BREAKING ADVANCES

3117 Highlights from Recent Cancer Literature

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3125 Cellular Constituents of Immune Escape within the Tumor Microenvironment
Sid P. Kerkar and Nicholas P. Restifo

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3131 The Continuum Model of Selection in Human Tumors: General Paradigm or Niche Product?
Simon Leedham and Ian Tomlinson

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3135 Stat3 Activation in Urothelial Stem Cells Leads to Direct Progression to Invasive Bladder Cancer
Philip Levy Ho, Erica Julianne Lay, Weiguo Jian, Diana Parra, and Keith Syson Chan

INTEGRATED SYSTEMS AND TECHNOLOGIES

3143 Antigen Shedding May Improve Efficiencies for Delivery of Antibody-Based Anticancer Agents in Solid Tumors
Youngshang Pak, Yujian Zhang, Ira Pastan, and Byungkook Lee

MICROENVIRONMENT AND IMMUNOLOGY

3153 Breast Cancer Cell Uptake of the Inflammatory Mediator Neutrophil Elastase Triggers an Anticancer Adaptive Immune Response
Elizabeth A. Mittendorf, Gheath Alatrash, Na Qiao, Yun Wu, Pariya Sukhumalchandra, Lisa S. St. John, Anne V. Philips, Haile Xiao, Mao Zhang, Kathryn Ruisaard, Karen Clise-Dwyer, Sijie Lu, and Jeffrey J. Moldrem

3163 Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Immunomodulatory Antibodies
Inge Verbrugge, Jim Hagekyriakou, Leslie L. Sharp, Mara Galli, Alison West, Nicole M. McLaughlin, Hélène Duret, Hideo Yagita, Rippy W. Johnstone, Mark J. Smyth, and Nicole M. Haynes

3175 CXCL10 Promotes Osteolytic Bone Metastasis by Enhancing Cancer Outgrowth and Osteoclastogenesis
Jong-Ho Lee, Ha-Neui Kim, Kyung-Ok Kim, Won Jong Jin, Seungbok Lee, Hong-Hee Kim, Hyunil Ha, and Zang Hee Lee

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.
MOLECULAR AND CELLULAR PATHOBIOLOGY

3187 Loss of Fibroblast HIF-1α Accelerates Tumorigenesis
Jung-whan 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 Kawai, 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, Kassandra 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
Masashi Takawa, Hyun-Soo Cho, Shinya Hayami, Goji Togosawa, Masaharu Kogure, Takaaki Kobayashi, Takehiko Taniai, Akiko Masuda, Naoshi Doi, Helen J. Field, Tatsuhiro Tsunoda, Takakji Ikawa, Masanori Sugiyama, Shin-ichi Ohnuma, Yutaka Atomi, Bruce A. Ponder, Yusuke Nakamura, and Ryuichi Hamamoto

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 PI3K3 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, Xiaoqiang 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 Tavvecchio, Sofia Lissanti, Jagadish C. Ghosh, Takehiko Dohi, Alice Faversani, Valentina Vaira, Silvano Bosari, Nobuhiro Taniigawa, Dominico Delia, Andrew V. Kossenkov, 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-kB–Dependent Cytokine Expression following Growth Factor Deprivation
Jessica E. Hutti, Adam D. Pfefferle, Sean C. Russell, 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.
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 L. 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, Juan-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.
### Tumor and Stem Cell Biology

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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.