The FGFR4-G388R Single-Nucleotide Polymorphism Alters Pancreatic Neuroendocrine Tumor Progression and Response to mTOR Inhibition Therapy
Stefano Serra, Lei Zheng, Manal Hassan, Alexandria T. Phan, Linda J. Woodhouse, James C. Yao, Sherseen Ezzat, and Sylvia L. Asa

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DNA Methylation Biomarkers Offer Improved Diagnostic Efficiency in Lung Cancer
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INTEGRATED SYSTEMS AND TECHNOLOGIES

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**MICROENVIRONMENT AND IMMUNOLOGY**

5721  **NLRP3 Suppresses NK Cell–Mediated Responses to Carcinogen-Induced Tumors and Metastases**  
Melvyn T. Chow, Jaclyn Sceney, Christophe Paget, Christina S.F. Wong, Helene Duret, Jürg Tschopp, Andreas Möller, and Mark J. Smyth  
*Précis:* Findings reveal a proinflammatory pathway that suppresses cancer-controlling NK cells along with a class of suppressor myeloid cells that actually promotes the anticancer activity of NK cells.

5733  **Endoneurial Macrophages Induce Perineural Invasion of Pancreatic Cancer Cells by Secretion of GDNF and Activation of RET Tyrosine Kinase Receptor**  
Oren Cavel, Olga Shomron, Ayelet Shabtay, Joseph Vital, Leonor Trejo-Leider, Noam Weizman, Yakov Krelin, Yuman Fong, Richard J. Wong, Moran Amit, and Ziv Gil  
*Précis:* A paracrine response between pancreatic adenocarcinoma cells and macrophages that rove nerve tracks appears to orchestrate nerve invasion by localized tumors, a type of invasion that occurs in various types of encapsulated glandular tumors.

5744  **Cross-Species Functional Analysis of Cancer-Associated Fibroblasts Identifies a Critical Role for CLCF1 and IL6 in Non–Small Cell Lung Cancer In Vivo**  
Silvestre Vicent, Leanne C. Sayles, Dedeepya Vaka, Purvesh Khatri, Olivier Gevaert, Ron Chen, Yanyan Zheng, Anna K. Gillespie, Nicole Clarke, Yue Xu, Joseph Shrager, Richard J. Wong, Morian Amit, and Ziv Gil  
*Précis:* A cross-species approach identifies 2 IL-6 family members as key contributors to paracrine signaling between cancer cells and cancer-associated fibroblasts in lung adenocarcinoma.

5757  **Galectin-3 Contributes to Melanoma Growth and Metastasis via Regulation of NFAT1 and Autotaxin**  
Russell R. Braeuer, Maya Zigler, Takafumi Kamiya, Andrey S. Dobroff, Li Huang, Woonyoung Choi, David J. McConkey, Einav Shoshan, Aaron K. Mobley, Renduo Song, Avraham Raz, and Menashe Bar-Eli  
*Précis:* This study elucidates a new mechanism by which galectin-3 contributes to tumor growth and metastasis by regulating the expression of protumorigenic genes, such as autotaxin.

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**MOLECULAR AND CELLULAR PATHOBIOLOGY**

5767  **Differential Effects of Polymorphic Alleles of FGFR4 on Colon Cancer Growth and Metastasis**  
Christine Heinzel, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gauglhofer, Stefan Stattner, Josef Karner, Martin Klimpfinger, Friedrich Wirba, Andrea Reti, Balazs Hegenus, Andreas Bairol, Bettina Grasli-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian  
*Précis:* A systematic comparison of 2 common polymorphic forms of FGFR4 reveals a higher risk of developing aggressive colorectal cancer for carriers of the FGFR4<sup>Arg</sup> allele, potentially offering a simple prognostic marker in this setting.

5778  **Prohibitin Attenuates Colitis-Associated Tumorigenesis in Mice by Modulating p53 and STAT3 Apoptotic Responses**  
*Précis:* Reduced levels of a mitochondrial protein during chronic intestinal inflammation may be an underlying factor promoting colitis-associated cancer by acting to modulate epithelial cell apoptosis.

5790  **Aryl Hydrocarbon Receptor-Induced Adrenomedullin Mediates Cigarette Smoke Carcinogenicity in Humans and Mice**  
Sergio Portal-Núñez, Uma T. Shankavaram, Mahadev Rao, Nicole Datrice, Scott Atay, Marta Aparicio, Kevin A. Camphausen, Pedro M. Fernández-Salgueiro, Han Chung, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cuttitta, and Enrique Zudaire  
*Précis:* Findings suggest that lung cancers arising in smokers may be susceptible to treatment with therapeutics that target a proinflammatory oncogenic pathway known to mediate tumor-immune cell crosstalk, angiogenesis, and metastasis.

5801  **Neuropilin-1–Dependent Regulation of EGF-Receptor Signaling**  
Sahrina Bizzoloi, Noa Babinowicz, Elena Rainero, Letizia Lanzetli, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone  
*Précis:* 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. McClendon, Adam S. Adler, Yonglei Shang, Thomas Hunsaker, 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

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 isof orm of this enzyme in a breast cancer subtype with few therapeutic options.

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

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.

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

Precise: Findings resolve long-standing questions about the pathological impact of the ability of the Kaposi’s sarcoma herpes virus to reprogram the tumor microenvironment, explaining why this process favors formation of Kaposi’s sarcomas, which are the most common forms of cancer in HIV patients.

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

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.

The Metabolomic Signature of Malignant Glioma Reflects Accelerated Anabolic Metabolism
Prakash Chinnainayi, Elizabeth Kenschik, Gregory Bloom, Antony Prabhu, Bhawwati Sarcar, Soumen Kahali, Steven Eschrich, Xiaotao Qu, Peter Forsyth, and Robert Gillies

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

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

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.

Inactivation of the Dlc1 Gene Cooperates with Downregulation of p15INK4b and p16INK4a, Leading to Neoplastic Transformation and Poor Prognosis in Human Cancer
Xiaolan 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: Diminished expression of a RhoGAP tumor suppressor along with the Cdk inhibitors p15 and p16 drives cell transformation in mouse cells and confers poor prognosis in clinical cases of lung and colon cancer.
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<td>OTX2 Represses Myogenic and Neuronal Differentiation in Medulloblastoma Cells</td>
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Rat Mcs1b Is Concordant to the Genome-Wide Association-Identified Breast Cancer Risk Locus at Human 5q11.2 and MIER3 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, Dragan Maric, 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.

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.