### BREAKING ADVANCES

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**Highlights from Recent Cancer Literature**

### REVIEWS

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**The Kynurenine Pathway in Brain Tumor Pathogenesis**  
Seray Adams, Nady Braidy, Alban Bessesde, Bruce J. Brew, Ross Grant, Charlie Teo, and Gilles J. Guillemin

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**FoxM1 and Wnt/β-Catenin Signaling in Glioma Stem Cells**  
Aihua Gong and Suyun Huang

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**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**  

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

### CLINICAL STUDIES

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

**Précis:** 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.

### 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 Anderliind, Marc E. Lemburg, Avrum Spira, and Andrea H. Bild

**Précis:** 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.

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 Orsecic, Tamar Geiger, and Eytan Ruppin

**Précis:** 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>NLRP3 Suppresses NK Cell–Mediated Responses to Carcinogen-Induced Tumors and Metastases</td>
<td>Melvyn T. Chow, Jaclyn Sceneay, Christophe Paget, Christina S.F. Wong, Helene Duret, Jürg Tschopp, Andreas Möller, and Mark J. Smyth</td>
<td><strong>Précis:</strong> 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.</td>
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<td>5733</td>
<td>Endoneurial Macrophages Induce Perineural Invasion of Pancreatic Cancer Cells by Secretion of GDNF and Activation of RET Tyrosine Kinase Receptor</td>
<td>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>Cross-Species Functional Analysis of Cancer-Associated Fibroblasts Identifies a Critical Role for CLCF1 and IL6 in Non–Small Cell Lung Cancer In Vivo</td>
<td>Silvestre Vicent, Leanne C. Sayles, Dedeepya Vaka, Purvesh Khatri, Olivier Gevaert, Ron Chen, Yanyan Zheng, Anna K. Gillespie, Nicole Clarke, Yue Xu, Joseph Shrager, Chong 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>Galectin-3 Contributes to Melanoma Growth and Metastasis via Regulation of NFAT1 and Autotaxin</td>
<td>Russell R. Braeuer, Maya Zigler, Takaomi Kamiya, Andrey S. Dobroff, Li Huang, Woonyong Choi, David J. McConkey, Einav Shoshan, Aaron K. Mohley, 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>Differential Effects of Polymorphic Alleles of FGF Receptor 4 on Colon Cancer Growth and Metastasis</td>
<td>Christine Heinzel, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gaughgloher, Stefan Stattner, Josef Karner, Martin Klimpfinger, Friedrich Wirba, Andrea Reti, Balazs Hegedus, Andreas Baierl, Bettina Gräsl-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian</td>
<td><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;α&lt;/sup&gt; allele, potentially offering a simple prognostic marker in this setting.</td>
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<td>5778</td>
<td>Prohibitin Attenuates Colitis-Associated Tumorigenesis in Mice by Modulating p53 and STAT3 Apoptotic Responses</td>
<td>Arwa S. Kathiria, William L. Neumann, Jennifer Rhes, Erin Hotchkiss, Yulan Cheng, Robert M. Genta, Stephen J. Meltzer, Rhonda F. Souza, and Arianne L. Theiss</td>
<td><strong>Précis:</strong> 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.</td>
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<td>Aryl Hydrocarbon Receptor-Induced Adrenomedullin Mediates Cigarette Smoke Carcinogenicity in Humans and Mice</td>
<td>Sergio Portal-Nuñez, Uma T. Shankavaram, Mahadev Rao, Nicole Datrice, Scott Atay, Marta Aparicio, Kevin A. Camphausen, Pedro M. Fernández-Salguero, Han Chung, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cuttitta, and Enrique Zudaire</td>
<td><strong>Précis:</strong> 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.</td>
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<td>5801</td>
<td>Neuropilin-1–Dependent Regulation of EGF-Receptor Signaling</td>
<td>Sabrina Rizzolio, Noa Babino, 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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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

 précision: 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.

Lymphatic Reprogramming by Kaposi Sarcoma Herpes Virus Promotes the Oncogenic Activity of the Virus-Encoded G-protein–Coupled Receptor

Berénice Aguilar, Inho Choi, Dongwon Choi, Hee Kyoung Chung, Sunju Lee, Jaehyuk Yoo, Yong Suk Lee, Yong Sun Maeng, Ha Neul Lee, Eunkyoung Park, Kw Eui Kim, Nam Yoon Kim, Jee Myung Baik, Jae U. Jung, Chester J. Koh, and Young-Kwon Hong

 précision: 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.

Cancer Cells Cue the p53 Response of Cancer-Associated Fibroblasts to Cisplatin

Jens O. Schmid, Meng Dong, Silke Haubaeiss, Godedahl Friedel, Sahine Boden, Andreas Grabner, German Ott, Thomas E. Mürcker, Moshe Oren, Walter E. Aulitzky, and Heiko van der Kuip

 précision: 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.

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

 précision: 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.

An Integrated Genomic Screen Identifies DLIB 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, Jingjing Zha, and Ron Firestein

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

The Metabolomic Signature of Malignant Glioma Reflects Accelerated Anabolic Metabolism

Prakash Chinnaiyan, Elizabeth Kensicki, Gregory Bloom, Antony Prabhu, Bhaswati Sarcar, Soumen Kahali, Steven Eschrich, Xiaotao Qu, Peter Forsyth, and Robert Gillies

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

An Integrated Genomic Screen Identifies DLIB 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, Jingjing Zha, and Ron Firestein

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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

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 précision: 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.

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

 précision: 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.

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 Kulaga, Theresa Guerin, Jerome Schlomer, Maureen Baran, Serguei 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.

OTX2 Represses Myogenic and Neuronal Differentiation in Medulloblastoma Cells
Ren-Yuan Bai, Verena Staedtke, Hart G. Lidov, Charles G. Eberhart, and Gregory J. Riggins

Precis: 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.

Brachytherapy Using Injectable Seeds That Are Self-Assembled from Genetically Encoded Polypeptides In Situ
Wenge Liu, Jonathan McDaniel, Xinhai 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.

The V-ATPase-Inhibitor Archazolid Abrogates Tumor Metastasis via Inhibition of Endocytic Activation of the Rho-GTPase Rac1
Romina M. Wiedmann, Karin V. Schwarzenberg, Andrea Palamidessi, Laura Schreiner, Rebekka Kubiisch, Johanna Liebl, Christina Schempp, Dirk Trauner, Gyorgy Vereb, Stefan Zahler, Ernst Wagner, Rolf Müller, Giorgio Scita, and Angelika M. Vollmar

Precis: Findings reveal insights into how a vacular proton pump drives tumor dissemination and metastasis, with implications for how to apply therapeutics that can target this pump.

The V-ATPase-Inhibitor Archazolid Abrogates Tumor Metastasis via Inhibition of Endocytic Activation of the Rho-GTPase Rac1
Romina M. Wiedmann, Karin V. Schwarzenberg, Andrea Palamidessi, Laura Schreiner, Rebekka Kubiisch, Johanna Liebl, Christina Schempp, Dirk Trauner, Gyorgy Vereb, Stefan Zahler, Ernst Wagner, Rolf Müller, Giorgio Scita, and Angelika M. Vollmar

Precis: Findings offer preclinical proof-of-concept for a functionally pleiotropic kinase as a therapeutic target in KRAS-driven tumors, illustrating a key mechanism for its action through signaling by Erk but not Akt.

Findings reveal insights into how a vacular proton pump drives tumor dissemination and metastasis, with implications for how to apply therapeutics that can target this pump.
### 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 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.

### 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.

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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.

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