BREAKING ADVANCES

2773  Highlights from Recent Cancer Literature

REVIEWS

2775  TAM Receptor Tyrosine Kinases in Cancer Drug Resistance
Mikaella Vouri and Sassan Hafizi

2779  Therapeutic IgE Antibodies: Harnessing a Macrophage-Mediated Immune Surveillance Mechanism against Cancer
Sophia N. Karagiannis, Debra H. Josephs, Heather J. Bax, and James F. Spicer

PERSPECTIVE

2784  Widespread Use of Misidentified Cell Line KB (HeLa): Incorrect Attribution and Its Impact Revealed through Mining the Scientific Literature
Liwen Vaughan, Wolfgang Glanzel, Christopher Korch, and Amanda Capes-Davis

CLINICAL STUDIES

2789  BRCA2 Hypomorphic Missense Variants Confer Moderate Risks of Breast Cancer
Précis: These results show how BRCA2 missense variants that partially influence protein function can confer clinically relevant increased risks of breast cancer, with potential implications for risk management of women who harbor specific variants.

INTEGRATED SYSTEMS AND TECHNOLOGIES

2800  Mathematical Modeling Links Pregnancy-Associated Changes and Breast Cancer Risk
Daniel Temko, Yu-Kang Cheng, Kornelia Polyak, and Franziska Michor
Précis: A simple mathematical model demonstrates that pregnancy-associated reduction in p27\textsuperscript{+} cell frequency in human breast can explain the protective effect of pregnancy against ER\textsuperscript{+} breast cancer.

2810  Tissue-Specific Signaling Networks Rewired by Major Somatic Mutations in Human Cancer Revealed by Proteome-Wide Discovery
Jundei Zhao, Feixiong Cheng, and Zhongming Zhao
Précis: This systematic oncoproteomics analysis of kinome phosphorylation site mutations illustrates new capabilities to speed the development of precision oncology.
Variability in Chromatin Architecture and Associated DNA Repair at Genomic Positions Containing Somatic Mutations
Byungho Lim, Jihyeob Mun, Yong Sung Kim, and Seon-Young Kim

Précis: These findings increase our knowledge surrounding mutational processes and the identification of cancer type-specific mutations within the tissue-specific epigenomic landscape.

MICROENVIRONMENT AND IMMUNOLOGY

SETD1B Activates iNOS Expression in Myeloid-Derived Suppressor Cells

Précis: Tactics to blunt myeloid-derived suppressor cells in cancer are provided by this study, which shows that iNOS expression in such cells normally controlled by IRF8 under physiological conditions is bypassed by tumor cells through an alternate epigenetic pathway under pathological conditions.

GAD1 Upregulation Programs Aggressive Features of Cancer Cell Metabolism in the Brain Metastatic Microenvironment
Patricia M. Schnepp, Dennis D. Lee, Ian H. Guldner, Treasa K. O'Tighearnaigh, Erin N. Howe, Bhavana Palakurthi, Kaitlyn E. Eckert, Tiffany A. Toni, Brandon L. Ashfeld, and Siyuan Zhang

Précis: These results show how epigenetic changes in GAD1 expression alter local glutamate metabolism in the brain metastatic microenvironment, contributing to a metabolic adaption that facilitates metastasis outgrowth in that setting, with potential implications for repurposing certain clinical drugs to eradicate brain metastases.

Targeting Autocrine CCL5–CCR5 Axis Reprograms Immunosuppressive Myeloid Cells and Reinvigorates Antitumor Immunity
Yi Ban, Junhua Mai, Xin Li, Starisa Mitchell-Flack, Tuo Zhang, Lixin Zhang, Lotfi Choschane, Mauro Ferrari, HaiFa Shen, and Xiaoqiang Ma

Précis: This study offers preclinical proof of concept for therapeutic targeting of the CCL5–CCR5 signaling pathway in myeloid cells as a promising target for cancer immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

NRF2 Induction Supporting Breast Cancer Cell Survival Is Enabled by Oxidative Stress–Induced DPP3–KEAP1 Interaction
Kevin Lu, Allen L. Alcivar, Jianglin Ma, Tzeh Keong Foo, Susan Zywea, Amar Mahdi, Yanying Huo, Thomas W. Kensler, Michael L. Gatza, and Bing Xia


A PET Imaging Strategy to Visualize Activated T Cells in Acute Graft-versus-Host Disease Elicited by Allogenic Hematopoietic Cell Transplant

Précis: A radiotracer compound developed from the T-cell targeted cancer drug arabinofuranosylguanine (AraG) can be used for noninvasive PET imaging to detect activated donor T cells prior to overt clinical symptoms of graft-versus-host disease, a common dangerous side-effect of T-cell transplant immunotherapy strategies used to eradicate leukemia and other cancers.
 Metabolic Markers and Statistical Prediction of Serous Ovarian Cancer Aggressiveness by Ambient Ionization Mass Spectrometry Imaging

Précis: A rapid mass spectrometry method reveals distinct metabolic signatures in different ovarian tissue types, allowing diagnosis of specific types of ovarian cancer with an overall accuracy of >95% compared with traditional histopathological grading.

Cellular Prion Protein PrPC and Ecto-5′-Nucleotidase Are Markers of the Cellular Stress Response to Aneuploidy

Précis: A comprehensive atlas of cell surface marker expression in multiple models of aneuploidy offers a tool to analyze cells with aneuploid chromosome settings and consequential cellular stress responses.

CIC-DUX4 Induces Small Round Cell Sarcomas Distinct from Ewing Sarcoma

Précis: This study reports a useful mouse model for a highly aggressive type of soft tissue sarcoma, distinct from but similar to Ewing’s sarcoma, offering a new tool to explore biomarkers and therapies for this recently defined disease.

Spermidine Prolongs Lifespan and Prevents Liver Fibrosis and Hepatocellular Carcinoma by Activating MAP1S-Mediated Autophagy

Précis: This exciting and potentially seminal study offers a preclinical proof of concept for orally administered spermidine as a safe and cost-effective strategy to prevent liver fibrosis and hepatocellular carcinoma, and also to extend lifespan.

Tumor-Localized Secretion of Soluble PD1 Enhances Oncolytic Virotherapy

Précis: Soluble PD1 secretion from oncolytic myxoma virus improves response rates to checkpoint blockade, which could significantly improve immunotherapy against a variety of malignancies.

A Squalene-Based Nanomedicine for Oral Treatment of Colon Cancer

Preclinical Characterization of BET Family Bromodomain Inhibitor ABBV-075 Suggests Combination Therapeutic Strategies

Précis: Distinct proapoptotic activities of a BET inhibitor in clinical trials to treat hematological cancers may have uses to treat solid tumors in combination with anti-BH3 therapies.

SFK/FAK Signaling Attenuates Osimertinib Efficacy in Both Drug-Sensitive and Drug-Resistant Models of EGFR-Mutant Lung Cancer

Précis: These findings identify SFK/FAK family member upregulation as a mechanism of resistance to the recently approved EGFR inhibitor osimertinib, enabling physicians and researchers to design clinical trials to overcome resistance.
Table of Contents

3001 Modulation of Bax and mTOR for Cancer Therapeutics

Précis: These findings provide preclinical evidence for a pharmacologic combination of Bax activation and mTOR inhibition as a rational strategy to improve lung cancer treatment.

3013 Expression of Neuroendocrine Factor VGF in Lung Cancer Cells Confers Resistance to EGFR Kinase Inhibitors and Triggers Epithelial-to-Mesenchymal Transition
Wen Hwang, Yu-Fan Chiu, Ming-Han Kuo, Kuan-Lin Lee, An-Chun Lee, Chia-Cherng Yu, Jinn-Liang Chang, Wen-Chien Huang, Shih-Hsin Hsiao, Sey-En Lin, and Yu-Ting Chou

Précis: When upregulated in lung cancer cells, a neuropeptide cleaved into multiple hormone-like factors promotes energy production and confers aggressive features, with possible implications for prognosis and therapy in this setting.

3027 E3 Ligase cIAP2 Mediates Downregulation of MRE11 and Radiosensitization in Response to HDAC Inhibition in Bladder Cancer
Judith Nicholson, Sarah J. Jevons, Blaz Groselj, Sophie Ellermann, Rebecca Konietzny, Martin Kerr, Benedict M. Kessler, and Anne E. Kiltie

Précis: These findings identify MRE11 as a substrate of cIAP2-mediated ubiquitination and open new routes towards defining bladder cancer biomarkers and improving chemoradiation strategies.

3040 ATM Deficiency Is Associated with Sensitivity to PARP1 and ATR Inhibitors in Lung Adenocarcinoma
Anna Schmitt, Gero Knittel, Daniela Welcker, Tsun-Po Yang, Julie George, Michael Nowak, Utschi Leeser, Reinhard Buttner, Sven Permer, Martin Pieler, and Hans Christian Reinhardt

Précis: The results of this preclinical study provide a functional rationale to profile KRAS-mutant human tumors for disabling mutations in the DNA damage response kinase ATM, which increase sensitivity to inhibitors of topoisomerase II, PARP1, and ATR.

3057 Integrative Cancer Pharmacogenomics to Infer Large-Scale Drug Taxonomy
Nehme El-Hachem, Deena M.A. Gendoo, Laleh Soltan Choraei, Zahaleh Safikhani, Petr Smirnov, Christina Chung, Kenan Deng, Ailsa Fang, Erin Birkwood, Chantal Ho, Ruth Isserlin, Gary D. Bader, Anna Goldenberg, and Benjamin Halbe-Kains

Précis: The Drug Network Fusion approach predicts mechanism of action of poorly characterized compounds and highlights the potential to repurpose approved drugs with new anticancer indications.

TUMOR AND STEM CELL BIOLOGY

3070 Combination Therapy Targeting BCL6 and Phospho-STAT3 Defeats Intratumor Heterogeneity in a Subset of Non–Small Cell Lung Cancers
Dhiruba De, Satwik Rajaram, Jill E. Larsen, Patrick D. Dospoy, Rossella Marullo, Long Shan Li, Kimberley Avila, Fongtian Xue, Leandro Cerchietti, John D. Minna, Steven J. Altschuler, and Lani F. Wu

Précis: A comprehensive atlas of cell surface marker expression in multiple models of aneuploidy offers a tool to analyze cells with aneuploid chromosome settings and consequential cellular stress responses.

3082 NOTCH1 Signaling Regulates Self-Renewal and Platinum Chemoresistance of Cancer Stem–like Cells in Human Non–Small Cell Lung Cancer
Yun Zhang, Wei Xu, Huikin Guo, Yanmei Zhang, Yuexi He, Sau Har Lee, Xin Song, Xiaoyan Li, Yongqing Guo, Yunlong Zhao, Cheng Ding, Fei Ning, Yuanyuan Ma, Qin-Ying Lei, Xiaoju Hu, Shengnan Li, and Wei Guo

Précis: These results define the pathogenic character of a cancer stem-like subpopulation in lung cancers, the targeting of which may relieve platinum resistance in this disease.

3092 The p53/p21 Complex Regulates Cancer Cell Invasion and Apoptosis by Targeting Bcl-2 Family Proteins
Eun Mi Kim, Chan-Hun Jung, Jongdoo Kim, Sang-Gu Hwang, Jong Kuk Park, and Hong-Duck Um

Précis: These findings provide a new foundation for understanding aberrant p53 signaling processes that lead to tumor progression and therapy resistance.
Disrupting Androgen Receptor Signaling Induces Snail-Mediated Epithelial–Mesenchymal Plasticity in Prostate Cancer


Précis: This seminal report shows how targeting the androgen receptor may lead to undesirable phenotypic plasticity in prostate cancer cells, suggesting a general mechanism of resistance to hormonal therapies in prostate and breast cancers.

Multinuclear NMR and MRI Reveal an Early Metabolic Response to mTOR Inhibition in Sarcoma


Précis: These results illustrate the use of hyperpolarized MRI as a sensitive technique to monitor drug-induced perturbation of the PI3K/mTOR pathway in sarcomas, with implications for use in recruiting responsive patients to rapalog clinical trials.

Water Concentration Analysis of the Surgical Margin—Letter

C. Murali Krishna and Aditi Sahu

Water Concentration Analysis of the Surgical Margin—Response

Gerwin J. Puppels

CORRECTIONS

Correction: Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer

Correction: Chromosome Instability Modulated by BMI1–AURKA Signaling Drives Progression in Head and Neck Cancer

Correction: Connective Tissue Growth Factor Activates Pluripotency Genes and Mesenchymal–Epithelial Transition in Head and Neck Cancer Cells

About the Cover

Autophagy is a major pathway for degradation of dysfunctional organelles and misfolded or aggregated proteins, and its defects trigger oxidative stresses to induce cell death, promote liver fibrosis and HCC, and reduce lifespans. Natural component spermidine enhances autophagy flux by depleting cytosolic histone deacetylase 4 and reducing its interaction with autophagy activator microtubule-associated protein MAP1S to dramatically expand lifespans and to prevent liver fibrosis and hepatocellular carcinomas. For details, see article by Yue and colleagues on page 2938.
Cancer Research

77 (11)

Cancer Res 2017;77:2773-3127.

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