

BREAKING ADVANCES

- 1319 | **Highlights from Recent Cancer Literature**

REVIEWS

- 1321 | **Endoplasmic Reticulum Stress, the Unfolded Protein Response, Autophagy, and the Integrated Regulation of Breast Cancer Cell Fate**
Robert Clarke, Katherine L. Cook, Rong Hu, Caroline O.B. Facey, Iman Tavassoly, Jessica L. Schwartz, William T. Baumann, John J. Tyson, Jianhua Xuan, Yue Wang, Anni Wärrri, and Ayesha N. Shajahan

- 1332 | **Acetylation: A Novel Link between Double-Strand Break Repair and Autophagy**
Ghadeer Shubassi, Thomas Robert, Fabio Vanoli, Saverio Minucci, and Marco Foiani

PRIORITY REPORT

- 1336 | **Direct Therapeutic Applications of Calcium Electroporation to Effectively Induce Tumor Necrosis**
Stine Krog Frandsen, Hanne Gissel, Pernille Hojman, Trine Tramm, Jens Eriksen, and Julie Gehl
Précis: This provocative report offers a preclinical proof-of-concept that calcium overloading of tumor cells by electroporation, which is already used clinically to deliver chemotherapy in some settings, can be used as a therapeutic strategy to induce extensive tumor necrosis through cellular energy depletion.

MICROENVIRONMENT AND IMMUNOLOGY

- 1342 | **Proinflammatory Characteristics of SMAC/DIABLO-Induced Cell Death in Antitumor Therapy**
Perpetua U. Emeagi, Sandra Van Lint, Cleo Goyvaerts, Sarah Maenhout, Anje Cauwels, Iain A. McNeish, Tomas Bos, Carlo Heirman, Kris Thielemans, Joeri L. Aerts, and Karine Breckpot

Précis: Mimetics of the proapoptotic molecule SMAC that are being tested for anticancer properties appear to be able to trigger pro-inflammatory cell deaths that are sufficient to activate adaptive antitumor immune responses, with implications for understanding how to re-program an inflammatory microenvironment for therapeutic ends.

- 1353 | **Extracellular Matrix Protein CCN1 Limits Oncolytic Efficacy in Glioma**
Amy Haseley, Sean Boone, Jeffrey Wojton, Lianbo Yu, Ji Young Yoo, Jianhua Yu, Kazuhiko Kurozumi, Joseph C. Glorioso, Michael A. Caligiuri, and Balveen Kaur

Précis: This important study may explain why, despite early promise, oncolytic viral therapy for brain cancer has tended to be rather disappointing in its efficacy, perhaps reflecting elements of the tumor cell microenvironment that support an anti-viral defense program restricting oncolysis.

- 1363 | **Macrophage-Induced Tumor Angiogenesis Is Regulated by the TSC2-mTOR Pathway**
Wei Chen, Tao Ma, Xu-ning Shen, Xue-feng Xia, Guo-dong Xu, Xue-li Bai, and Ting-bo Liang

Précis: By defining the mTOR pathway as a key determinant in the generation of tumor-associated macrophages that drive angiogenesis, this study suggests that mTOR inhibitors may not only block tumor growth directly, acting at the level of tumor cell growth, but that they also act indirectly to block macrophage-driven angiogenesis in the tumor microenvironment.

- 1373 | **Aptamer-Mediated Blockade of IL4R α Triggers Apoptosis of MDSCs and Limits Tumor Progression**
Felix Roth, Adriana C. De La Fuente, Jennifer L. Vella, Alessia Zoso, Luca Inverardi, and Paolo Serafini

Précis: This important study offers a targeted tool to better elucidate the functional contributions of myeloid cells to cancer progression, and it offers an incisive mechanistic perspective on how to defeat the contributions of myeloid cells to immune escape for therapeutic purposes.

1384 **Myeloid Progenitor Cells in the Premetastatic Lung Promote Metastases by Inducing Mesenchymal to Epithelial Transition**

Dingcheng Gao, Natasha Joshi, Hyejin Choi, Seongho Ryu, Mary Hahn, Raul Catena, Helen Sadik, Pedram Argani, Patrick Wagner, Linda T. Vahdat, Jeffrey L. Port, Brendon Stiles, Saraswati Sukumar, Nasser K. Altorki, Shahin Rafii, and Vivek Mittal

Précis: Bone marrow cells attracted to the lungs of breast cancer patients interact with metastatic tumor cells to stimulate mesenchymal to epithelial transition, thereby promoting tumor progression.

1395 **Bioactivity and Prognostic Significance of Growth Differentiation Factor GDF15 Secreted by Bone Marrow Mesenchymal Stem Cells in Multiple Myeloma**

Jill Corre, Elodie Labat, Nicolas Espagnolle, Benjamin Hébraud, Hervé Avet-Loiseau, Murielle Roussel, Anne Huynh, Mélanie Gadelorge, Pierre Cordelier, Bernard Klein, Philippe Moreau, Thierry Facon, Jean-Jacques Fournié, Michel Attal, and Philippe Bourin

Précis: A cytokine commonly oversecreted by the bone marrow microenvironment in multiple myeloma acts as a critical cell survival and chemoprotective factor in this deadly cancer, providing insight into how the microenvironment sustains the disease and how its support might be curtailed.

1407 **Melanoma Cells Inhibit Natural Killer Cell Function by Modulating the Expression of Activating Receptors and Cytolytic Activity**

Gabriella Pietra, Claudia Manzini, Silvia Rivara, Massimo Vitale, Claudia Cantoni, Andrea Petretto, Mirna Balsamo, Romana Conte, Roberto Benelli, Simona Minghelli, Nicola Solari, Marina Gualco, Paola Queirolo, Lorenzo Moretta, and Maria Cristina Mingari

Précis: This study reveals that tumors erect immunosuppressive barriers against natural killer cells that are mechanistically related to the barriers used to thwart antitumor T cells, unifying the strategies used by tumors to achieve immune escape.

1416 **Leptin Mediates Tumor–Stromal Interactions That Promote the Invasive Growth of Breast Cancer Cells**

Ines Barone, Stefania Catalano, Luca Gelsomino, Stefania Marsico, Cinzia Giordano, Salvatore Panza, Daniela Bonofiglio, Gianluca Bossi, Kyle R. Covington, Suzanne A.W. Fuqua, and Sebastiano Andò

Précis: A cytokine that drives obesity is found to promote breast cancer progression by supporting cross-talk between estrogen receptor–positive breast cancer cells and cancer-supporting stromal cells in the tumor microenvironment.

1428 **Endothelial Expression of TNF Receptor-1 Generates a Proapoptotic Signal Inhibited by Integrin $\alpha 6\beta 1$ in Glioblastoma**

Ping Huang, M.R. Sandhya Rani, Manmeet S. Ahluwalia, Eunnyung Bae, Richard A. Prayson, Robert J. Weil, Amy S. Nowacki, Hiram Hedayat, Andrew E. Sloan, Justin D. Lathia, Jeremy N. Rich, Russell Tipps, and Candace L. Gladson

Précis: Findings provide new insights into the dual nature of TNF α in cancer by showing here how it acts in tumor-associated endothelial cells to force the tumor to evolve mechanisms of survival that rely upon a laminin-binding integrin that can attenuate the death signals induced by TNF.

1438 **Modulation of Glucose Metabolism by CD44 Contributes to Antioxidant Status and Drug Resistance in Cancer Cells**

Mayumi Tamada, Osamu Nagano, Seiji Tateyama, Mitsuyo Ohmura, Toshifumi Yae, Takatsugu Ishimoto, Eiji Sugihara, Nobuyuki Onishi, Takehiro Yamamoto, Hiroshi Yanagawa, Makoto Suematsu, and Hideyuki Saya

Précis: CD44, a marker of cancer stem-like cells, is found to promote glycolytic energy production and drug resistance by regulating pyruvate kinase M2, an enzyme emerging as a key nodal point in cancer cell metabolism.

1449 **CD44 Proteolysis Increases CREB Phosphorylation and Sustains Proliferation of Thyroid Cancer Cells**

Valentina De Falco, Anna Tamburrino, Simona Ventre, Maria Domenica Castellone, Mouhannad Malek, Serge N. Manié, and Massimo Santoro

Précis: Important connections are found for a suspected regulator of cancer stem-like properties and epithelial–mesenchymal transition with a master transcription factor that globally controls cell growth, division, survival, and invasion processes in cancer.

PREVENTION AND EPIDEMIOLOGY

1459 **Dietary Cadmium Exposure and Risk of Postmenopausal Breast Cancer: A Population-Based Prospective Cohort Study**

Bettina Julin, Alicja Wolk, Leif Bergkvist, Matteo Bottai, and Agneta Åkesson

Précis: Dietary intake of the food contaminant cadmium, recently shown to exert an estrogen-like activity in vivo, is reported in this study to be associated with increased breast cancer incidence.

1467 **3'-UTR and Functional Secretor Haplotypes in Mannose-Binding Lectin 2 Are Associated with Increased Colon Cancer Risk in African Americans**

Krista A. Zanetti, Majda Haznadar, Judith A. Welsh, Ana I. Robles, Brid M. Ryan, Andrew C. McClary, Elise D. Bowman, Julie E. Goodman, Toralf Bernig, Stephen J. Chanock, and Curtis C. Harris

Précis: Genetic variants in a lectin molecule that regulates the innate immune system appear to affect the risk of colon cancer in U.S. individuals of African but not Caucasian descent.

1478 **Mammographic Breast Density and Breast Cancer: Evidence of a Shared Genetic Basis**

Jajini S. Varghese, Deborah J. Thompson, Kyriaki Michailidou, Sara Lindström, Clare Turnbull, Judith Brown, Jean Leyland, Ruth M.L. Warren, Robert N. Luben, Ruth J. Loos, Nicholas J. Wareham, Johanna Rommens, Andrew D. Paterson, Lisa J. Martin, Celine M. Vachon, Christopher G. Scott, Elizabeth J. Atkinson, Fergus J. Couch, Carmel Apicella, Melissa C. Southey, Jennifer Stone, Jingmei Li, Louise Eriksson, Kamila Czene, Norman F. Boyd, Per Hall, John L. Hopper, and Rulla M. Tamimi for the MODE Consortium, Nazneen Rahman, and Douglas F. Easton

Précis: Genome-wide analysis confirms that breast density is in fact significantly associated with breast cancer risk, suggesting that the two traits have a shared polygenic basis.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1485 **Ultrasound Increases Nanoparticle Delivery by Reducing Intratumoral Pressure and Increasing Transport in Epithelial and Epithelial-Mesenchymal Transition Tumors**

Katherine D. Watson, Chun-Yen Lai, Shengping Qin, Dustin E. Kruse, Yueh-Chen Lin, Jai Woong Seo, Robert D. Cardiff, Lisa M. Mahakian, Julie Beegle, Elizabeth S. Ingham, Fitz-Roy Curry, Rolf K. Reed, and Katherine W. Ferrara

Précis: This seminal study offers a preclinical demonstration of how therapeutic ultrasound-based methods currently available in the clinic can be used to enhance in vivo nanoparticle delivery to epithelial and epithelial-mesenchymal transition tumors, and how these methods can be combined with positron emission tomography for pharmacokinetic analysis of vascular permeability and nanoparticle accumulation in tumors.

1494 **ARN-509: A Novel Antiandrogen for Prostate Cancer Treatment**

Nicola J. Clegg, John Wongvipat, James D. Joseph, Chris Tran, Samedy Ouk, Anna Dilhas, Yu Chen, Kate Grillot, Eric D. Bischoff, Ling Cai, Anna Aparicio, Steven Dorow, Vivek Arora, Gang Shao, Jing Qian, Hong Zhao, Guangbin Yang, Chunyan Cao, John Sensintaffar, Teresa Wasielewska, Mark R. Herbert, Celine Bonnefous, Beatrice Darimont, Howard I. Scher, Peter Smith-Jones, Mark Klang, Nicholas D. Smith, Elisa De Stanchina, Nian Wu, Ouathek Ouerfelli, Peter J. Rix, Richard A. Heyman, Michael E. Jung, Charles L. Sawyers, and Jeffrey H. Hager

Précis: This study offers preclinical proof-of-concept for a second-generation antiandrogen, now in phase I/II clinical trials, which offers superior characteristics predicting more robust and durable clinical responses and fewer side effects compared with related competing agents.

1504 **Inhibition of Fatty Acid Synthase Attenuates CD44-Associated Signaling and Reduces Metastasis in Colorectal Cancer**

Yekaterina Y. Zaytseva, Piotr G. Rychahou, Pat Gulhati, Victoria A. Elliott, William C. Mustain, Kathleen O'Connor, Andrew J. Morris, Manjula Sunkara, Heidi L. Weiss, Eun Y. Lee, and B. Mark Evers

Précis: Long implicated in cancer, fatty acid synthase is reported here to contribute strongly to metastatic progression of colorectal cancer, increasing its potential attractiveness as a therapeutic target for advanced stages of this disease where effective treatments remain badly needed.

TUMOR AND STEM CELL BIOLOGY

1518 **Tpx2 Controls Spindle Integrity, Genome Stability, and Tumor Development**

Cristina Aguirre-Portolés, Alexander W. Bird, Anthony Hyman, Marta Cañamero, Ignacio Pérez de Castro, and Marcos Malumbres

Précis: Findings establish a key functional role in human cancer for an activator of the mitotic kinase Aurora A, a target of small-molecule drugs currently being tested in clinical trials.

1529 **PTP1B Is an Androgen Receptor–Regulated Phosphatase That Promotes the Progression of Prostate Cancer**

Laurent Lessard, David P. Labbé, Geneviève Deblois, Louis R. Bégin, Serge Hardy, Anne-Marie Mes-Masson, Fred Saad, Lloyd C. Trotman, Vincent Giguère, and Michel L. Tremblay

Précis: Findings offer preclinical support for a protein tyrosine phosphatase as a candidate therapeutic target in both early androgen-dependent or more advanced castration-resistant prostate cancers.

1538 **PGC-1 α Promotes the Growth of ErbB2/Neu–Induced Mammary Tumors by Regulating Nutrient Supply**

Eva Klimcakova, Valérie Chénard, Shawn McGuiirk, David Germain, Daina Avizonis, William J. Muller, and Julie St-Pierre

Précis: Findings suggest that breast cancer patients with HER2-positive tumors might benefit the most from treatment with antiangiogenic drugs, addressing an important question of great current interest.

1547 **Differential WNT Activity in Colorectal Cancer Confers Limited Tumorigenic Potential and Is Regulated by MAPK Signaling**

David Horst, Justina Chen, Teppei Morikawa, Shuji Ogino, Thomas Kirchner, and Ramesh A. Shivdasani

Précis: Findings that MAPK pathway status is a critical modifier of WNT signaling in colorectal cancers challenge the idea that WNT pathway activation on its own is sufficient for tumor-initiating potential, with potential implications for understanding how tumor heterogeneity affects molecular targeted therapeutic approaches.

1557 **Kras^{G12D} and p53 Mutation Cause Primary Intrahepatic Cholangiocarcinoma**

Michael R. O'Dell, Jing Li Huang, Christa L. Whitney-Miller, Vikram Deshpande, Paul Rothberg, Valerie Grose, Randall M. Rossi, Andrew X. Zhu, Hartmut Land, Nabeel Bardeesy, and Aram F. Hezel

Précis: This study addresses the persistent need for a histologically accurate model of cholangiocarcinoma, a relatively rare but deadly cancer of the liver bile duct that is rising worldwide in incidence in recent decades without a useful animal model for preclinical drug development.

1568 **Mammary Tumor Regression Elicited by Wnt Signaling Inhibitor Requires IGFBP5**

Bob Y. Liu, Irina Soloviev, XiaoDong Huang, Peter Chang, James A. Ernst, Paul Polakis, and Chie Sakanaka

Précis: This study of Wnt-driven mammary tumors in mice suggests that Wnt-driven tumor growth is based on the same proliferation pathways used during normal mammary gland development, which converge on the control of IGF signaling.

1579 **BMK1 Kinase Suppresses Epithelial–Mesenchymal Transition through the Akt/GSK3 β Signaling Pathway**

Runqiang Chen, Qingkai Yang, and Jiing-Dwan Lee

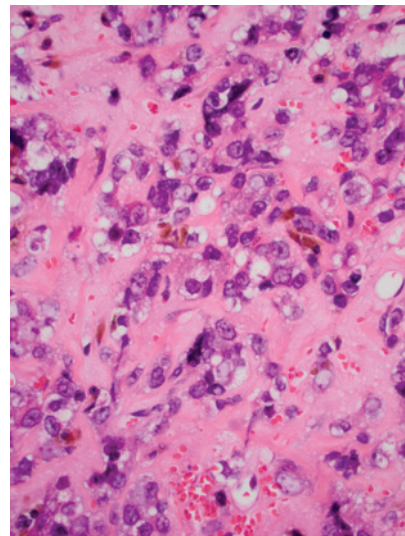
Précis: In contrast to other MAP kinase pathways that promote epithelial–mesenchymal transition (EMT) in cancer cells, activation of the MAP kinase BMK1 inhibits EMT and suppresses tumor metastasis.

CORRECTION

1588 **Correction: Expression of the Neurotrophin Receptor TrkA Down-Regulates Expression and Function of Angiogenic Stimulators in SH-SY5Y Neuroblastoma Cells**

ABOUT THE COVER

ARN-509 is a clinical stage, nonsteroidal antiandrogen discovered in an effort to identify full androgen receptor (AR) antagonists in the setting of AR overexpression, a key determinant of acquired resistance to first generation antiandrogens. ARN-509 exhibits robust antitumor activity in the clinically validated LNCaP/AR model of castration-resistant prostate cancer (CRPC), resulting in tumor regression via a decrease in proliferation and increase in apoptosis. The cover shows a hematoxylin and eosin stained tissue section from a LNCaP/AR xenograft tumor following ARN-509 treatment. There is significantly reduced cellularity with increased deposition of extracellular matrix compared to vehicle treatment. Based on preclinical efficacy coupled with its excellent pharmacokinetic properties and high therapeutic index, ARN-509 has entered clinical development in men with CRPC. For details, see the article by Clegg and colleagues on page 1494 of this issue.



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