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**INTEGRATED SYSTEMS AND TECHNOLOGIES**

Précis: Striking findings suggest that IL10 might be administered orally as a microparticle formulation that can be used to reprogram the inflammatory state of intestinal immunity in colon cancer–prone patients to reduce their risk of cancer development.

Précis: These results offer preclinical proof-of-concept for a mitotic kinase inhibitor as a new therapeutic for the most deadly type of brain cancer.

Précis: By combining a mathematical model of hematopoiesis with data from a large randomized trial of acute promyelocytic leukemia, this study offers the first determination of the average duration of therapy required to eliminate all stem-like cells in a human tumor.

Précis: These important study describes a rapid, noninvasive method to detect micrometastases in sentinel lymph nodes, providing an alternative to traditional sentinel node analyses that are widely used to stage resectable tumors.
MICROENVIRONMENT AND IMMUNOLOGY

5409 Cryotherapy with Concurrent CpG Oligonucleotide Treatment Controls Local Tumor Recurrence and Modulates HER2/neu Immunity
Jesse J. Veenstra, Heather M. Gibson, Peter J. Littrup, Joyce D. Reyes, Michael L. Cher, Akira Takashima, and Wei-Zen Wei

Précis: The liberation of tumor-associated antigens by freezing tumors in situ cooperates with peritumoral CpG injection to increase innate and adaptive immunity, leveraging a minimally invasive treatment for patients who are not candidates for surgical resection.

5421 Paclitaxel Therapy Promotes Breast Cancer Metastasis in a TLR4-Dependent Manner
Lisa Volk-Draper, Kelly Hall, Caitlin Griggs, Sandeep Rajput, Pascaline Kohio, David DeNardo, and Sophia Ran

Précis: These provocative findings suggest that expression of the Toll-like receptor TLR4 on cancer cells changes their systemic reaction to treatment with paclitaxel, a drug used widely in the oncology clinic, promoting risks of future drug resistance and metastatic disease.

5435 Novel Paracrine Modulation of Notch–DLL4 Signaling by Fibulin-3 Promotes Angiogenesis in High-Grade Gliomas

Précis: This study focuses on a proangiogenic signal that mediates anti-VEGF resistance in aggressive brain tumors, with implications on how to improve antiangiogenic therapy in this setting, where anti-VEGF treatments are widely used clinically but with little frank efficacy.

5449 Gangliosides Drive the Tumor Infiltration and Function of Myeloid-Derived Suppressor Cells
Assefa Wondimu, Yihui Liu, Yan Su, Daniel Bobb, Jennifer S.Y. Ma, Lina Chakrabarti, Sasˇa Radoja, and Stephan Ladisch

Précis: This important article suggests that immunosuppressive gangliosides, a type of glycolipid shed by many human tumors, function to attract MDSC into the tumor environment, suggesting a broadly applicable strategy to thwart this common mechanism of immune escape.

5458 Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade

Précis: The benefits of fractionated radiotherapy in cancer patients might be improved greatly by blocking an adaptive mechanism of immunosuppression that limits therapeutic efficacy, with immediate implications for clinical evaluation of a new type of combination immunoradiotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

5469 Complex Formation and Function of Estrogen Receptor α in Transcription Requires RIP140
Meritxell Rosell, Ekaterina Nevedomskaya, Suzan Stellos, Jaya Nautiyal, Ariel Poliandri, Jennifer H. Steel, Lodewyk F.A. Wessels, Jason S. Carroll, Malcolm G. Parker, and Wilbert Zwart

Précis: A transcriptional coregulator involved in energy homeostasis, ovulation, and mammary gland development is found to play a critical role in breast cancer and the response to tamoxifen treatment.

5480 CDC42 Inhibition Suppresses Progression of Incipient Intestinal Tumors
Ryotaro Sakamori, Shiyuan Yu, Xiao Zhang, Andrew Hoffman, Jiaxin Sun, Soumyashree Das, Pavan Vedula, Guangxun Li, Jiang Fu, Francesca Walker, Chung S. Yang, Zheng Yi, Wei Hsu, Da-Hai Yu, Lianlan Shen, Alexis J. Rodriguez, Makoto M. Taketo, Edward M. Bonder, Michael P. Verzi, and Nan Gao

Précis: A Rho family small GTPase activated in early-stage APC/β-catenin-driven colorectal cancers may offer a biomarker and therapeutic target to prevent progression.

5493 EFA6B Antagonizes Breast Cancer
Joséphine Zangari, Mariagrazia Partisani, François Bertucci, Julie Milanini, Ghislain Bidaut, Carole Berruyer-Pouyet, Pascal Finetti, Elodie Long, Frédéric Brau, Olivier Cabaud, Bruno Chetaille, Daniel Birnbaum, Marc Lopez, Paul Hofman, Michel Franco, and Frédéric Luton

Précis: A regulator of tight junction and apico-basal polarity in breast cancer cells prevents EMT, and its loss is correlated with the aggressive behavior of triple-negative and basal-like breast cancers, with implications for new therapeutic targets in these largely intractable diseases.
The SIRT1/HIF2α Axis Drives Reductive Glutamine Metabolism under Chronic Acidosis and Alters Tumor Response to Therapy

Cyril Corbet, Nihed Draoui, Florence Polet, Adan Pinto, Xavior Drozak, Olivier Riant, and Olivier Feron

Précis: While extracellular tumor acidosis is largely described as the main consequence of the high glycolytic flux in cancer cells, the current study demonstrates that, in turn, tumor cells may shift their metabolism toward glutamine to adapt to acidosis.

PAK1 Tyrosine Phosphorylation Is Required to Induce Epithelial–Mesenchymal Transition and Radioresistance in Lung Cancer Cells

EunGi Kim, HyeSook Youn, TaeWoo Kwon, Beomseok Son, JiHoon Kang, Hee Jung Yang, Ki Moon Seong, Wanyeon Kim, and BuHyun Youn

Précis: These results offer a preclinical rationale for the use of JAK2 inhibitors to radiosensitize lung adenocarcinomas based on blockade of a PAK1 kinase-dependent pathway that mediates EMT and radioresistance in this setting.

Transcriptional Dynamics in Colorectal Carcinogenesis: New Insights into the Role of c-Myc and miR17 in Benign to Cancer Transformation

Eyal Ben-David, Assaf C. Bester, Sagiv Shifman, and Batsheva Kerem

Précis: This study sheds light on the temporal process of how neoplastic transformation occurs in normal colon tissue cells, with new information on the roles of c-Myc and miR-17 in the development of colorectal cancer.

Uncontrolled Inflammation Induced by AEG-1 Promotes Gastric Cancer and Poor Prognosis

Guanghua Li, Zhao Wang, Jinning Ye, Xinhua Zhang, Hui Wu, Jianjun Peng, Wu Song, Chuangqi Chen, Shirong Cai, Yulong He, and Jianbo Xu

Précis: An oncoenic protein also known as the metastasis-associated protein MTDH is found to function in a vicious positive feedback loop of TLR4–NF-κB inflammatory signaling, with implications for therapeutic strategies to limit cancer progression.

GBV-C Infection and Risk of NHL among U.S. Adults


Précis: This provocative study suggests the likelihood of a causative role for a viral infection in subsequent development of non-Hodgkin lymphoma.

Antitumor Efficacy of a Bispecific Antibody That Targets HER2 and Activates T Cells

Teemu T. Junttila, Ji Li, Jennifer Johnston, Maria Hristopoulou, Robyn Clark, Diego Ellerman, Bu-Er Wang, Yijin Li, Mary Mathieu, Guangmin Li, Judy Young, Elizabeth Luis, Gail Lewis Phillips, Eric Stefanich, Christoph Spiess, Andrew Polson, Bryan Irving, Justin M. Scheer, Melissa R. Junttila, Mark S. Dennis, Robert Kelley, Klara Totpal, and Allen Ebens

Précis: These results highlight a new type of potent immunotherapy for HER2⁺ breast cancer, which targets HER2, delivers T cells to HER2⁺ tumors, and can be further leveraged with PD-L1 antibody to help defeat tumoral immune escape, engendering more durable therapeutic responses.

EGFR Blockade Enriches for Lung Cancer Stem–like Cells through Notch3-Dependent Signaling

Rajeswara Rao Arasada, Joseph M. Amann, Mohammad A. Rahman, Stacey S. Hupertt, and David P. Carbone

Précis: These findings may explain why some studies of the EGFR inhibitor erlotinib appeared to worsen survival in early-stage lung cancer patients, implicating a novel combination regimen to overcome this effect.

Translesion Polymerase η Is Upregulated by Cancer Therapeutics and Confers Anticancer Drug Resistance

Maja T. Tomicic, Dorthe Aasland, Steffen C. Naumann, Ruth Meise, Christina Barchhausen, Bernd Kaina, and Markus Christmann

Précis: Induction of a particular DNA repair polymerase by DNA-crosslinking drugs limits their cancer cell killing activity, with implications for how to best use these types of drugs.
TUMOR AND STEM CELL BIOLOGY

5597 SIX1 Promotes Tumor Lymphangiogenesis by Coordinating TGFβ Signals That Increase Expression of VEGF-C
Dan Liu, Li Li, Xiao-Xue Zhang, Dong-Yi Wan, Bi-Xin Xi, Zheng Hu, Wen-Cheng Ding, Da Zhu, Xiao-Li Wang, Wei Wang, Zuo-Hua Feng, Hui Wang, Ding Ma, and Qing-Lei Gao

Précis: These findings suggest mechanistic insights into the formation of tumoral lymph vessels that can drain metastatic cells to distant sites, with possible implications for blocking this process as a therapeutic strategy.

5608 A Comprehensive DNA Methylation Profile of Epithelial-to-Mesenchymal Transition

Précis: An understanding of how global DNA methylation patterns are altered by EMT in cancer may more deeply illuminate common pathogenic processes and broad-based prognostic markers.

5620 Trim32 Facilitates Degradation of MYCN on Spindle Poles and Induces Asymmetric Cell Division in Human Neuroblastoma Cells
Hideki Izumi and Yasuhiro Kaneko

Précis: These results offer important insights into asymmetric cell division, a special type of cell division in stem cells also found to occur in cancer stem-like cells, adding to the ongoing discussion of what precisely defines "stemness" in cancer cells.

5631 Androgen Receptor Is the Key Transcriptional Mediator of the Tumor Suppressor SPOP in Prostate Cancer
Chuandong Geng, Kimal Rajapakse, Shrijal S. Shah, John Shou, Vijay Kumar Edunuri, Christopher Foley, Warren Fiskus, Mahitha Rajendran, Sue Anne Chew, Martin Zimmermann, Richard Bond, Bin He, Cristian Coarfa, and Nicholas Mitsiades

Précis: These results offer a mechanistic explanation for understanding the basis of the tumor suppressor activity of an E3 ubiquitin ligase adapter that is mutated in ~15% of human prostate cancers.

CORRECTION

5644 NQO1 Suppresses NF-κB–p300 Interaction to Regulate Inflammatory Mediators Associated with Prostate Tumorigenesis
Dinesh Thapa, Peng Meng, Robie G. Bedolla, Robert L. Reddick, Addanki P. Kumar, and Rita Ghosh

Précis: Genetic findings suggest that a pivotal regulator of redox status can promote androgen independence in prostate cancer cells by helping establish a self-reinforcing inflammatory microenvironment.

5656 PRMT7 Induces Epithelial-to-Mesenchymal Transition and Promotes Metastasis in Breast Cancer
Ruosi Yao, Hao Jiang, Yuhui Ma, Liping Wang, Lin Wang, Juan Du, Pingfu Hou, Yanyan Gao, Li Zhao, Guannan Wang, Yu Zhang, Dong-Xu Liu, Baiqiu Huang, and Jun Lu

Précis: These results define a protein arginine methyltransferase as an inducer of breast cancer metastasis, with potential implications for the development of a targeted therapeutic to treat highly invasive breast cancers.

5668 IGF1R Inhibition in Mammary Epithelia Promotes Canonical Wnt Signaling and Wnt1-Driven Tumors
Lauren M. Rota, Lidia Albanito, Marcus E. Shin, Corey L. Goyeneche, Sain Shushanov, Emily J. Gallagher, Derek LeRoith, Deborah A. Lazzarino, and Teresa L. Wood

Précis: Although IGF1R inhibitors are being considered for treatment of basal-like breast cancers, the results of this preclinical study suggest that attenuating IGF1R in the context of activated Wnt signaling leads to negative outcomes in this disease subtype, with possible implications for attendant clinical cautions.

CORRECTION

5680 Correction: Role of the Neural Niche in Brain Metastatic Cancer

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ABOUT THE COVER

Oral administration of BSA-FITC-loaded polylactic acid microparticles (green) prepared via phase inversion nanoencapsulation (PIN) resulted in rapid uptake (within 15 minutes) and persistence (for at least 24 hours) in the Peyer's patches (PP) of 10-week-old APC<sup>min/+</sup> mice (magenta, dendritic cells; blue, B-cells). Uptake in the PP was followed by trafficking of the particles to the mesenteric lymph nodes. Particles could not be visualized in the villi or the enterocytes of the small intestine or in the colon. Oral IL-10 PIN particles ameliorated intestinal polyposis and systemic symptoms of disease in the APC<sup>min/+</sup> mice via neutralization of CD4<sup>+</sup> Foxp3<sup>+</sup> ROR<sup>gt</sup> IL-17<sup>+</sup> pathogenic T-regulatory cells found in the immune structures of the gastrointestinal tract. For details, see article by Chung and colleagues on page 5377.
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