## BREAKING ADVANCES

5647 Highlights from Recent Cancer Literature

## REVIEWS

5649 The Kynurenine Pathway in Brain Tumor Pathogenesis

Seray Adams, Nady Braidy, Alban Bessesde, Bruce J. Brew, Ross Grant, Charlie Teo, and Gilles J. Guillemin

5658 FoxM1 and Wnt/β-Catenin Signaling in Glioma Stem Cells

Aihua Gong and Suyun Huang

5663 Realizing the Clinical Potential of Cancer Nanotechnology by Minimizing Toxicologic and Targeted Delivery Concerns

Sanjay Singh Arati Sharma, and Gavin P. Robertson

## PRIORITY REPORT

5669 Cytomegalovirus Infection Leads to Pleomorphic Rhabdomyosarcomas in Trp53+/−/− Mice


Precis: Findings offer perhaps the first causative evidence that cytomegalovirus infections may contribute to the development of certain human cancers, where p53 mutation occurs frequently.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

5702 SIRT1 Pathway Dysregulation in the Smoke-Exposed Airway Epithelium and Lung Tumor Tissue

Jennifer Beane, Luis Cheng, Raffaella Soldi, Xiaohui Zhang, Gang Liu, Christina Anderlind, Marc E. Lenburg, Avrum Spira, and Andrea H. Bild

Precis: Gene expression analysis in airway epithelium exposed to cigarette smoke reveals dysregulation of SIRT1, which is also implicated as a tumor suppressor gene in lung cancer.

## CLINICAL STUDIES

5675 Clinicopathological Features of Homologous Recombination–Deficient Epithelial Ovarian Cancers: Sensitivity to PARP Inhibitors, Platinum, and Survival


Precis: Defects in DNA repair mediated by the homologous recombination machinery define a subset of ovarian cancers that are sensitive to PARP inhibitors and that have favorable survival outcomes when cotreated with platinum chemotherapy.

5712 Metabolic Associations of Reduced Proliferation and Oxidative Stress in Advanced Breast Cancer

Livnat Jerby, Lior Wolf, Carsten Denkert, Gideon Y. Stein, Mika Hilvo, Matej Oresic, Tamar Geiger, and Eytan Ruppin

Precis: This study presents the first genome-scale study of the metabolism of breast cancer, providing new system-level insights into the metabolic progression of different subsets of this disease.
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<td>5721</td>
<td><strong>MOLECULAR AND CELLULAR PATHOBIOLOGY</strong></td>
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<td><strong>Differential Effects of Polymorphic Alleles of FGF Receptor 4 on Colon Cancer Growth and Metastasis</strong>&lt;br&gt;Christine Heinzle, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gaughofer, Stefan Stattner, Josef Karner, Martin Klimpfinger, Friedrich Wirba, Andrea Reti, Balazs Hegedus, Andreas Baierl, Bettina Grasl-Kräupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian&lt;br&gt;<strong>Précis:</strong> A systematic comparison of 2 common polymorphic forms of FGFR4 reveals a higher risk of developing aggressive colorectal cancer for carriers of the FGFR4&lt;sup&gt;arg&lt;/sup&gt; allele, potentially offering a simple prognostic marker in this setting.</td>
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<td>5733</td>
<td><strong>Endoneurial Macrophages Induce Perineural Invasion of Pancreatic Cancer Cells by Secretion of GDNF and Activation of RET Tyrosine Kinase Receptor</strong>&lt;br&gt;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</td>
<td><strong>Précis:</strong> 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.</td>
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<td>5744</td>
<td><strong>Cross-Species Functional Analysis of Cancer-Associated Fibroblasts Identifies a Critical Role for CLCF1 and IL6 in Non–Small Cell Lung Cancer In Vivo</strong>&lt;br&gt;Silvestre Vicent, Leanne C. Sayles, Dedeepta Vaka, Purvesh Khatri, Olivier Gevaert, Ron Chen, Yanyan Zheng, Anna K. Gillespie, Nicole Clarke, Yue Xu, Joseph Shrager, Chuong D. Hoang, Sylvia Plevritis, Atul J. Butte, and E. Alejandro Sweet-Cordero</td>
<td><strong>Précis:</strong> 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.</td>
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<td>5757</td>
<td><strong>Galectin-3 Contributes to Melanoma Growth and Metastasis via Regulation of NFAT1 and Autotaxin</strong>&lt;br&gt;Russell R. Braeuer, Maya Zigler, TakaTami Kamiya, Andrey S. Dobroff, Li Huang, Woonyoung Choi, David J. McConkey, Einav Shoshan, Aaron K. Mobley, Renduo Song, Avraham Raz, and Menashe Bar-Eli</td>
<td><strong>Précis:</strong> 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.</td>
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<td>5767</td>
<td><strong>Neuropilin-1–Dependent Regulation of EGF-Receptor Signaling</strong>&lt;br&gt;Sabrina Bizzoloi, Noa Babinowicz, Elena Rainero, Letizia Lanzetti, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone</td>
<td><strong>Précis:</strong> 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.</td>
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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  

Cancer Cells Cue the p53 Response of Cancer-Associated Fibroblasts to Cisplatin  
Jens O. Schmid, Meng Dong, Silke Haubiss, Godoehard Friedel, Sahine Boden, Andreas Grabner, German Ott, Thomas E. Mürdter, 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  
Berenice Aguilar, Inho Choi, Dongwon Choi, Hee Kyoung Chung, Sunju Lee, Jaehyuk Yoo, Yong Suk Lee, Yong Sun Maeng, Ha Neul Lee, Eunkyung Park, Kyo Eui Kim, Nam Yoon Kim, Jae Myung Baik, Jae U. Jung, Chester J. Koh, and Young-Kwon Hong  

FGFR3 Stimulates Stearoyl CoA Desaturase 1 Activity to Promote Bladder Tumor Growth  
Xiangnan Du, Qian-Rena Wang, Emily Chan, Mark Merchant, Jinfeng Liu, Dorothy French, Avi Ashkenazi, and Jing Qing  

Basal but not Luminal Mammary Epithelial Cells Require PI3K/mTOR Signaling for Ras-Driven Overgrowth  
Kristin A. Plichta, Jessica L. Mathers, Shelley A. Gestl, Adam B. Glick, and Edward J. Gunther  

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  

The Metabolomic Signature of Malignant Glioma Reflects Accelerated Anabolic Metabolism  
Prakash Chinnayani, Elizabeth Kensicki, Gregory Bloom, Antony Prabhu, Bhawati Sarcar, Soumen Kahali, Steven Esrich, Xiaotao Qu, Peter Forsyth, and Robert Gillies  

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  
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  

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.  

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

Precis: Hedgehog signaling is emerging as a major driver in the development and progression of liver cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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 Kulaaga, Theresa Guerin, Jerome Scholmer, Maureen Baran, Sergio Kozlov, Thomas McCann, Salvador Mena, Fatima Al-Shahrour, Danny Alexander, Kwok-Kin Wong, and Terry Van Dyke

Precis: 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-Chea, Gary K. Freschauf, Samar Hegazy, Raymond Lai, Edan Foley, and Michael Weinfeld

Precis: 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

Precis: Defeating acquired resistance to platinum 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

Precis: 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.
6002 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.

6013 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.

6024 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.

6036 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 malignant transformed epithelial cells.

6051 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 Chiu, 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.

6065 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.