## BREAKING ADVANCES

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## REVIEWS

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<td>MAX and MYC: A Heritable Breakup</td>
<td>Alberto Cascón and Mercedes Robledo</td>
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<td>Cellular Constituents of Immune Escape within the Tumor Microenvironment</td>
<td>Sid P. Kerkar and Nicholas P. Restifo</td>
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## PERSPECTIVE

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<td>The Continuum Model of Selection in Human Tumors: General Paradigm or Niche Product?</td>
<td>Simon Leedham and Ian Tomlinson</td>
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## PRIORITY REPORT

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<td>Stat3 Activation in Urothelial Stem Cells Leads to Direct Progression to Invasive Bladder Cancer</td>
<td>Philip Levy Ho, Erica Julianne Lay, Weiguo Jian, Diana Parra, and Keith Syson Chan</td>
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## INTEGRATED SYSTEMS AND TECHNOLOGIES

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<td>Antigen Shedding May Improve Efficiencies for Delivery of Antibody-Based Anticancer Agents in Solid Tumors</td>
<td>Youngshang Pak, Yujian Zhang, Ira Pastan, and Byungkook Lee</td>
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## MICROENVIRONMENT AND IMMUNOLOGY

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**Précis:** Findings reveal an intriguing mechanism through which tumor-associated neutrophils present in the tumor microenvironment can trigger an antigen-specific cytolytic T-cell response against the malignant cells present there.

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<td>3163</td>
<td>Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Imunnonodulatory Antibodies</td>
<td>Inge Verbrugge, Jim Hagekyriakou, Leslie L. Sharp, Mara Galli, Alison West, Nicole M. McLaughlin, Hélène Duret, Hideo Yagita, Rikky W. Johnstone, Mark J. Smyth, and Nicole M. Haynes</td>
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**Précis:** Findings show how systemically delivered monoclonal antibodies that can concomitantly stimulate antitumor immunity and degrade tumoral immunosuppression can act as powerful adjuvants to improve the efficacy of cancer radiotherapy, with immediate translational potential as immunoradiotherapy.

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<td>3175</td>
<td>CXCL10 Promotes Osteolytic Bone Metastasis by Enhancing Cancer Outgrowth and Osteoclastogenesis</td>
<td>Jong-Ho Lee, Ha-Neui Kim, Kyung-Ok Kim, Won Jong Jin, Seungbok Lee, Hong-Hee Kim, Hyunil Ha, and Zang Hee Lee</td>
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**Précis:** Findings advance understanding of the microenvironmental contributions in the bone that permit the development of osteolytic bone metastasis, with implications for treatment of this common aspect of malignant progression in some common cancers.
MOLECULAR AND CELLULAR PATHOBIOLOGY

3187

**Loss of Fibroblast HIF-1α Accelerates Tumorigenesis**

Jung-wha Kim, Colin Evans, Alexander Weidemann, Norihiko Takeda, Yun Sok Lee, Christian Stockmann, Cristina Branco-Price, Filip Brandberg, Gustavo Leone, Michael C. Ostrowski, and Randall S. Johnson

*Précis:* 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.

3196

**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 Kawabe, William E. Gooding, and Walter J. Storkus

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

3207

**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

*Précis:* 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.

3217

**Histone Lysine Methyltransferase SETD8 Promotes Carcinogenesis by Deregulating PCNA Expression**


*Précis:* 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.

3228

**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

*Précis:* 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.

3238

**DEDD Interacts with PI3KΔC3 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

*Précis:* 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.

3251

**Chk2 Phosphorylation of Survivin–ΔEx3 Contributes to a DNA Damage–Sensing Checkpoint in Cancer**

Alessia Lopergolo, Michele Tavecchia, Sofia Lisanti, Jagadish C. Ghosh, Takehiko Dohi, Alice Faversani, Valentina Vaira, Silvano Bosari, Nobuhiko Taniyagawa, Domenico Delia, Andrew V. Kosenkov, Louise C. Showe, and Darío C. Altieri

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

3260

**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

*Précis:* 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.

3270

**TMEM16A Induces MAPK and Contributes Directly to Tumorigenesis and Cancer Progression**


*Précis:* 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.
### Prevention and Epidemiology

**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.

### Therapeutics, Targets, and Chemical Biology

**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.

**Antibody Targeting of Cell-Bound MUC1 SEA Domain Kills Tumor Cells**
Edward Pichinuk, Itai Benhar, Oded Jacob, Michael Chalik, Lotem Weiss, Ravit Ziv, Carolyn Sympson, Amol Kumar Karwa, Nechama I. Smorodinsky, Daniel B. Rubinstein, and Daniel H. Wreschner

*Précis:* Findings explore the development of a universal class of anticancer antibodies, showing high-affinity binding and potent killing of cancer and cancer stem cells that highly express a common cancer antigen.

**Glucose-Regulated Protein 78 Controls Cross-talk between Apoptosis and Autophagy to Determine Antiestrogen Responsiveness**
Katherine L. Cook, Ayesha N. Shajahan, Anni Wärri, Lu Jin, Leena A. Hilakivi-Clarke, and Robert Clarke

*Précis:* Expression of an endoplasmic reticulum-located chaperone protein is shown to play a role in the development of acquired antiestrogen resistance, suggesting that the unfolded protein response may be an adaptation to stress in estrogen receptor–positive breast cancer.

**Sensitivity of Glioblastomas to Clinically Available MEK Inhibitors Is Defined by Neurofibromin 1 Deficiency**
Wendy L. See, I-Li Tan, Joydeep Mukherjee, Theodore Nicolaides, and Russell O. Pieper

*Précis:* This study offers immediate implications for stratification of brain cancer patients who might be treated with MEK inhibitors.

**The Nedd8-Activating Enzyme Inhibitor MLN4924 Induces Autophagy and Apoptosis to Suppress Liver Cancer Cell Growth**
Zhongguang Luo, Guangyang Yu, Hyuk Woo Lee, Libui Li, Lingyan Wang, Dongjin Yang, YoungJu Pan, Chan Ding, Jing Qian, Lijun Wu, Yiwei Chu, Jing Yi, Xiangdong Wang, Yi Sun, Lak Shin Jeong, Jie Liu, and Lijun Jia

*Précis:* Findings offer preclinical evidence for therapeutic efficacy of a first-in-class neddylation inhibitor to treat liver cancer and provide a mechanistic rationale for its combination with an autophagy inhibitor.
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

Precise: 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.

TUMOR AND STEM CELL BIOLOGY

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. Pfenniger, Isabella Artner, Gaëlle Prost, Xinbin Chen, Jaclyn A. Biegel, Alexander R. Judkins, Elisabet Englund, and Ulrike A. Nuber

Precise: 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.

Distinct microRNA Expression Profiles in Prostate Cancer Stem/Progenitor Cells and Tumor-Suppressive Functions of let-7
Can Liu, Kevin Kelnmar, Alexander V. Vlassov, David Brown, Jun chen Wang, and Dean G. Tang

Precise: 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.

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. Rahmann, Adrienne L. Watson, Barbara R. Tschiida, Christopher L. Moertel, Walter J. Jessen, Tilat A. Rizvi, Margaret H. Collins, Nancy Ratner, and David A. Largaespada

Precise: 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.

CD44s Regulates the TGF-β–Mediated Mesenchymal Phenotype and Is Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma
Kosuke Mima, Hirohisa Okabe, Takatsu I shimoto, Hiromitsu Hayashi, Shigeki Nakagawa, Hideyuki Kuroki, Masayuki Watanabe, Toru Beppu, Mayumi Tamada, Osamu Nagato, Hideyuki Saya, and Hideo Baba

Precise: 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.

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

Precise: 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.