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Ira Pastan and Raffit Hassan

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- 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

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- 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, Håkan 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, Márcia 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.Y. Ng, Britta Weigelt, Roger A'Hern, Francois-Clement Bidard, Christophe Lemetre, Charles Swanton, Ronglai 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, Jiu-feng 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.

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2986 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. Cleary, 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.*

2999 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.*

3011 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 inhibits inflammation leading to colon cancer, with important implications for prevention or treatment.*

3020 Thrombin Drives Tumorigenesis in Colitis-Associated Colon Cancer

Brian Turpin, Whitney Miller, Leah Rosenfeldt, Keith Kombrinck, Matthew J. Flick, Kris A. Steinbrecher, Eleana 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.*

MOLECULAR AND CELLULAR PATHOBIOLOGY

3031 miR-483-5p Promotes Invasion and Metastasis of Lung Adenocarcinoma by Targeting RhoGDI1 and ALCAM

Qiancheng Song, Yuanfei Xu, Cuilan Yang, Zhenguo Chen, Chunhong Jia, Juan Chen, Yue Zhang, Pinglin Lai, Xiaorong Fan, Xuan Zhou, Jun Lin, Ming Li, Wenli Ma, Shenqiu Luo, and Xiaochun Bai

Précis: *These findings uncover mechanisms of action of a nodal acting microRNA for EMT, invasion, and metastasis in lung adenocarcinoma.*

3043 LEO1 Is Regulated by PRL-3 and Mediates Its Oncogenic Properties in Acute Myelogenous Leukemia

Phyllis S.Y. Chong, Jianbiao Zhou, Lip-Lee Cheong, Shaw-Cheng Liu, Jingru Qian, Tiannan Guo, Siu Kwan Sze, Qi Zeng, and Wee Joo Chng

Précis: *This study advances our understanding of an important oncogenic phosphatase in AML by identifying a critical downstream target in mediating its effects, with possible implications for prognosis and therapy.*

3054 Phosphatidylinositol 4-Phosphate in the Golgi Apparatus Regulates Cell-Cell Adhesion and Invasive Cell Migration in Human Breast Cancer

Emi Tokuda, Toshiki Itoh, Junya Hasegawa, Takeshi Ijuin, Yukiko Takeuchi, Yasuhiro Irino, Miki Fukumoto, and Tadaomi Takenawa

Précis: *These findings suggest that invasive progression of breast cancer cells may be directed by formation of a procancerous phospholipid in the Golgi apparatus.*

3067 Endogenous Two-Photon Fluorescence Imaging Elucidates Metabolic Changes Related to Enhanced Glycolysis and Glutamine Consumption in Precancerous Epithelial Tissues

Antonio Varone, Joanna Xylas, Kyle P. Quinn, Dimitra Pouli, Gautham Sridharan, Margaret E. McLaughlin-Drubin, Carlo Alonzo, Kyongbum Lee, Karl Mürger, and Irene Georgakoudi

Précis: *Fully exploiting noninvasive optical metabolic imaging systems may improve our understanding of how metabolic changes affect cancer development, diagnosis, and treatment.*

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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

Précis: *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. Kalli, 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

Précis: *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

Précis: *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

Précis: *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**

Genee Y. Lee, Peter M. Haverty, Li Li, Noelyn M. Kljavin, Richard Bourgon, James Lee, Howard Stern, Zora Modrusan, Somasekar Seshagiri, Zemin Zhang, David Davis, David Stokoe, Jeffrey Settleman, Frederic J. de Sauvage, and Richard M. Neve

Précis: *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 **Genetic and Pharmacological Strategies to Refunctionalize the von Hippel Lindau R167Q Mutant Protein**

Zhiyong Ding, Peter German, Shanshan Bai, A. Srinivas Reddy, Xian-De Liu, Mianen Sun, Lijun Zhou, Xiaohua Chen, Xiaobei Zhao, Chengbiao Wu, Shuxing Zhang, Gordon B. Mills, and Eric Jonasch

Précis: *These findings offer a rationale for a new approach to treatment of certain aggressive cancers of the kidney and other organs that are driven by inactivation of the VHL tumor suppressor gene.*

3137 **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 Bruijn, Ron H.J. Mathijssen, and Alex Sparreboom

Précis: *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.*

3146 **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

Précis: *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.*

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TUMOR AND STEM CELL BIOLOGY

- 3157** **Genomic Rearrangements Define Lineage Relationships between Adjacent Lepidic and Invasive Components in Lung Adenocarcinoma**
Stephen J. Murphy, Dennis A. Wigle, Joema 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 Vasmatazis

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

- 3168** **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.

- 3180** **Mislocalization of the Cell Polarity Protein Scribble Promotes Mammary Tumorigenesis and Is Associated with Basal Breast Cancer**



Michael E. Feigin, S. Dipikaa Akshinhala, Kiyomi Araki, Avi Z. Rosenberg, Lakshmi B. Muthuswamy, Bernard Martin, Brian D. Lehmann, Hal K. Berman, Jennifer A. Pietenpol, Robert D. Cardiff, and Senthil K. Muthuswamy

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.

CORRECTIONS

- 3195** **Correction: VISTA Is an Immune Checkpoint Molecule for Human T Cells**

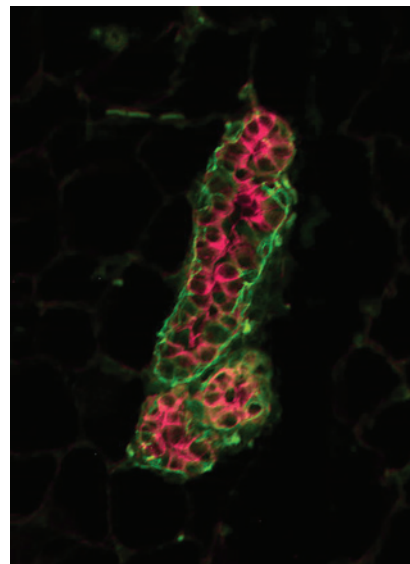
- 3196** **Correction: Novel Methylated Biomarkers and a Robust Assay to Detect Circulating Tumor DNA in Metastatic Breast Cancer**

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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, Prol305Leu, 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.



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