
Stine F. Pedersen and Christian Stock

## PRIORITY REPORTS

1662  
**G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin**  
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher  
**Précis:** This important study suggests a rational approach to limiting the well-known cardiotoxic effects of doxorubicin (adriamycin), one of the most effective and widely used cytotoxic chemotherapy drugs for cancer treatment.

1668  
**Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network**  
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui  
**Précis:** Findings reveal a previously unappreciated function for p53 in maintaining an immunological microenvironment that can suppress tumorigenesis and progression.

## CLINICAL STUDIES

1676  
**Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients**  
**Précis:** Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

1689  
**Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model**  
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann  
**Précis:** This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.

1699  
**Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response**  
David L. Masica and Rachel Karchin  
**Précis:** New methods are offered to improve the identification of drug response biomarkers in cancer cells.

## MICROENVIRONMENT AND IMMUNOLOGY

1709  
**Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer**  
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr  
**Précis:** The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

Précis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma


Précis: HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

IFN-γ-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence

Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

Précis: By helping resolve an inflammatory response, IFNγ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth

Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Bishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

Précis: This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsigh, Stine Kjelbæk Andersen, Tobias Virendradou Jensens, Inge Marie Svane, and Mads Hald Andersen

Précis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.
1821 Dormant Cancer Cells Contribute to Residual Disease in a Model of Reversible Pancreatic Cancer


1831 Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation
Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel

Precis: Findings argue that tyrosine kinase growth factor signaling directly affects glucose metabolism in glioma and is not a secondary response to enhanced proliferation, as suggested in other cancer models.

1844 Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C
Geridine J. Stout and Maria A. Blasco

Precis: Findings reveal a role for the DNA repair protein XPC in telomere stability and how activation occurs for the ALT pathway of telomere maintenance, a broadly important aspect of tumor formation.

1855 xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma
Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshifumi Yae, Takeshi Motohara, Eiji Suqihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshizawa, Shuichi Kawashiri, Makio Mukai, Seiji Asoda, Hirohisa Kawamura, Taneaki Nakagawa, Hideyuki Saya, and Osamu Nagano

Precis: Cells that express variant isoforms of the stem cell-determining factor CD44 rely on the activity of a cystine transporter subunit that affects redox status and EGFR function.

1867 MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients
Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu

Precis: This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.

1876 Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women
Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Strom, Mimi C. Yu, and Anna H. Wu

Precis: Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.

1883 Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer
Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Helo Nevanlinna, Jianjun Liu, and Diana Eccles

Precis: This study maps host genetic variations that affect risks of poor prognosis in early onset breast cancer patients, with implications for how aggressive treatments should be used to improve survival outcomes.

1892 Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors
Ryan Alkins, Alison Burgess, Milan Ganguly, Giulio Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen

Precis: Noninvasive MR-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.

1900 Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer
Salahaldin A. Tahir, Guang Yang, Alexei Goltsov, Ki-Duk Song, Chengzheng Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson

Precis: This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.
1958 Phenotypic Profiling of ALPPL-2 Is a Novel Inhibitor of STAT3

Alkaline Phosphatase ALPPL-2 Is a Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation

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Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein

mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis

Phenotypic Profiling of DPYD Variations Relevant to 5-Fluorouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity

TUMOR AND STEM CELL BIOLOGY

Involvement of Lyn and the Atypical Kinase Skg269/PEAK1 in a Basal Breast Cancer Signaling Pathway

FOX2 Expression Links Epithelial–Mesenchymal Transition and Stem Cell Properties in Breast Cancer

Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity

Genetic Amplification of the NOTCH Modulator LN2X Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer

Gene

Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis

ROBERT B. DIASIO
CROIX FOSSUM, KANGSHENG WANG, AND STEVEN M. OFFER

NATALIE J. WEGNER, SHI-YONG SUN, LIQUN ZHAO, PING YUE, FADLO R. KHURI, AND MING-SOUND TSAO

SOYOUN KIM, AND DONG-KI LEE

Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Nicholas J. Lawrence, and Saïd M. Sebti

Harshani R. Lawrence, Wayne C. Guida, Hua Yang, Murali K. Urlam, Xiaolei Zhang, Ying Sun, Roberta Pireddu, Antonio Marchetti, and Alberto Bardelli

Davide Romanelli, Milo Frattini, Emily Hannah Crowley, Francesco Sassi, Simona Lamba, Elisa VitIELLO, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli

Précis: Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

Précis: Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

Précis: This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

Précis: Findings of this study suggest an aptamer selection strategy identifies an enzyme that may be useful for blood-based detection of pancreatic cancer.

Précis: Findings support the development of small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

Précis: Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

Précis: This study provides critical support in cancer cells and the immune microenvironment in tumors, but bioactive small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

Précis: Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

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ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.