

BREAKING ADVANCES

- 4327 | **Highlights from Recent Cancer Literature**

REVIEW

- 4329 | **FoxM1: A Master Regulator of Tumor Metastasis**
Pradip Raychaudhuri and Hyun Jung Park

PERSPECTIVE

- 4334 | **The Death of the Cancer Cell**
Carlos Sonnenschein and Ana M. Soto

MEETING REPORT

- 4338 | **Tumor Immunology: Basic and Clinical Advances**
Pamela L. Beatty, Sandra Cascio, and Eric Lutz

PRIORITY REPORTS

- 4344 | **Luminal Expression of *PIK3CA* Mutant H1047R in the Mammary Gland Induces Heterogeneous Tumors**
Dominique S. Meyer, Heike Brinkhaus, Urs Müller, Matthias Müller, Robert D. Cardiff, and Mohamed Bentires-Alj

Précis: When engineered for expression in luminal mammary cells of the mouse, mutations in the catalytic subunit of PI3K that occur commonly in human breast cancer are capable of generating heterogeneous carcinomas that recapitulate features of the human disease including expression of the estrogen receptor.

- 4352 | **Genome-Wide "Pleiotropy Scan" Identifies HNF1A Region as a Novel Pancreatic Cancer Susceptibility Locus**
Brandon L. Pierce and Habibul Ahsan

Précis: Genetic polymorphisms in a homeobox transcription factor implicated in diabetes, cholesterol levels, and inflammation are linked here to pancreatic cancer susceptibility.

- 4359 | **Functional Parsing of Driver Mutations in the Colorectal Cancer Genome Reveals Numerous Suppressors of Anchorage-Independent Growth**
Ugur Eskioçak, Sang Bum Kim, Peter Ly, Andres I. Roig, Sebastian Biglione, Kakajan Komurov, Crystal Cornelius, Woodring E. Wright, Michael A. White, and Jerry W. Shay

Précis: Many mutated genes in cancer that are tumor suppressors may also be involved in anchorage-independent growth, perhaps helping explain the roots of tumor heterogeneity.

- 4366 | **Metformin, Independent of AMPK, Induces mTOR Inhibition and Cell-Cycle Arrest through REDD1**
Isaam Ben Sahra, Claire Regazzetti, Guillaume Robert, Kathiane Laurent, Yannick Le Marchand-Brustel, Patrick Auberger, Jean-François Tanti, Sophie Giorgetti-Peraldi, and Frédéric Bost

Précis: Findings suggest a mechanistic basis for understanding the anticancer effects of metformin, a widely prescribed diabetes drug.

- 4373 | **Physical Association of HDAC1 and HDAC2 with p63 Mediates Transcriptional Repression and Tumor Maintenance in Squamous Cell Carcinoma**
Matthew R. Ramsey, Lei He, Nicole Forster, Benjamin Ory, and Leif W. Ellisen

Précis: Findings identify an association between the transcription factor p63 and histone deacetylases in squamous cell carcinoma, raising the possibility of therapeutic intervention with HDAC inhibitors.

4380 **HER2 Overexpression Elicits a Proinflammatory IL-6 Autocrine Signaling Loop That Is Critical for Tumorigenesis**

Zachary C. Hartman, Xiao-Yi Yang, Oliver Glass, Gangjun Lei, Takuya Osada, Sandeep S. Dave, Michael A. Morse, Timothy M. Clay, and Herbert K. Lyerly

Précis: HER2 activation in breast cancer is typically thought to act through tumor cell autonomous effects, but this is not the case, as revealed by these findings that HER2 activation also supports the inflammatory tumor microenvironment that is essential to license tumor cell growth.

MOLECULAR AND CELLULAR PATHOBIOLOGY

4392 **Blocking EphB1 Receptor Forward Signaling in Spinal Cord Relieves Bone Cancer Pain and Rescues Analgesic Effect of Morphine Treatment in Rodents**

Su Liu, Wen-Tao Liu, Yue-Peng Liu, Hai-Long Dong, Mark Henkemeyer, Li-Ze Xiong, and Xue-Jun Song

Précis: This study reveals a mechanistic basis for the pathogenesis of bone cancer pain and suggests potential therapeutic strategy to improve the analgesic effects of morphine in this setting.

4403 **Anaplastic Thyroid Cancers Harbor Novel Oncogenic Mutations of the ALK Gene**

Avaniyapuram Kannan Murugan and Mingzhao Xing

Précis: Findings reveal oncogenic mutations in the ALK kinase in anaplastic thyroid cancer, a deadly endocrine cancer, which suggest new strategies for therapeutic management with ALK kinase inhibitors presently in clinical development.

4412 **HDAC4-Regulated STAT1 Activation Mediates Platinum Resistance in Ovarian Cancer**

Euan A. Stronach, Albandri Alfraidi, Nona Rama, Christoph Datler, James B. Studd, Roshan Agarwal, Tankut G. Guney, Charlie Gourley, Bryan T. Hennessy, Gordon B. Mills, Antonello Mai, Robert Brown, Roberto Dina, and Hani Gabra

Précis: Through an inpatient analysis of acquired platinum resistance, this study reveals a new strategy to blunt or deter resistance and improve treatment outcomes.

4423

Tumor Galectin-1 Mediates Tumor Growth and Metastasis through Regulation of T-Cell Apoptosis

Alice Banh, Jing Zhang, Hongbin Cao, Donna M. Bouley, Shirley Kwok, Christina Kong, Amato J. Giaccia, Albert C. Koong, and Quynh-Thu Le

Précis: Findings establish that galectin-1 secreted by tumors rather than the host is more important to cancer progression, and that the key function of this molecule among its roles in cancer is to promote immune escape.

4432

Pancreatic Ductal Adenocarcinoma Mice Lacking Mucin 1 have a Profound Defect in Tumor Growth and Metastasis

Dahlia M. Besmer, Jennifer M. Curry, Lopamudra D. Roy, Teresa L. Tinder, Mahnaz Sahraei, Jorge Schettini, Sun-Il Hwang, Yong Y. Lee, Sandra J. Gendler, and Pinku Mukherjee

Précis: MUC1 glycoprotein is essential for the growth and progression of pancreatic cancer via activation of the MAPK signaling pathway, blocking of which impedes cancer cell proliferation.

4443

MicroRNA Sequence and Expression Analysis in Breast Tumors by Deep Sequencing

Thalia A. Farazi, Hugo M. Horlings, Jelle J. ten Hoeve, Aleksandra Mihailovic, Hans Halfwerk, Pavel Morozov, Miguel Brown, Markus Hafner, Fabien Reyat, Marieke van Kouwenhove, Bas Kreike, Daoud Sie, Volker Hovestadt, Lodewyk F.A. Wessels, Marc J. van de Vijver, and Thomas Tuschl

Précis: Using a newly devised, cost-effective sequencing method, this study identifies miRNAs that are deregulated in breast cancer and assesses the potential of miRNAs as prognostic and diagnostic markers.

4454

Hedgehog-Producing Cancer Cells Respond to and Require Autocrine Hedgehog Activity

Samer Singh, Zhiqiang Wang, Dennis Liang Fei, Kendall E. Black, John A. Goetz, Robert Tokhunts, Camilla Giambelli, Jezabel Rodriguez-Blanco, Jun Long, Ethan Lee, Karoline J. Briegel, Pablo A. Bejarano, Ethan Dmitrovsky, Anthony J. Capobianco, and David J. Robbins

Précis: Findings question the presently accepted view that autocrine signaling has no role in Hedgehog-dependent cancers.

4464 **Splicing Factor hnRNP A2/B1 Regulates Tumor Suppressor Gene Splicing and Is an Oncogenic Driver in Glioblastoma**
Regina Golan-Gerstl, Michal Cohen, Asaf Shilo, Sung-Suk Suh, Arianna Bakàcs, Luigi Coppola, and Rotem Karni

Précis: Increasing evidence points to a critical role for dysregulated patterns of alternate splicing in tumorigenesis, here illustrated by the definition of an RNA splicing factor and its key targets that drive the formation of aggressive brain tumors.

4473 **Nicotinamide Blocks Proliferation and Induces Apoptosis of Chronic Lymphocytic Leukemia Cells through Activation of the p53/miR-34a/SIRT1 Tumor Suppressor Network**
Valentina Audrito, Tiziana Vaisitti, Davide Rossi, Daniela Gottardi, Giovanni D'Arena, Luca Laurenti, Gianluca Gaidano, Fabio Malavasi, and Silvia Deaglio

Précis: Findings suggest a mechanistic rationale to combine vitamin B3 with DNA-damaging chemotherapeutics to improve therapeutic responses in chronic lymphocytic leukemia.

4506 **Erythropoietin Induces Lymph Node Lymphangiogenesis and Lymph Node Tumor Metastasis**
Ae Sin Lee, Duk Hoon Kim, Jung Eun Lee, Yu Jin Jung, Kyung Pyo Kang, Sik Lee, Sung Kwang Park, Jae Yong Kwak, Sang Yong Lee, Suk Tae Lim, Mi Jung Sung, Suk Ran Yoon, and Won Kim

Précis: Risks may exist for a treatment used widely in the oncology clinic to relieve chemotherapy-induced anemia, as a result of its ability to promote cancer progression by stimulating lymphangiogenesis and nodal metastasis.

4518 **Navitoclax (ABT-263) Accelerates Apoptosis during Drug-Induced Mitotic Arrest by Antagonizing Bcl-xL**
Jue Shi, Yuan Zhou, Hsiao-Chun Huang, and Timothy J. Mitchison

Précis: This study shows how a compound that antagonizes a key Bcl-2 family member can enhance the cytotoxicity of paclitaxel, which is used widely in human cancer treatment.

4527 **Cancer Cell-Associated MT1-MMP Promotes Blood Vessel Invasion and Distant Metastasis in Triple-Negative Mammary Tumors**
Jean Y. Perentes, Nathaniel D. Kirkpatrick, Satoshi Nagano, Eve Y. Smith, Christine M. Shaver, Dennis Sgroi, Igor Garkavtsev, Lance L. Munn, Rakesh K. Jain, and Yves Boucher

Précis: Findings identify a targetable pathway used by aggressive hormone-independent breast cancers to invade blood vessels and metastasize to the lung.

4539 **Imaging DNA Damage In Vivo Using γ H2AX-Targeted Immunoconjugates**
Bart Cornelissen, Veerle Kersemans, Sonali Darbar, James Thompson, Ketan Shah, Kate Sleeth, Mark A. Hill, and Katherine A. Vallis

Précis: This proof-of-principle study describes the use of anti- γ H2AX-based radioimmunoconjugates for noninvasive imaging of DNA damage, which offers potential applications for cancer diagnosis and treatment.

4484 **A Low Carbohydrate, High Protein Diet Slows Tumor Growth and Prevents Cancer Initiation**
Victor W. Ho, Kelvin Leung, Anderson Hsu, Beryl Luk, June Lai, Sung Yuan Shen, Andrew I. Minchinton, Dawn Waterhouse, Marcel B. Bally, Wendy Lin, Brad H. Nelson, Laura M. Sly, and Gerald Krystal

Précis: Striking preclinical findings offer a dramatic illustration of how reducing dietary carbohydrates can reduce cancer incidence, slow tumor growth, and cooperate with growth restrictive or anti-inflammatory agents to block cancer development.

4550 **Correlation of Somatic Mutation and Expression Identifies Genes Important in Human Glioblastoma Progression and Survival**
David L. Masica and Rachel Karchin

Précis: Findings define a novel automated method to discover genes and gene networks critical to tumorigenesis, cancer-specific survival, and synthetic lethal interactions.

PREVENTION AND EPIDEMIOLOGY

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4494 **MET-Independent Lung Cancer Cells Evading EGFR Kinase Inhibitors Are Therapeutically Susceptible to BH3 Mimetic Agents**
Weiwen Fan, Zhe Tang, Lihong Yin, Bei Morrison, Said Hafez-Khayyata, Pingfu Fu, Honglian Huang, Rakesh Bagai, Shan Jiang, Adam Kresak, Scott Howell, Amit Vasanthi, Chris A. Flask, Balazs Halmos, Henry Koon, and Patrick C. Ma

Précis: Findings provide a rationale for lung cancer clinical trials to combine BH3 mimetic drugs and receptor tyrosine kinase inhibitors, based on understanding of how early resistance to the latter drugs emerge.

4562 **High Phosphoantigen Levels in Bisphosphonate-Treated Human Breast Tumors Promote V γ 9V δ 2 T-Cell Chemotaxis and Cytotoxicity *In Vivo***
Ismahène Benzaid, Hannu Mönkkönen, Verena Stresing, Edith Bonnelye, Jonathan Green, Jukka Mönkkönen, Jean-Louis Touraine, and Philippe Clézardin

Précis: An approved osteoporosis drug might be repositioned in cancer patients to promote chemotaxis of V γ 9V δ 2 T cells to tumors and trigger their destruction.

4573 **Combination of PI3K/mTOR Inhibitors: Antitumor Activity and Molecular Correlates**
Marco Mazzeo, Francesca Bortolin, Laura Brunelli, Roberta Pastorelli, Silvana Di Giandomenico, Eugenio Erba, Paolo Ubezio, and Massimo Broggin

Précis: Combining allosteric and catalytic inhibitors of the PI3K/mTOR pathway is much more efficacious than single drug treatment.

4585 **Overcoming Trastuzumab Resistance in Breast Cancer by Targeting Dysregulated Glucose Metabolism**
Yuhua Zhao, Hao Liu, Zixing Liu, Yan Ding, Susan P. LeDoux, Glenn L. Wilson, Richard Voellmy, Yifeng Lin, Wensheng Lin, Rita Nahta, Bolin Liu, Oystein Fodstad, Jieqing Chen, Yun Wu, Janet E. Price, and Ming Tan

Précis: Resistance to ErbB2/HER2-based therapy for breast cancer occurs widely, necessitating strategies to restore therapeutic responses in this disease.

4598 **RECQL1 and WRN Proteins Are Potential Therapeutic Targets in Head and Neck Squamous Cell Carcinoma**
Akihito Arai, Tokuhiko Chano, Kazunobu Futami, Yasuhiro Furuichi, Kaichiro Ikebuchi, Takuma Inui, Hitosuke Tameno, Yasuko Ochi, Taketoshi Shimada, Yasuo Hisa, and Hidetoshi Okabe

Précis: This study provides preclinical proof-of-concept for two RECQ DNA helicases as novel therapeutic targets to treat aggressive head and neck cancers that are rising rapidly in incidence.

4608 **Analysis of Mitosis and Antimitotic Drug Responses in Tumors by *In Vivo* Microscopy and Single-Cell Pharmacodynamics**
James D. Orth, Rainer H. Kohler, Floris Fojijer, Peter K. Sorger, Ralph Weissleder, and Timothy J. Mitchison

Précis: This is the first study to use high resolution in vivo microscopy to follow the phenotypic effects of a cancer drug in single tumor cells within the context of the tumor microenvironment.

4617 ***In Vivo* Persistence, Tumor Localization, and Antitumor Activity of CAR-Engineered T Cells Is Enhanced by Costimulatory Signaling through CD137 (4-1BB)**

De-Gang Song, Qunrui Ye, Carmine Carpenito, Mathilde Poussin, Li-Ping Wang, Chunyan Ji, Mariangela Figini, Carl H. June, George Coukos, and Daniel J. Powell Jr.

Précis: Findings suggest a strategy to increase the efficacy of T cell-based cancer immunotherapies being tested in the clinic which utilize chimeric antigen receptors.

TUMOR AND STEM CELL BIOLOGY

4628 **Tumor Suppressor *miR*-22 Determines p53-Dependent Cellular Fate through Post-transcriptional Regulation of p21**

Naoto Tsuchiya, Masashi Izumiya, Hiroko Ogata-Kawata, Koji Okamoto, Yuko Fujiwara, Makiko Nakai, Atsushi Okabe, Aaron J. Schetter, Elise D. Bowman, Yutaka Midorikawa, Yasuyuki Sugiyama, Hiroyuki Aburatani, Curtis C. Harris, and Hitoshi Nakagama

Précis: This study identifies a microRNA that acts as an intrinsic molecular switch in determining p53-dependent apoptosis.

4640 **HIF Induces Human Embryonic Stem Cell Markers in Cancer Cells**

Julie Mathieu, Zhan Zhang, Wenyu Zhou, Amy J. Wang, John M. Heddleston, Claudia M.A. Pinna, Alexis Hubaud, Bradford Stadler, Michael Choi, Merav Bar, Muneesh Tewari, Alvin Liu, Robert Vessella, Robert Rostomily, Donald Born, Marshall Horwitz, Carol Ware, C. Anthony Blau, Michele A. Cleary, Jeremy N. Rich, and Hannele Ruohola-Baker

Précis: This study reveals a general mechanism by which hypoxic regions in tumors may impose a selection for cancer stem cell development and aggressive chemotherapy-resistant malignancies.

4653 **Targeted Methylation of Two Tumor Suppressor Genes Is Sufficient to Transform Mesenchymal Stem Cells into Cancer Stem/Initiating Cells**

I-Wen Teng, Pei-Chi Hou, Kuan-Der Lee, Pei-Yi Chu, Kun-Tu Yeh, Victor X. Jin, Min-Jen Tseng, Shaw-Jenq Tsai, Yu-Sun Chang, Chi-Sheng Wu, H. Sunny Sun, Kuen-daw Tsai, Long-Bin Jeng, Kenneth P. Nephew, Tim H.-M. Huang, Shu-Huei Hsiao, and Yu-Wei Leu

Précis: This study provides the first direct demonstration that hypermethylation of a specific tumor suppressor gene is sufficient to fully transform a somatic stem cell into a cancer initiating/stem cell.

4664 **c-Myc Regulates RNA Splicing of the A-Raf Kinase and Its Activation of the ERK Pathway**
Jens Rauch, Kim Moran-Jones, Valerie Albrecht, Thomas Schwarzl, Keith Hunter, Olivier Gires, and Walter Kolch

Précis: Findings prompt a new paradigm to understand how Myc coordinates diverse cell functions, through its ability to directly affect patterns of alternate RNA splicing for central signaling components.

4675 **Perinatal or Adult *Nf1* Inactivation Using Tamoxifen-Inducible *PlpCre* Each Cause Neurofibroma Formation**
Debra A. Mayes, Tilat A. Rizvi, Jose A. Cancelas, Nathan T. Kolasinski, Georgianne M. Ciraolo, Anat O. Stemmer-Rachamimov, and Nancy Ratner

Précis: This study of a pediatric human tumor suppressor gene illustrates that acute inactivation of a critical tumor suppressor gene can rapidly stimulate tumor growth even in adults.

4686 **Susceptible Stages in Schwann Cells for *NF1*-Associated Plexiform Neurofibroma Development**
Lu Q. Le, Chiachi Liu, Tracey Shipman, Zhiguo Chen, Ueli Suter, and Luis F. Parada

Précis: This study identifies a specific period in which Schwann cell precursors show enhanced susceptibility to formation of neurofibroma, with implication for developing novel therapeutic approaches.

4696 **Stromal Niche Cells Protect Early Leukemic *FLT3-ITD*⁺ Progenitor Cells against First-Generation *FLT3* Tyrosine Kinase Inhibitors**
Amanda Parmar, Stefanie Marz, Sally Rushton, Christina Holzwarth, Katarina Lind, Sabine Kayser, Konstanze Döhner, Christian Peschel, Robert A.J. Oostendorp, and Katharina S. Götze

Précis: Leukemic stem/progenitor cells can not be readily eradicated by *FLT3* kinase inhibition in acute myeloid leukemia, due to robust protection of these cells by the bone marrow stromal microenvironment.

4707 **TGF β /TNF α -Mediated Epithelial-Mesenchymal Transition Generates Breast Cancer Stem Cells with a Claudin-Low Phenotype**
Michael K. Asiedu, James N. Ingle, Marshall D. Behrens, Derek C. Radisky, and Keith L. Knutson

Précis: This study explores the in vitro generation of stable breast cancer stem cells, a system with potential utility for therapeutic targeting and drug screening in breast cancer.

4720 **Akt2 Regulates All Akt Isoforms and Promotes Resistance to Hypoxia through Induction of miR-21 upon Oxygen Deprivation**
Christos Polytarchou, Dimitrios Iliopoulos, Maria Hatzia Apostolou, Filippos Kottakis, Ioanna Maroulakou, Kevin Struhl, and Philip N. Tsichlis

Précis: Findings highlight the identification of a novel hypoxia-activated, Akt2-dependent pathway that contributes to tumor adaptation independent of HIF-1.

CORRECTIONS

4732 **Correction: Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer**

4733 **Correction: Targeting Tumor Hypoxia: Suppression of Breast Tumor Growth and Metastasis by Novel Carbonic Anhydrase IX Inhibitors**

4734 **Correction: Reprogramming CD19-Specific T Cells with IL-21 Signaling Can Improve Adoptive Immunotherapy of B-Lineage Malignancies**

ABOUT THE COVER

Low carbohydrate, high protein diets slow/prevent cancer. Mice fed low carbohydrate (Carbs), high protein diets have lower insulin (Ins) and blood glucose levels than mice on Western-like diets. If these mice are injected with tumor cells or are genetically predisposed to mammary tumors, the growth rate or incidence, respectively, of their tumors is significantly reduced. Moreover, these low Carb, high protein diets reduce tumor growth in an additive fashion when combined with the mTOR inhibitor CCI-779 or the COX-2 inhibitor Celebrex. For details, see the article by Ho and colleagues on page 4484 of this issue.

