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**MOLECULAR AND CELLULAR PATHOBIOLOGY**

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**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 Schölch, Murat Iskar, Georg Zeller, Kristina Ostertag, Christine Schweitzer, Kristin Werner, Jürgen Weitz, Moritz Koch, and Peer Bork

**Precis:** 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

**Precis:** 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, Yuan Chen, John Z. Xue, Ashok I. Handa, Michael J. Greenall, Kenneth Walsh, and Shao-An Xue

**Precis:** 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

**Precis:** 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, Yanhui Yin, Qinyuan Liao, Yang Meng, Yingmei Zhang, Dalong Ma, and Xiaoian Qiu

**Precis:** 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.

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-Fang Ping, Jing Yang, Sen-Lin Xu, Xian-Zong Ye, Chuan Xu, Long Yang, Cheng Qian, Ji Ming Wang, You-Hong Cui, Xia Zhang, and Xiu-Wu Bian

**Precis:** 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


**Precis:** 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 AEG-1 Promoter–Mediated Imaging of Prostate Cancer

**Prevention and Epidemiology**

5808  The 19q12 Bladder Cancer GWAS Signal: Association with Cyclin E Function and Aggressive Disease

5819  Copper Signaling Axis as a Target for Prostate Cancer Therapeutics

5822  Metabolic Vulnerabilities in Endometrial Cancer

**Therapeutics, Targets, and Chemical Biology**

5832  Metabolic Vulnerabilities in Endometrial Cancer


**Preciso:** This study reports key progress in identifying a marker of aggressive behavior in bladder cancer, a disease in which there has been a paucity of knowledge about key genetic drivers.
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, Maziyar 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.

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, Shanghai Yu, Denzil 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.

Dsh Homolog DVL3 Mediates Resistance to IGFIR Inhibition by Regulating IGF-RAS Signaling
Shan Gao, Ilijana Bajrami, Clare Verrill, Asha Kigozi, Djamila Ouaret, Tamara Aleksic, Ruth Asher, Cheng Han, Paul Allen, Deborah Bailey, Stephan Feller, Takeshi Kashima, Nicholas Athanasou, Jean-Yves Blay, Sandra Schmitz, Jean-Pascal Machiels, Nav Upile, Terry M. Jones, George Thalmann, Shazad Q. Ashraf, Jennifer L. Wilding, Walter F. Bodmer, Mark R. Middleton, Alan Ashworth, Christopher J. Lord, and Valentine M. Machiels

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.

AXL Inhibition Sensitizes Mesenchymal Cancer Cells to Antimitotic Drugs
Catherine Wilson, Xiaolen Ye, Thinh Pham, Eva Lin, Sara Chan, Erin McNamara, Richard M. Neve, Lisa Belmont, Hartmut Koeppen, Robert L. Yauch, Avi Ashkenazi, and Jeff Settleman

Précis: These findings challenge a purported role for AXL in drug resistance while offering a novel rationale to combine AXL-targeting drugs with antimitotic agents to eradicate invasive cancers.

β-Catenin Contributes to Lung Tumor Development Induced by EGFR Mutations

Précis: Drug resistance to EGFR receptor antagonists in lung cancer may be mediated in part by activation of the β-catenin pathway, reinforcing its importance as an oncogenic driver in this setting.

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.

Zfx Facilitates Tumorigenesis Caused by Activation of the Hedgehog Pathway
Colin J. Palmer, Jose M. Galan-Caridad, Stuart P. Weisberg, Liang Lei, Jose M. Esquillín, 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.
5925  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.