Précis: This study challenges our expectations by presenting a mathematical model suggesting that antigen shedding will enhance rather than inhibit the delivery of recombinant immunotoxins.
Loss of Fibroblast HIF-1α Accelerates Tumorigenesis
Jung-wha Kim, Colin Evans, Alexander Weidemann, Norihiko Takeda, Yoon Sok Lee, Christian Stockmann, Cristina Branco-Price, Filip Brandberg, Gustavo Leone, Michael C. Ostrowski, and Randall S. Johnson

Precise: The unexpected finding that HIF-1α can exert tumor-suppressive effects in cancer-associated fibroblasts contrasts radically with the protumorigenic effects of this factor in cancer cells themselves, with potential implications for manipulation of this important pathway for therapeutic benefit.

Combination Therapy with HSP90 Inhibitor 17-DMAG Reconditions the Tumor Microenvironment to Improve Recruitment of Therapeutic T cells
Aparna Rao, Jennifer L. Taylor, Nina Chi-Sabins, Mayumi Kawaihe, William E. Gooding, and Walter J. Storkus

Precise: Used in combination studies for immunochemotherapy, a chaperone small-molecule inhibitor might generally heighten antitumor responses mediated by specific CD8-positive T cells.

Molecular and Cellular Pathobiology

Induction of the RNA Regulator LIN28A Is Required for the Growth and Pathogenesis of RESTless Breast Tumors
Kearney T.W. Gunsalus, Matthew P. Wagoner, Kassondra Meyer, Wyatt B. Potter, Barry Schoenike, Soyoung Kim, Caroline M. Alexander, Andreas Friedl, and Avtar Roopra

Precise: This study offers pivotal mechanistic insights into how the loss of a transcriptional repressor that occurs frequently in breast cancer leads to an increase in tumor growth.

Histone Lysine Methyltransferase SETD8 Promotes Carcinogenesis by Deregulating PCNA Expression

Precise: By revealing a specific mechanism of epigenetic regulation of a central cell-cycle regulator implicated in many cancers, this study establishes a lysine methylation pathway as a potential target for generalized cancer treatment.

MEK Inhibition Leads to PI3K/AKT Activation by Relieving a Negative Feedback on ERBB Receptors
Alexa B. Turke, Youngchul Song, Carlotta Costa, Rebecca Cook, Carlos L. Arteaga, John M. Asara, and Jeffrey A. Engelman

Precise: Findings suggest that, by unleashing ERBB/PI3K/AKT signaling in cancer cells, MEK inhibitors might have complex effects on cancer pathophysiology, with implications for clinical trial design.

DEDD Interacts with PI3K/C3 to Activate Autophagy and Attenuate Epithelial–Mesenchymal Transition in Human Breast Cancer
Qi Lv, Wei Wang, Jianfei Xue, Fang Hua, Rong Mu, Heng Lin, Jun Yan, Xiaoxi Lv, Xiaoguang Chen, and Zhuo-Wei Hu

Precise: A key effector molecule for cell death signaling receptors activates autophagy but also attenuates epithelial-mesenchymal transition, placing it at an important intersection to modify metabolic and metastatic pathways in cancer.

Chk2 Phosphorylation of Survivin–ΔEx3 Contributes to a DNA Damage–Sensing Checkpoint in Cancer
Alessia Lopergolo, Michele Tavecchio, Sofia Lisanti, Jagadish C. Ghosh, Takehiko Dohi, Alice Faversani, Valentina Vaira, Silvano Bosari, Nobuhiko Taniigawa, Domenico Delia, Andrew V. Kossenkov, Louise C. Showe, and Dario C. Altieri

Precise: This study identifies a novel role of the checkpoint kinase Chk2 in controlling sensing of double-strand DNA breaks in tumor cells.

Oncogenic PI3K Mutations Lead to NF-κB–Dependent Cytokine Expression following Growth Factor Deprivation
Jessica E. Hutti, Adam D. Pfefferle, Sean C. Russell, Mayukh Sircar, Charles M. Perou, and Albert S. Baldwin

Precise: This important study furthers a deepening trend in the field by enhancing our understanding of how the most common mutations in cancer not only exert autonomous effects in cancer cells but also powerfully influence the local tumor microenvironment to support the outgrowth of these cells.

TMEM16A Induces MAPK and Contributes Directly to Tumorigenesis and Cancer Progression
Unmaheshwar Durvani, Daniel J. Shiwarski, Dong Xiao, Carol Bertrand, Xin Huang, Robert S. Edinger, Jason R. Rock, Brian D. Harfe, Brian J. Henson, Karl Kunzelmann, Rainer Schreiber, Robert L. Storkus, Jie Zhou, William E. Gooding, and Dario C. Altieri

Precise: A calcium-activated chloride channel is shown to promote tumorigenesis in head and neck cancers via signaling through the Ras/Raf/MEK pathway and therefore may represent a novel therapeutic target.
Increased Caffeine Intake Is Associated with Reduced Risk of Basal Cell Carcinoma of the Skin

Fengju Song, Abrar A. Qureshi, and Jiali Han

Précis: This prospective analysis shows an inverse association between caffeine intake and the risk of basal cell carcinoma in 2 large national cohorts.

Cancer Cell Secretion of the DAMP Protein HMGB1 Supports Progression in Malignant Mesothelioma

Sandro Jube, Zeyana S. Rivera, Marco E. Bianchi, Amy Powers, Ena Wang, Ian Pagano, Harvey I. Pass, Giovanni Gaudino, Michele Carbone, and Haining Yang

Précis: This study offers a preclinical proof-of-principle that therapies aimed at blocking HMGB1-driven inflammation may be beneficial to patients with mesothelioma, especially at early stages of tumor growth.

Combined EGFR/MET or EGFR/HSP90 Inhibition Is Effective in the Treatment of Lung Cancers Codriven by Mutant EGFR Containing T790M and MET

Lu Xu, Eiki Kikuchi, Chunxiao Xu, Hiromichi Ebi, Dalia Ercan, Katherine A. Cheng, Robert Padera, Jeffrey A. Engelman, Pasi A. Jänne, Geoffrey I. Shapiro, Takeshi Shimamura, and Kwok-Kin Wong

Précis: Using a bitransgenic murine lung cancer model, this study offers preclinical proof-of-principle that combination therapies targeting EGFR and MET overcome tyrosine kinase inhibitor resistance in non–small cell lung cancer.

Identification of Anaplastic Lymphoma Kinase as a Potential Therapeutic Target in Ovarian Cancer

Hong Ren, Zhi-Ping Tan, Xin Zhu, Katherine Crosby, Herbert Haack, Jian-Min Ren, Sean Beausoleil, Albrecht Moritz, Gregory Innocenti, John Rush, Yi Zhang, Xin-Min Zhou, Ting-Lei Gu, Yi-Feng Yang, and Michael J. Comb

Précis: Findings suggest the use of ALK kinase inhibitors now in clinical development as potential agents for treatment of some patients with serous ovarian carcinoma or stromal sarcoma.
| 3372 | **Acquired Resistance to Tamoxifen Is Associated with Loss of the Type I Insulin-like Growth Factor Receptor: Implications for Breast Cancer Treatment**  
Dedra H. Fagan, Ryan R. Uselman, Deepali Sachdev, and Douglas Yee  
**Précis:** Findings in a preclinical breast cancer model of tamoxifen resistance may explain the reason for the lack of clinical benefit observed in trials that combine anti-IGF1 receptor and antiestrogen therapies. |
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| 3405 | **PTEN and NF1 Inactivation in Schwann Cells Produces a Severe Phenotype in the Peripheral Nervous System That Promotes the Development and Malignant Progression of Peripheral Nerve Sheath Tumors**  
Vincent W. Keng, Eric P. Rahrmann, Adrienne L. Watson, Barbara R. Tschida, Christopher L. Moertel, Walter J. Jessen, Tilat A. Rizvi, Margaret H. Collins, Nancy Ratner, and David A. Largaespada  
**Précis:** This study establishes a mouse model that can rapidly recapitulate the histologies associated with onset of human neurofibromas and their malignant progression to high-grade malignant nerve tumors, based on genetic mutations that are relevant to the human tumor setting. |
| 3381 | **Definition of Genetic Events Directing the Development of Distinct Types of Brain Tumors from Postnatal Neural Stem/Progenitor Cells**  
Falk Hertwig, Katharina Meyer, Sebastian Braun, Sara Ek, Rainer Spang, Cosima V. Pfenninger, Isabella Artner, Gaëlle Prost, Xinbin Chen, Jaclyn A. Biegel, Alexander R. Judkins, Elisabet Englund, and Ulrike A. Nuber  
**Précis:** This study reveals that, within malignant brain tumors derived from a common precursor cell pool, the temporal order of genetic events that accumulate is a critical determinant of the histopathologic phenotype that emerges. |
| 3414 | **CD44s Regulates the TGF-β–Mediated Mesenchymal Phenotype and Is Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma**  
Kosuke Mima, Hirohisa Okabe, Takatsugu Ishimoto, Hiromitsu Hayashi, Shigeki Nakagawa, Hideyuki Kuroki, Masayuki Watanabe, Toru Beppu, Mayumi Tamada, Osamu Nagatomo, Hideyuki Saya, and Hideo Baba  
**Précis:** The so-called standard isoform of a stem cell marker plays a crucial role in mesenchymal phenotypes associated with progression of hepatocellular carcinoma, with implications for therapeutic targeting of this deadly disease. |
| 3393 | **Distinct microRNA Expression Profiles in Prostate Cancer Stem/Progenitor Cells and Tumor-Suppressive Functions of let-7**  
Can Liu, Kevin Kelmar, Alexander V. Vlassov, David Brown, JunCheen Wang, and Dean G. Tang  
**Précis:** microRNA expression profiling performed in prostate cancer stem/progenitor cells identifies a relatively small signature of functionally significant tumor-suppressive genes in the control of prostate cancer stem cell activity. |
| 3424 | **FRMD4A Upregulation in Human Squamous Cell Carcinoma Promotes Tumor Growth and Metastasis and Is Associated with Poor Prognosis**  
Stephen J. Goldie, Klaas W. Mulder, David Wei-Min Tan, Scott K. Lyons, Andrew H. Sims, and Fiona M. Watt  
**Précis:** A candidate stem cell marker implicated in epithelial polarization is found to be a key regulator of metastatic growth in head and neck cancers, with implications for therapeutic targeting of this aggressive and increasingly common disease. |
ABOUT THE COVER

Malignant mesothelioma cells secrete the damage-associated molecular pattern protein HMGB1 that promotes tumor progression and sustains the malignant phenotype. HMGB1-secreting mesothelioma cells are addicted to HMGB1, and their anchorage independent growth is impaired by the antagonist BoxA or by a HMGB1 specific monoclonal antibody (mAb), or by a mAb against HMGB1 receptor RAGE, as indicated by the reduced number and size of colonies, compared to controls. For details, see article by Jube et al. on page 3290 of this issue.