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  *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, Marcia 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.

## MICROENVIRONMENT AND IMMUNOLOGY

- **2962** Myeloid WNT7b Mediates the Angiogenic Switch and Metastasis in Breast Cancer  
  Eun-Jin Yeo, Luca Cassetta, Bin-Zhi Qian, Ian Lewko, 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.
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 Sjoberg, 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 inhibits 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 F. 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.

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
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 RNA-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 Moghadam-Helmantel, Alice A. Gibson, Peter de Brujin, Ron H.J. Mathijsen, 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.
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, 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.

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.

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

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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