Breaking Advances

5681 Highlights from Recent Cancer Literature

Review

5683 DEAR1, a Novel Tumor Suppressor That Regulates Cell Polarity and Epithelial Plasticity
Nanyue Chen, Seetharaman Balasenthil, Jacquelyn Reuther, and Ann McNeill Killary

Integrated Systems and Technologies

5690 Novel Drug Candidates for the Treatment of Metastatic Colorectal Cancer through Global Inverse Gene-Expression Profiling
Vera van Noort, Sebastian Scholch, Murat Iskar, Georg Zeller, Kristina Ostertag, Christine Schweitzer, Kristin Werner, Jürgen Weitz, Moritz Koch, and Peer Bork
Précis: These findings provide a rationale to reposition the antidepressant drug citalopram for treatment of late-stage colorectal cancers, with immediate implications for clinical evaluation of this drug.

5700 Development of Novel ADCs: Conjugation of Tubulysin Analogues to Trastuzumab Monitored by Dual Radiolabeling
Ruth Cohen, Danielle J. Vugts, Gerard W.M. Visser, Marijke Stigter-van Walsum, Marije Bolijn, Marco Spiga, Paolo Lazzari, Sreejith Shankar, Monica Sani, Matteo Zanda, and Guus A.M.S. van Dongen
Précis: Radiolabeling both a synthetic tubulysin and the antibody to which it is attached facilitated preclinical validation of a new antibody-drug conjugate (ADC) with excellent tumor-targeting performance and efficacy.

Microenvironment and Immunology

5711 Adiponectin Receptor Signaling on Dendritic Cells Blunts Antitumor Immunity
Peng H. Tan, Helen E.J. Tyrrell, Liquan Gao, Danmei Xu, Jianchao Quan, Dipender Gill, Lena Rai, Yunchuan Ding, Gareth Plant, Yuanhui Yin, Qiuyuan Liao, Yang Meng, Yiming Zhang, Dalong Ma, and Xiaoyan Qiu
Précis: Novel adiponectin signaling pathways revealed in this report are shown to promote immune tolerizing signals in dendritic cells that drive tumoral immune escape in cancer, suggesting broadly applicable new strategies for the immunometabolic control of cancer.

5723 HMGB1 Enhances Immune Suppression by Facilitating the Differentiation and Suppressive Activity of Myeloid-Derived Suppressor Cells
Katherine H. Parker, Pratima Sinha, Lucas A. Horn, Virginia K. Clements, Huan Yang, Jianhua Li, Kevin J. Tracey, and Suzanne Ostrand-Rosenberg
Précis: A secreted alarmin that is ubiquitously present in the tumor microenvironment provides a pivotal proinflammatory contribution to the differentiation and suppressive potency of myeloid-derived suppressor cells, an important driver of immune escape in many solid tumors.

5734 Cytokine-like Molecule CCDC134 Contributes to CD8+ T-cell Effector Functions in Cancer Immunotherapy
Jing Huang, Lin Xiao, Xiaoting Gong, Wenwei Shao, Yanzhi Yan, Qiuyuan Liao, Yang Meng, Yiming Zhang, Dalong Ma, and Xiaoyan Qiu
Précis: These findings offer strong evidence for a new member of the yc cytokine family that provides powerful support for CD8+ T-cell-mediated immunity, with potential implications for therapeutic applications.

Molecular and Cellular Pathobiology

5746 Metastatic Consequences of Immune Escape from NK Cell Cytotoxicity by Human Breast Cancer Stem Cells
Bin Wang, Qiang Wang, Zhe Wang, Jun Jiang, Shi-Cang Yu, Yi-Ping Ping, Jing Yang, Sen-Lin Xu, Xian-Zong Ye, Chuan Xu, Lang Yang, Cheng Qian, Ji Ming Wang, You-Hong Cui, Xia Zhang, and Xiu-Wu Bian
Précis: These findings reveal how metastasis-initiating breast cancer stem-like cells evade immune surveillance by natural killer cells.

5758 Cellular Disposal of miR23b by RAB27-Dependent Exosome Release Is Linked to Acquisition of Metastatic Properties
Précis: This interesting study suggests that exosome secretion serves as a disposal mechanism for tumor suppressor microRNA during tumor progression, thereby enabling the acquisition of metastatic capabilities.
The 19q12 Bladder Cancer GWAS Signal: PCTAIRE1 Phosphorylates p27 and Regulates Mycoplasma Hyorhinis Infection

Précis: This study offers a sensitive, specific, and noninvasive method to image prostate cancer, including in bone metastases that lack a reliable clinical imaging agent, offering a preclinical proof of concept that rationalizes immediate clinical translation and evaluation in patients with advanced prostate cancer.

Mycoplasma Hyorhinis Infection Promotes NF-κB-Dependent Migration of Gastric Cancer Cells

Précis: These findings unveil the effect of a mycoplasmic infection that has been linked to stomach cancer and other types of cancer but not understood in terms of its possible functional contributions, as revealed for the first time in this study.

PCTAIRE1 Phosphorylates p27 and Regulates Mitosis in Cancer Cells

Précis: These results reveal an unexpected role for the distant CDK relative PCTAIRE1 in cancer cell division and offer a preclinical proof of concept for its candidacy as a new disease-selective target for cancer treatment.

Copper Signaling Axis as a Target for Prostate Cancer Therapeutics

Précis: Clinical trials in oncology of an approved dithiol compound have failed to produce efficacy, but the findings of this study suggest that this compound should be reexplored with the addition of copper to the regimen, particularly with regard to treatment of prostate cancers resistant to androgen ablation.

Metabolic Vulnerabilities in Endometrial Cancer

Précis: This study reveals that the survival of endometrial cancer cells relies critically on GLUT6-mediated glucose transport, along with glycolytic and lipogenic metabolic pathways, with implications for therapeutic strategies in this setting.
**In Vivo Localization of 90Y and 177Lu Radioimmunoconjugates Using Cerenkov Luminescence Imaging in a Disseminated Murine Leukemia Model**
Ethan R. Balkin, Aimee Kenoyer, Johnnie J. Orozco, Alexandra Hernandez, Maziar Shadman, Darrell R. Fisher, Damian J. Green, Mark D. Hylarides, Oliver W. Press, D. Scott Wilbur, and John M. Pagel

**Précis:** Results demonstrate the feasibility of using a novel noninvasive imaging technique called Cerenkov Light Imaging (CLI) to optimize the use of radioimmunoconjugates used to treat aggressive leukemias.

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**SAR405838: An Optimized Inhibitor of MDM2–p53 Interaction That Induces Complete and Durable Tumor Regression**
Shaomeng Wang, Wei Sun, Yujun Zhao, Donna McEachern, Isabelle Meaux, Cédric Barrière, Jeanne A. Stuckey, Jennifer L. Meagher, Longchuan Bai, Liu Liu, Cassandra Gianna Hoffman-Luca, Jianfeng Lu, Sanjeev Shangary, Shanghui Yu, Dënisl Bernard, Angelo Aguilar, Odette Dos-Santos, Laurent Besret, Stéphane Guerif, Pascal Pannier, Dimitri Gorge-Bernat, and Laurent Debussche

**Précis:** Despite the risk of applying a selection for p53 mutations that escape MDM2 control, blocking MDM2–p53 protein–protein interaction has long been considered by many to offer an attractive cancer therapeutic strategy, a position strongly supported by the findings of this preclinical study.

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**Dsh Homolog DVL3 Mediates Resistance to IGFIR Inhibition by Regulating IGF-RAS Signaling**
Shan Gao, Ilirjana Bajrami, Clare Verrill, Asha Kigozi, Djamila Ouaret, Tamara Aleksic, Ruth Asher, Cheng Han, Paul Allen, Deborah Bailey, Stephan Feller, Takeshi Kashima, Longhuan Bai, Liu Liu, Cassandra Gianna Hoffman-Luca, Jianfeng Lu, Sanjeev Shangary, Shanghui Yu, Dënisl Bernard, Angelo Aguilar, Odette Dos-Santos, Laurent Besret, Stéphane Guerif, Pascal Pannier, Dimitri Gorge-Bernat, and Laurent Debussche

**Précis:** This mechanistic study is important because it addresses the lack of predictive biomarkers for stratifying and recruiting cancer patients who might benefit from IGF-1 inhibitors, a key gap in their clinical development as cancer drugs.

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**MYC Activates Stem-like Cell Potential in Hepatocarcinoma by a p53-Dependent Mechanism**
Hirofumi Akita, Jens U. Marquardt, Marian E. Durkin, Mitsuteru Kitade, Daekwan Seo, Elizabeth A. Conner, Jesper B. Andersen, Valentina M. Factor, and Snorri S. Thorgeirsson

**Précis:** Cancer stem-like cell populations in liver cancer appear to be expanded under conditions in which MYC is activated and p53 is downregulated, with potential implications for understanding etiology, progression, and treatment in this disease.

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**Zfx Facilitates Tumorogenesis Caused by Activation of the Hedgehog Pathway**
Colin J. Palmer, Jose M. Galan-Caridad, Stuart P. Weisberg, Liang Lei, Jose M. Esquilin, Gist F. Croft, Brandon Wainwright, Peter Canoll, David M. Owens, and Boris Reizis

**Précis:** This preclinical genetic study identifies new candidate targets for the control of tumors driven by the Hedgehog pathway, the aberrant activation of which has been implicated widely in many types of human solid tumors.
SIRT6 Promotes COX-2 Expression and Acts as an Oncogene in Skin Cancer
Mei Ming, Weinong Han, Baozhong Zhao, Nagalingam R. Sundaresan, Chu-Xia Deng, Mahesh P. Gupta, and Yu-Ying He

Précis: This study challenges an existing view of the Sir2-related protein SIRT6 as a tumor suppressor, finding instead in a genetically deficient mouse that it functions as an oncogene in the skin epidermis.

ABOUT THE COVER

The AXL receptor tyrosine kinase has been implicated as a cellular signaling protein that is specifically upregulated in the context of the epithelial-to-mesenchymal transformation seen in some epithelial cancers and the emergence of acquired drug resistance. Among the tumor types in which a mesenchymal, largely drug-refractory phenotype appears to be prevalent is triple-negative breast cancer (TNBC). This immunohistological image illustrates the expression of AXL in a TNBC tumor specimen, revealing punctate cytoplasmic staining of AXL in tumor cells as well as focal vascular staining. For details, see article by Wilson and colleagues on page 5878.