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

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

Realizing the Clinical Potential of Cancer Nanotechnology by Minimizing Toxicologic and Targeted Delivery Concerns
Sanjay Singh Arati Sharma, and Gavin P. Robertson

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

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Stefano Serra, Lei Zheng, Manal Hassan, Alexandria T. Phan, Linda J. Woodhouse, James C. Yao, Sherreen Ezzat, and Sylvia L. Asa

DNA Methylation Biomarkers Offer Improved Diagnostic Efficiency in Lung Cancer
Georgios Nikolaidis, Olaide Y. Raji, Soultana Markopoulou, John R. Gosney, Julie Bryan, Chris Warburton, Martin Walshaw, John Sheard, John K. Field, and Triantafillos Liloglou

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Precise: A coding SNP in the FGFR4 gene correlates with progression status in pancreatic neuroendocrine tumors and also with the response to everolimus, an mTOR inhibitor of therapeutic interest in this setting, potentially offering a simple stratification marker.

Precise: Determination of a simple DNA methylation signature in cells obtained from bronchial washings may improve the accuracy of clinical diagnoses of lung cancer.

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

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Precise: 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.

Precise: 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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<th>MICROENVIRONMENT AND IMMUNOLOGY</th>
<th>MOLECULAR AND CELLULAR PATHOBIOLOGY</th>
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<td>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  <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>
<td>Differential Effects of Polymorphic Alleles of FGF Receptor 4 on Colon Cancer Growth and Metastasis Christine Heinzel, Andrea Gsur, Monika Hunjadi, Zeynep Erdem, Christine Gaugholfer, Stefan Stattner, Josef Karner, Martin Klipplinger, Friedrich Wiba, Andrea Reti, Balazs Hegedus, Andreas Bairol, Bettina Grasl-Kraupp, Klaus Holzmann, Michael Grusch, Walter Berger, and Brigitte Marian  <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;res&lt;/sup&gt; allele, potentially offering a simple prognostic marker in this setting.</td>
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<td>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  <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>
<td>Prohibitin Attenuates Colitis-Associated Tumorigenesis in Mice by Modulating p53 and STAT3 Apoptotic Responses Arwa S. Kathiria, William L. Neumann, Jennifer Rhees, Erin Hotchkiss, Yulan Cheng, Robert M. Genta, Stephen J. Meltzer, Rhonda F. Souza, andariane L. Theiss  <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>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, Choung D. Hoang, Sylvia Plevritis, Atul J. Butte, and E. Alejandro Sweet-Cordero  <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>
<td>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 Chung, Pinpin Lin, David S. Schrump, Stavros Garantziotis, Frank Cuttitta, and Enrique Zudaire  <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>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, Woonlyoung Choe, David J. McConkey, Einav Shoshan, Aaron K. Mobley, Renduo Song, Avraham Raz, and Menashe Bar-Eli  <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>
<td>Neuprolin-1–Dependent Regulation of EGF-Receptor Signaling Sabrina Bizzoloi, Noa Babinowicz, Elena Rainero, Letizia Lanzetti, Guido Serini, Jim Norman, Gera Neufeld, and Luca Tamagnone  <strong>Précis:</strong> Findings reveal a new mechanism for controlling EGFR signaling in cancer cells through clustering and endocytosis of the receptor Neuprolin-1, which highlights its identification as a rational therapeutic target for cancer treatment.</td>
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<td>Inactivation of the Dlc1 Gene Cooperates with Downregulation of p15INK4b and p16INK4a, Leading to Neoplastic Transformation and Poor Prognosis in Human Cancer</td>
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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.

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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 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.

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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 Msc1b 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, Jesse 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, Dragun 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.
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