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513 A Breakthrough: Macrophage-Directed Cancer Immunotherapy

Charles D. Mills, Laurel L. Lenz, and Robert A. Harris

### Priority Report

517 VEGF-A/VEGFR Inhibition Restores Hematopoietic Homeostasis in the Bone Marrow and Attenuates Tumor Growth

Rebelkah K. O’Donnell, Beverly Falcon, Jeff Hanson, Whitney E. Goldstein, Carole Perruzzi, Shahin Rafii, William C. Aird, and Laura E. Benjamin

**Précis:** This study provides preclinical proof of concept that the bone marrow hematopoietic niche can be directly targeted and opposed by antiangiogenic therapy.

### Integrated Systems and Technologies

535 Modeling Spontaneous Metastasis following Surgery: An In Vivo-In Silico Approach

Sebastien Benzekry, Amanda Tracz, Michalis Mastri, Ryan Corbelli, Dominique Barbolosi, and John M.L. Ebos

**Précis:** A data-based mathematical model that assesses the impact of surgery on metastatic potential may have clinical uses to individualize adjuvant therapies that can extend cancer remission.

### Microenvironment and Immunology

548 Citrullinated Vimentin Presented on MHC-II in Tumor Cells Is a Target for CD4⁺ T-Cell–Mediated Antitumor Immunity

Victoria A. Brentville, Rachael L. Metheringham, Barbara Gunn, Peter Symonds, Ian Daniels, Mohamed Gijon, Katherine Cook, Wei Xue, and Lindy G. Durrant

**Précis:** Results show how CD4 cells can mediate potent antitumor responses against modified self-epitopes presented on tumor cells, and they illustrate for the first time how the citrullinated peptides may offer especially attractive subjects for cancer vaccine development.

### Molecular and Cellular Pathobiology

561 Balancing Protein Stability and Activity in Cancer: A New Approach for Identifying Driver Mutations Affecting CBL Ubiquitin Ligase Activation

Minghui Li, Stephen C. Kales, Ke Ma, Benjamin A. Shoemaker, Juan Crespo-Barreto, Andrew L. Cangelosi, Stanley Lipkowitz, and Anna R. Panchenko

**Précis:** This study describes a new computational approach to identify the functional consequences of cancer mutations using the ubiquitin ligase CBL as a model for proof of concept.

572 HEATR1 Negatively Regulates Akt to Help Sensitize Pancreatic Cancer Cells to Chemotherapy

Tongzheng Liu, Yuan Fang, Haoxing Zhang, Min Deng, Bowen Gao, Nifang Niu, Jia Yu, SeungBae Lee, JungJin Kim, Bo Qin, FangXie, Debra Evans, Liewei Wang, Wenhui Lou, and Zhenkun Lou

**Précis:** This study offers several lines of evidence for a new predictive and prognostic biomarker of chemotherapy response and outcome in pancreatic cancer patients, with additional implications for methods to sensitize pancreatic tumors to therapeutic eradication.
Aberrant Activation of Notch Signaling Inhibits PROX1 Activity to Enhance the Malignant Behavior of Thyroid Cancer Cells
Dongwon Choi, Swapnika Renu, Eunkyung Park, Eunson Jung, Sara Yang, Wonyeuk Jung, Inho Choi, Sunju Lee, Kyu Eui Kim, Young Jin Seoong, Mingu Hong, George Daghlian, Daniel Kim, Eugene Shin, Jung In Seo, Vicken Khatchadourian, Mengchen Zou, Wei Li, Roger De Filippo, Paul Kokorowski, Andy Chang, Steve Kim, Ana Bertoni, Tania Weber Furlanetto, Sung Shin, Meng Li, Yibu Chen, Alex Wong, Chester Koh, Jan Geliebter, and Young-Kwon Hong

Précis: This study provides new insights into a potentially actionable molecular alteration underlying progression of aggressive thyroid cancers.

DNA Hypomethylation and Histone Variant MacroH2A1 Synergistically Attenuate Chemotherapy-Induced Senescence to Promote Hepatocellular Carcinoma Progression

Précis: Epigenetic synergy between DNA methylation and histone variants contributes to the refractoriness of liver cancer cells to chemotherapy, with implications for identification of a biomarker of drug-induced senescent cells that may predict disease progression.

SIGMAR1 Regulates Membrane Electrical Activity in Response to Extracellular Matrix Stimulation to Drive Cancer Cell Invasiveness
David Crottès, Raphael Rapetti-Mauss, Francïsca Alcaraz-Perez, Mélanïe Tichet, Giuseppina Cariano, Sonia Martial, Hélène Guizouarn, Bernard Pelissier, Agnès Loubat, Alexandra Popa, Agnès Paquet, Marco Presta, Sophie Tartare-Deckert, Maria Luisa Cayuela, Patrick Martin, Franck Borgese, and Olivier Sordian

Précis: An important regulator of ion channel activity in cancer cells is found to promote aggressive and invasive behaviors, with potential implications for new therapeutic approaches to treat cancer.

PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease
Zequan Li, Ping Chen, Rui Su, Chao Hu, Yuanynuan Li, Abdel G. Elkahlan, Zhixiang Zuo, Sandeep Gurbuxani, Stephen Arnowitz, Henggou Weng, Yungui Wang, Shenglai Li, Hao Huang, Mary Beth Neilly, Gang Greg Wang, Xi Jiang, Paul P. Liu, Jie Jin, and Jianjun Chen

Précis: A gene expression signature stimulated by two homeobox transcription factors in hematopoietic precursor cells offers intriguing new insights into how acute myeloid leukemias may arise.

Systemic Chromosome Instability Resulted in Colonic Transcriptomic Changes in Metabolic, Proliferation, and Stem Cell Regulators in Sgo1+/- Mice
Chinhalapally V. Rao, Saiya Sanghara, Yuting Zhang, Laura Biddick, Arun Reddy, Stan Lightfoot, Naveena B. Janakiram, Altaf Mohammed, Wei Dai, and Hiroshi Y. Yamada

Précis: A mouse model of chromosome instability reveals aberrant regulation of unexpected pathways and offers new targets for therapeutic and preventive strategies.

Bereavement Is Associated with an Increased Risk of HPV Infection and Cervical Cancer: An Epidemiological Study in Sweden
Donghao Lu, Karin Sundström, Pär Sparén, Katja Fall, Arvid Sjölander, Joakim Dillner, Nathalie Ylitalo Helm, Hans-Olov Adami, Unnur Valdimarsdóttir, and Fang Fang

Précis: Women who experience the loss of an immediate family member are at a higher risk of developing cervical cancer, possibly related to an increased incidence of oncogenic HPV infections, with implications for identifying at-risk individuals who could benefit from increased screening.

Hydroxamic Acid and Benzoic Acid–Based STAT3 Inhibitors Suppress Human Glioma and Breast Cancer Phenotypes In Vitro and In Vivo
Peilin Yue, Francisco Lopez-Tapia, David Paladino, Yifei Li, Chih-Hong Chen, Andrew T. Namanja, Tyvette Hilliard, Yuan Chen, Marcus A. Tius, and James Turko

Précis: STAT3 offers an attractive target for cancer therapy, but small molecule inhibitors with appealing pharmacologic and biologic properties in animals have been elusive.
Elucidation and Pharmacological Targeting of Novel Molecular Drivers of Follicular Lymphoma Progression
Brygida Bisikirska, Mukesh Bansal, Yao Shen, Julie Tenya-Feldstein, Raju Chaganti, and Andrea Califano
Précis: Computational interrogation of human B-cell regulatory networks enables the identification of key drivers of follicular lymphoma and provides a generalized approach for the systematic analysis of drug combinations that may offer the strongest antitumor responses.

Modulation of EZH2 Expression by MEK-ERK or PI3K-AKT Signaling in Lung Cancer Is Dictated by Different KRAS Oncogene Mutations
Précis: For those lung cancer patients whose tumors harbor KRAS mutations, the specific type of mutation determines which kinase effector signaling pathways to target along with the histone methyltransferase EZH2, defined here as a novel KRAS effector.

Deguelin Analogue SH-1242 Inhibits Hsp90 Activity and Exerts Potent Anticancer Efficacy with Limited Neurotoxicity
Précis: This study reports an important advance in the development of Hsp90 inhibitors as cancer therapeutics, a drug class that is appealing in principle but limited to date by significant toxic side-effects that have impeded clinical development.

Agonists of the TRAIL Death Receptor DR5 Sensitize Intestinal Stem Cells to Chemotherapy-Induced Cell Death and Trigger Gastrointestinal Toxicity
Niklas K. Finnberg, Prashanth Gokare, Arunasalam Navaraj, Krystle A. Lang Klush, George Cerniglia, Hideo Yagita, Kazuyoshi Takeda, Noboru Motoyama, and Wafik S. El-Deiry
Précis: These findings suggest a strategy to reduce gastrointestinal toxicities that arise from combining chemotherapy with TRAIL death receptor agonists, with clinical implications for developing these agents for cancer therapy.
Integrated Genomic Analysis of Pancreatic Ductal Adenocarcinomas Reveals Genomic Rearrangement Events as Significant Drivers of Disease

Stephen J. Murphy, Steven N. Hart, Geoffrey C. Halling, Sarah H. Johnson, James B. Smadbeck, Travis Drucker, Joema Felipe Lima, Fariborz Rakhshan Rohakhtar, Faye R. Harris, Farhad Kosari, Subbaya Subramanian, Gloria M. Petersen, Timothy D. Wiltshire, Benjamin R. Kipp, Mark J. Truty, Robert R. McWilliams, Fergus J. Couch, and George Vasmatzis

Précis: Large genomic rearrangements may perturb signaling pathways that drive pancreatic cancer initiation, affecting progression to the same extent as point mutations, underscoring the need for comprehensive genomic analysis to elucidate disease mechanisms.

Correction: Development of a New Tracking Tool for the Human Monomeric Laminin-γ2 Chain In Vitro and In Vivo

ABOUT THE COVER

The monomeric Casitas B-lineage lymphoma (c-Cbl, CBL) RING finger ubiquitin ligase (blue) can bind to phosphorylated RTK (orange peptide) via the TKID domain. Upon phosphorylation, CBL undergoes a large conformational change that positions the ubiquitin-conjugating enzyme E2 (green) active site close to RTK. Cancer mutation sites are mapped on the structure of the complex and are shown in yellow; Zn ions are shown as blue balls. Other stages of the CBL activation cycle are depicted in Figure 1 of the article. For details, see article by Li and colleagues on page 561.