**BREAKING ADVANCES**

2905  Highlights from Recent Cancer Literature

**REVIEW**

2907  Discovery of Mesothelin and Exploiting It as a Target for Immunotherapy  
Ira Pastan and Raffit Hassan

**PERSPECTIVE**

2913  Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States  
Lola Rahib, Benjamin D. Smith, Rhonda Aizenberg, Allison B. Rosenzweig, Julie M. Fleshman, and Lynn M. Matrisian

**MEETING REPORT**

2922  Cancer Stem Cells: Constantly Evolving and Functionally Heterogeneous Therapeutic Targets  
Tao Yang, Kiera Rycaj, Zhong-Min Liu, and Dean G. Tang

**CLINICAL STUDIES**

2928  Loss of LRIG1 Locus Increases Risk of Early and Late Relapse of Stage I/II Breast Cancer  
Patricia A. Thompson, Ingrid Ljuslinder, Spyros Tsavachidis, Abenaa Brewster, Aysegul Sahin, Hakim Hedman, Roger Henriksson, Melissa L. Bondy, and Beatrice S. Melin  
Précis: This study addresses the lack of robust biomarkers that can predict relapse more than 5 years after diagnosis of early-stage breast cancer.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

2936  Selection of Personalized Patient Therapy through the Use of Knowledge-Based Computational Models That Identify Tumor-Driving Signal Transduction Pathways  
Wim Verhaegh, Henk van Ooijen, Marcella A. Inda, Pantelis Hatzis, Rogier Versteeg, Marcel Smid, John Martens, John Foekens, Paul van de Wiel, Hans Clevers, and Anja van de Stolpe  
Précis: By conducting an initial clinical validation, this study illustrates the power of a novel computational approach to model oncogenic signaling pathways from tissue-derived transcriptome data for use as a diagnostic tool to tailor therapy to individual cancer patients.

2946  Predictive Performance of Microarray Gene Signatures: Impact of Tumor Heterogeneity and Multiple Mechanisms of Drug Resistance  
Charlotte K. Ng, Britta Weigelt, Roger A’Hern, Francois-Clement Bidard, Christophe Lemetre, Charles Swanton, Rongli Shen, and Jorge S. Reis-Filho  
Précis: This bioinformatics study offers an explanation why gene signatures generally offer such poor utility as clinical predictors, based on the presence of multiple drug resistance mechanisms that can vary among patients for any particular therapy.

**MICROENVIRONMENT AND IMMUNOLOGY**

2962  Myeloid WNT7b Mediates the Angiogenic Switch and Metastasis in Breast Cancer  
Eun-Jin Yeo, Luca Cassetta, Bin-Zhi Qian, Ian Lewkowich, Jiufeng Li, James A. Stefater III, April N. Smith, Lisa S. Wiechmann, Yihong Wang, Jeffrey W. Pollard, and Richard A. Lang  
Précis: These findings suggest a unified mechanism through which macrophages roving breast tumors can support blood vessel growth, invasion, and metastasis, with implications for attacking both tumor cells and tumor stroma at one stroke.

2974  Accumulation of Memory Precursor CD8 T Cells in Regressing Tumors following Combination Therapy with Vaccine and Anti-PD-1 Antibody  
Lavakumar Karyampudi, Purushottam Lamichhane, Adam D. Scheid, Kimberly R. Kalli, Barath Shreeder, James W. Krempski, Marshall D. Behrens, and Keith L. Knutson  
Précis: These findings suggest that PD-1 blockade during cancer vaccination triggers formation of memory T cells with an enhanced survival capacity, greatly encouraging the evaluation of combination therapies that combine cancer vaccines with immune checkpoint inhibitors.
Fatty Acid-Binding Protein E-FABP Restricts Tumor Growth by Promoting IFN-β Responses in Tumor-Associated Macrophages
Yuwen Zhang, Yanwen Sun, Enyu Rao, Fei Yan, Qiang Li, Ying Zhang, Kevin A.T. Silverstein, Shujun Liu, Edward Sauter, Margot P. Chary, and Bing Li
Précis: This study establishes a specific fatty acid–binding protein as a new host-derived protective factor in restricting tumor growth, acting to enhance a mechanism of immune surveillance that involves natural killer immune cells.

Cancer-Associated Fibroblasts Expressing CXCL14 Rely upon NOS1-Derived Nitric Oxide Signaling for Their Tumor-Supporting Properties
Martin Augsten, Elin Sjöberg, Oliver Frings, Sabine U. Vorrink, Jeroen Frijhoff, Eleonor Olsson, Åke Borg, and Arne Östman
Précis: These findings define key components of a chemokine-directed signaling network that maintains the protumoral functions of cancer-associated fibroblasts.

Mast Cell–Derived Prostaglandin D2 Inhibits Colitis and Colitis-Associated Colon Cancer in Mice
Koichi Iwanaga, Tatsuro Nakamura, Shingo Maeda, Kosuke Aritake, Masatoshi Hori, Yoshihiro Urade, Hiroshi Ozaki, and Takahisa Murata
Précis: Unlike prostaglandin E2, the COX-2 product that drives chronic inflammation leading to colon cancer, this study finds that the COX-2 product prostaglandin D2 inhibit inflammation leading to colon cancer, with important implications for prevention or treatment.

Thrombin Drives Tumorigenesis in Colitis-Associated Colon Cancer
Brian Turpin, Whitney Miller, Leah Rosenfeldt, Keith Kombrinck, Matthew J. Flick, Kris A. Steinbrecher, Elena Harmel-Laws, Eric S. Mullins, Maureen Shaw, David P. Witte, Alexey Revenko, Brett Monia, and Joseph S. Palumbo
Précis: Thrombin-mediated proteolysis drives tumorigenesis and progression in the context of colitis-associated colon cancer, revealing that this central hemostatic protease has the potential to control both early and late events in cancer pathogenesis.
PREVENTION AND EPIDEMIOLOGY

3076 Breast Cancer Risk after Occupational Solvent Exposure: the Influence of Timing and Setting
Christine C. Ekenga, Christine G. Parks, Aimee A. D’Aloisio, Lisa A. DeRoo, and Dale P. Sandler

Precis: In this large prospective study, solvent exposure prior to first full-term birth was associated with an increased risk of breast cancer.

3084 Tumor Hypomethylation at 6p21.3 Associates with Longer Time to Recurrence of High-Grade Serous Epithelial Ovarian Cancer
Chen Wang, Mine S. Cicek, Bridget Charbonneau, Kimberly R. Kalll, Sebastian M. Armasu, Melissa C. Larson, Gottfried E. Konecny, Boris Winterhoff, Jian-Bing Fan, Marina Bibikova, Jeremy Chien, Viji Shridhar, Matthew S. Block, Lynn C. Hartmann, Daniel W. Visscher, Julie M. Cunningham, Keith L. Knutson, Brooke L. Fridley, and Ellen L. Goode

Precis: This study suggests that an immune response mediated by DNA methylation changes in high-grade serous ovarian cancers may predict recurrence and possibly treatment responses.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3092 Redox Modulation of Adjacent Thiols in VLA-4 by AS101 Converts Myeloid Leukemia Cells from a Drug-Resistant to Drug-Sensitive State
Adi Layani-Bazar, Itai Skornick, Alain Berrebi, Maor H. Pauker, Elad Noy, Alon Silberman, Michael Albeck, Dan L. Longo, Yona Kalechman, and Benjamin Sredni

Precis: These findings offer a rationale to reposition an experimental drug in human trials to reverse an integrin-mediated mechanism of chemoresistance in acute myeloid leukemia, with immediate translational implications for clinical evaluation in patients.

3104 Identification and Characterization of Small Molecules That Inhibit Nonsense-Mediated RNA Decay and Suppress Nonsense p53 Mutations
Leenus Martin, Arsen Grigoryan, Ding Wang, Jinhua Wang, Laura Breda, Stefano Rivella, Timothy Cardozo, and Lawrence B. Gardner

Precis: This study offers a proof-of-concept that inhibitors of nonsense-mediated RNA decay can be used in strategies to restore full-length protein expression in cancer and other genetic disorders.

3114 Comparative Oncogenomics Identifies PSMB4 and SHMT2 as Potential Cancer Driver Genes

Precis: This study reports the discovery of two broadly involved, targetable oncogenic drivers in human cancer, which were identified by combining a gene amplification search with RNAi-based functional screening.

3127 Influence of Drug Formulation on OATP1B-Mediated Transport of Paclitaxel
Annemieke J.M. Nieuweboer, Shuiying Hu, Chunshan Gui, Bruno Hagenbuch, Inge M. Ghobadi Moghaddam-Helmantel, Alice A. Gibson, Peter de Brujin, Ron H.J. Mathijssen, and Alex Sparreboom

Precis: These findings suggest that drug–drug interactions for taxanes that have clinical importance in combination treatment settings are not due to the drugs themselves, but rather to differences in the formulants used for the drugs that might be varied to address clinical issues.

3137 Failure to Induce Apoptosis via BCL-2 Family Proteins Underlies Lack of Efficacy of Combined MEK and PI3K Inhibitors for KRAS-Mutant Lung Cancers
Aaron N. Hata, Alan Yeo, Anthony C. Faber, Eugene Lifshits, Zhao Chen, Katherine A. Cheng, Zandra Walton, Kristopher A. Sarosiek, Anthony Letai, Rebecca S. Heist, Mari Mino-Kenudson, Kwok-Kin Wong, and Jeffrey A. Engelman

Precis: The clinical efficacy of combined MEK and PI3K inhibitors for KRAS-mutant non–small cell lung cancer may be limited by variability in the ability to induce an apoptotic response.
Genomic Rearrangements Define Lineage Relationships between Adjacent Lepidic and Invasive Components in Lung Adenocarcinoma

Stephen J. Murphy, Dennis A. Wigle, Joena Felipe Lima, Faye R. Harris, Sarah H. Johnson, Geoffrey Halling, Michael K. Asiedu, Charlie T. Seto, Simone Terra, Farhad Kosari, Tobias Peikert, Ping Yang, Marie-Christine Aubry, and George Vasmatzis

Précis: These results offer a genome-wide perspective on the molecular pathogenesis underlying lung adenocarcinoma development and its clinical management.

HMMR Maintains the Stemness and Tumorigenicity of Glioblastoma Stem-like Cells

Jessica Tilghman, Hao Wu, Yingying Sang, Xiaohai Shi, Hugo Guerrero-Cazares, Alfredo Quinones-Hinojosa, Charles G. Eberhart, John Laterra, and Mingyao Ying

Précis: This study advances our knowledge about how cancer stem-like cells in aggressive brain tumors are regulated, with implications for their therapeutic targeting.

Mislocalization of the Cell Polarity Protein Scribble Promotes Mammary Tumorigenesis and Is Associated with Basal Breast Cancer


Précis: This report shows how cell polarity proteins activate PI3K signaling to promote cytoplasmic localization of PTEN, a negative regulator of PI3K signaling involved in controlling malignant development in breast cancer and other solid tumors.

Correction: VISTA Is an Immune Checkpoint Molecule for Human T Cells

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

ABOUT THE COVER

Scribble is a cell polarity protein that localizes to cell-cell junctions and cell membranes. Loss of Scribble expression is known to function as a tumor suppressor in multiple organs. However, Scribble is frequently amplified and mislocalized in multiple carcinoma including breast, prostate, lung, and head and neck. To begin to understand the effect of mislocalizing Scribble, we generated a transgenic mouse model expressing a mislocalizing mutant, Pro305Leu, under the control of the MMTV promoter. In the transgenic mouse mammary gland, SCRIB protein is expressed in the cytosol (green) of luminal epithelial cells and not in the CK14 positive (red) basal epithelia. These mice develop spontaneous tumors after a long latency, demonstrating that mislocalization of Scribble is sufficient to initiate tumorigenesis. For details, see article by Feigin and colleagues on page 3180.
Cancer Research

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