Cancer Research
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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
Péris: 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, Márícia A. Inda, Pantelis Hatzis, Rogier Versteeg, Marcel Smid, John Martens, John Foekens, Paul van de Wiel, Hans Clevers, and Anja van de Stolpe
Péris: 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’Herne, Francois-Clement Bidard, Christophe Lemetre, Charles Swanton, Rongli Shen, and Jorge S. Reis-Filho
Péris: 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
Péris: 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
Péris: 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.

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**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.

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**Mast Cell–Derived Prostaglandin D2 Inhibits Colitis and Colitis-Associated Colon Cancer in Mice**

Koichi Iwanaga, Tatsuro Nakamura, Shingo Maeda, Kosuke Aritake, Masatoshi Hori, Yoshhiro 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.

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**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.

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

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

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

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**LE01 Is Regulated by PRL-3 and Mediates Its Oncogenic Properties in Acute Myelogenous Leukemia**

Phylis S.Y. Chong, Jianbiao Zhou, Lip-Lee Cheong, Shao-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.

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**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 Juin, Yukiko Takechi, Yoshio Ueno, Hiroshi Kawan, Miki Fukumoto, and Tadaomi Takenawa

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

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**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, Dinitra Poli, Gautham Sridaran, Margaret E. McLaughlin-Drubin, Carlo Alonzo, Kyongbum Lee, Karl Münger, 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.
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, Vij 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.

3096 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.

3104 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 RNAi-based functional screening.

3114 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.

3127 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.

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 Bruïjn, 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 THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3146 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.

3146 Comparative Oncogenomics Identifies PSMB4 and SHMT2 as Potential Cancer Driver Genes
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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, 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 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.

3180 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.

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, Pro185Leu, 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.