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DIFFERENTIAL EFFECTS OF POLYMORPHIC ALLELES OF FGF RECEPTOR 4 ON COLON CANCER GROWTH AND METASTASIS
Christine Heinzle, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gauglhofer, Stefan Stattner, Josef Karner, Martin Klimplinger, Friedrich Wirba, Andrea Reti, Balazs Hegedus, Andreas Baierl, Bettina Grasu-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian

PROHIBITIN ATTENUATES COLITIS-ASSOCIATED TUMORIGENESIS IN MICE BY MODULATING p53 AND STAT3 APOPTOTIC RESPONSES

ARYL HYDROCARBON RECEPTOR-INDUCED ADRENOMEDULLIN MEDIATES CIGARETTE SMOKE CARCINOGENICITY IN HUMANS AND MICE
Sergio Portal-Nuñez, Uma T. Shankavaram, Mahadev Rao, Nicole Datrice, Scott Atay, Marta Aparicio, Kevin A. Camphausen, Pedro M. Fernández-Salgueiro, Han Chang, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cuttitta, and Enrique Zudaire

FINDINGS SUGGEST THAT LUNG CANCERS ARISING IN SMOokers MAY BE SUSCEPTIBLE TO TREATMENT WITH THERAPEUTICS THAT TARGET A PROINFLAMMATORY ONCOGENIC PATHWAY KNOWN TO MEDIATE TUMOR-IMMUNE CELL CROSS-TALK, ANGIogenesis, AND METASTASIS.

NEUROPILIN-1-DEPENDENT REGULATION OF EGF-RECEPTOR SIGNALING
Sabrina Bizzoio, Noa Babinowicz, Elena Rainero, Letizia Lanzetti, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone

FINDINGS REVEAL A NEW MECHANISM FOR CONTROLLING EGFR SIGNALING IN CANCER CELLS THROUGH CLUSTERING AND ENDOCYTOSIS OF THE RECEPTOR NEUROPILIN-1, WHICH HIGHLIGHTS ITS IDENTIFICATION AS A RATIONAL THERAPEUTIC TARGET FOR CANCER TREATMENT.
An Integrated Genomic Screen Identifies LDHB as an Essential Gene for Triple-Negative Breast Cancer
Mark L. McCleland, Adam S. Adler, Yonglei Shang, Thomas Hunssaker, Tom Truong, David Peterson, Eric Torres, Li Li, Benjamin Haley, Jean-Philippe Stephan, Marcia Belvin, Georgia Hatzivassiliou, Elizabeth M. Blackwood, Laura Corson, Marie Evangelista, Jiping Zha, and Ron Firestein

Cancer Cells Cue the p53 Response of Cancer-Associated Fibroblasts to Cisplatin
Jens O. Schmid, Meng Dong, Silke Haubeiss, Godsebald Friedel, Sahine Bod, Andreas Grabner, German Ott, Thomas E. Mürdtter, Moshe Oren, Walter E. Aulitzky, and Heiko van der Kuip

Lymphatic Reprogramming by Kaposi Sarcoma Herpes Virus Promotes the Oncogenic Activity of the Virus-Encoded G-protein–Coupled Receptor
Berenece Aguilar, Inho Choi, Dongwon Choi, Hee Kyoung Chung, Sunju Lee, Jaeyuk Yoo, Yong Suk Lee, Yong Sun Maeng, Hs Neul Lee, Eunkyung Park, Kyu Eui Kim, Nam Yoon Kim, Jae Myung Baik, Jae U. Jung, Chester J. Koh, and Young-Kwon Hong

DDX31 Regulates the p53-HDM2 Pathway and rRNA Gene Transcription through Its Interaction with NPM1 in Renal Cell Carcinomas
Tomoya Fukawa, Masaya Ono, Taisuke Matsuo, Hisanori Uehara, Tsuneharu Miki, Yusuke Nakamura, Hiro-omi Kanayama, and Toyomasa Katagiri

Identification of FoxM1/Bub1b Signaling Pathway as a Required Component for Growth and Survival of Rhabdomyosarcoma
Xiaolin Wan, Choh Yeung, Su Young Kim, Joseph G. Dolan, Vu N. Ngo, Sandra Burkett, Javed Khan, Louis M. Staudt, and Lee J. Helman

Inactivation of the Dlc1 Gene Cooperates with Downregulation of p15Ink4b and p16Ink4a, Leading to Neoplastic Transformation and Poor Prognosis in Human Cancer
Xiaoan Qian, Marian E. Durkin, Dunrui Wang, Brajendra K. Tripathi, Lyra Olson, Xu-Yu Yang, William C. Vass, Nicholas C. Popescu, and Douglas R. Lowy

Precise: Oncogenic Ras uses distinct effector pathways to drive dysregulated proliferation of the cells derived from different layers of a stratified epithelium.

Precise: While the glycolytic regulator lactate dehydrogenase has been studied previously in breast cancer, this study offers an incisive advance by defining a crucial specific role for a particular isoform of this enzyme in a breast cancer subtype with few therapeutic options.

Precise: Within the tumor microenvironment, the p53 response of cancer cell determines the p53 response within adjacent cancer-associated fibroblasts, illustrative of the master-slave relationship that cancer cells enforce on their neighboring cells.

Precise: Global metabolomic analysis identifies key features underlying the aggressive phenotype of malignant glioma, providing novel strategies for therapeutic intervention.

Precise: Findings offer potentially seminal insights into the origins of renal cell cancer, addressing long standing questions about how sporadic forms of this cancer develop.

Precise: Dysregulation of a mitotic checkpoint signaling pathway has a critical role in the growth of pediatric tumors, defining direct interactions between the oncogenic transcription factor, FoxM1, and the key mitotic checkpoint protein, Bub1B.

Precise: Findings resolve long-standing questions about how sporadic forms of this cancer develop into the origins of renal cell cancer, addressing long standing questions about how sporadic forms of this cancer develop.

Precise: Findings reveal a previously unrecognized role for the FGF receptor FGFR3 in regulating lipid metabolism to maintain tumor growth and survival.
Hedgehog Signaling Blockade Delays Hepatocarcinogenesis Induced by Hepatitis B Virus X Protein
Alla Arzumanyan, Vaishnavi Sambandam, Marcia M. Clayton, Steve S. Choi, Guanhua Xie, Anna Mae Diehl, Dae-Yeul Yu, and Mark A. Feitelson
Précis: Hedgehog signaling is emerging as a major driver in the development and progression of liver cancer.

Temporal Molecular and Biological Assessment of an Erlotinib-Resistant Lung Adenocarcinoma Model Reveals Markers of Tumor Progression and Treatment Response
Zoe Weaver, Simone Difilippantonio, Julian Carretero, Philip L. Martin, Rajaa El Meskini, Anthony J. Iacovelli, Michelle Gumprecht, Alan Kulaqa, Theresa Guerin, Jerome Scholmer, Maureen Baran, Serguei Kozlov, Thomas McCann, Salvador Mena, Fatima Al-Shahrour, Danny Alexander, Kwok Kin Wong, and Terry Van Dyke
Précis: This study illustrates the importance of longitudinal therapeutic studies in preclinical assessment of drug principles by offering in vivo evidence that tyrosine kinase inhibitors can exert a strong, unexpected impact on specific metabolic controls.

Genetic Screening for Synthetic Lethal Partners of Polynucleotide Kinase/Phosphatase: Potential for Targeting SHP-1–Depleted Cancers
Todd R. Mereniuk, Robert A. Maranchuk, Anja Schindler, Jonathan Penner-Che, Gary K. Freschauf, Samar Hegazy, Raymond Lai, Edan Foley, and Michael Weinfeld
Précis: This paper elucidates a synthetic lethal combination of target inactivation events that can increase levels of DNA damage that escape repair, suggesting an effective killing paradigm to exploit therapeutically.

Cisplatin Sensitivity Mediated by WEE1 and CHK1 Is Mediated by miR-155 and the miR-15 Family
Lynn M. Pouliot, Yu-Chi Chen, Jennifer Bai, Rajarshi Guha, Scott E. Martin, Michael M. Gottesman, and Matthew D. Hall
Précis: Defeating acquired resistance to platin drugs remains a major goal in the oncology clinic, given the large and diverse number of cancers that use these chemotherapeutic agents in treatment.

Brachytherapy Using Injectable Seeds That Are Self-Assembled from Genetically Encoded Polypeptides In Situ
Wenge Liu, Jonathan McDaniel, Xinghai Li, Daisuke Asai, Felipe Garcia Quiroz, Jeffery Schaal, Ji Sun Park, Michael Zalutsky, and Ashutosh Chilkoti
Précis: A novel injectable modality that can self-assemble a polypeptide-based radionuclide seed at tumor sites could radically improve treatment of prostate cancers that are presently treated by brachytherapy, an invasive radiotherapeutic procedure.

OTX2 Represses Myogenic and Neuronal Differentiation in Medulloblastoma Cells
Ren-Yuan Bai, Verena Staedtke, Hart G. Lidov, Charles G. Eberhart, and Gregory J. Riggins
Précis: Findings may hold the key to understanding the etiology of medulloblastoma, a subtype of the common pediatric brain tumor medulloblastoma that is marked by the presence of differentiated muscle cells.
Rat *Mcs1b* Is Concordant to the Genome-Wide Association-Identified Breast Cancer Risk Locus at Human 5q11.2 and *Miere3* Is a Candidate Cancer Susceptibility Gene

Aaron D. denDekker, Xin Xu, M. Derek Vaughn, Aaron H. Puckett, Louis L. Gardner, Courtney J. Lambring, Lucas Deschenes, and David J. Samuelson

**Précis:** Genetic studies in the rat suggest a good candidate for a breast cancer susceptibility gene that has been mapped previously to human chromosome 5q11.2.

A Synthetic Matrix with Independently Tunable Biochemistry and Mechanical Properties to Study Epithelial Morphogenesis and EMT in a Lung Adenocarcinoma Model

Bartley J. Gill, Don L. Gibbons, Laila C. Roudsari, Jennifer E. Saik, Zain H. Rizvi, Jonathon D. Roybal, Jonathan M. Kurie, and Jennifer L. West

**Précis:** Findings illuminate the extracellular cues that influence epithelial morphogenesis by showing how a synthetic ECM mimetic can affect metastatic properties.

Rab25 Is a Tumor Suppressor Gene with Antiangiogenic and Anti-Invasive Activities in Esophageal Squamous Cell Carcinoma

Man Tong, Kwok Wah Chan, Jessie Y.J. Bao, Kai Yau Wong, Jin-Na Chen, Pak Shing Kwan, Kwan Ho Tang, Li Fu, Yan-Ru Qin, Si Lok, Xin-Yuan Guan, and Stephanie Ma

**Précis:** This study advances progress in the acute need for identifying biomarkers that can assist the diagnosis, prognosis, and treatment of esophageal cancer, a deadly disease with a rising incidence.

Loss of SNAIL Regulated miR-128-2 on Chromosome 3p22.3 Targets Multiple Stem Cell Factors to Promote Transformation of Mammary Epithelial Cells

PengXu Qian, Arindam Banerjee, Zheng-Sheng Wu, Xiao Zhang, Hong Wang, Vijay Pandey, Wei-Jie Zhang, Xue-Fei Lv, Sheng Tan, Peter E. Lobie, and Tao Zhu

**Précis:** Results elucidate a signaling axis that drives mesenchymal character and stem cell-like traits in malignantly transformed epithelial cells.

Oncostatin M Modulates the Mesenchymal–Epithelial Transition of Lung Adenocarcinoma Cells by a Mesenchymal Stem Cell-Mediated Paracrine Effect

Mong-Lien Wang, Chih-Ming Pan, Shih-Hwa Chiou, Wen-Hsin Chen, Hsiang-Yi Chang, Oscar Kuang-Sheng Lee, Han-Sui Hsu, and Cheng-Wen Wu

**Précis:** A molecule secreted by mesenchymal stem cells attracted to tumors is found to exert an anticancer effect in lung cancer, with potential implications for cancer therapy.

Gliomagenesis Arising from Pten- and Ink4a/Arf-Deficient Neural Progenitor Cells Is Mediated by the p53-Fbxw7/Cdc4 Pathway, Which Controls c-Myc

Hong Sug Kim, Kevin Woolard, Chen Lai, Peter O. Bauer, Dragun Marie, Hua Song, Aiguo Li, Svetlana Kotliarova, Wei Zhang, and Howard A. Fine

**Précis:** A sophisticated genetically engineered mouse model confirms that p53 mutations contribute to formation of aggressive brain tumors by supporting c-Myc overexpression but also by protecting cells against c-Myc-induced apoptosis.

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**ABOUT THE COVER**

Perineural invasion of cancer cells is found in most patients with pancreatic adenocarcinoma and is common in other tumors as well. Immunohistochemical analysis of specimens excised from patients with pancreatic cancer showed a significant increase in the number of endoneurial macrophages around nerves invaded by cancer. Using animal models and time-lapse analysis, we noticed that these endoneurial macrophages facilitated cancer cells dissociation from tumors and the formation of cell clusters that migrated in a unidirectional fashion along the nerve toward the ganglion. The study identified a paracrine response between endoneurial macrophages and cancer cells, which orchestrates the formation of nerve invasion. For details, see article by Cavel and colleagues on page 5733.