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. Tyson, Jianhua Xuan, Yue Wang, Anni Warr, 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

MICROENVIRONMENT AND IMMUNOLOGY

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

1353 Extracellular Matrix Protein CCN1 Limits Oncolytic Efficacy in Glioma
Amy Haseley, Sean Boone, Jeffrey Vojton, Linbo Yu, Ji Young Yoo, Jianhua Yu, Kazuhiro Kurozumi, Joseph C. Grilloso, Michael A. Caligiuri, and Balveen Kaur

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 Bui, and Ting-bo Liang

1373 Aptamer-Mediated Blockade of IL-4Rα Triggers Apoptosis of MDCs and Limits Tumor Progression
Felix Roth, Adriana C. De La Fuente, Jennifer L. Vella, Alessia Zoso, Luca Inverardi, and Paolo Serafini

PRIORITY REPORT

1336 Direct Therapeutic Applications of Calcium Electroporation to Effectively Induce Tumor Necrosis
Stine Krog Frandsen, Hamme Gissel, Pernille Hojman, Trine Tramm, Jens Erikson, and Julie Gehl

1352 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.

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Wei Chen, Tao Ma, Xu-ning Shen, Xue-feng Xia, Guo-dong Xu, Xue-li Bui, and Ting-bo Liang

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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.
Myeloid Progenitor Cells in the Premetastatic Lung Promote Metastases by Inducing Mesenchymal to Epithelial Transition
Dingcheng Gao, Natasha Joshi, Hyejin Choi, Seoungho 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.

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 H.ebraud, 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.

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.

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. Covingthton, 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.

Endothelial Expression of TNF Receptor-1 Generates a Proapoptotic Signal Inhibited by Integrin α6β1 in Glioblastoma

Précis: Findings provide new insights into the dual nature of TNFs 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.

Modification 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.

CD44 Proteolysis Increases CREB Phosphorylation and Sustains Proliferation of Thyroid Cancer Cells
Valentina De Falco, Anna Tamburrino, Simona Ventre, Maria Domenica Castellone, Mouhammad 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.
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

Precis: 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.

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, Torall Bernig, Stephen J. Chanock, and Curtis C. Harris

Precis: 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.

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

Precis: 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.

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

Precis: 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.

ARN-509: A Novel Antiandrogen for Prostate Cancer Treatment
Nicola J. Clegg, John Wongvipat, James D. Joseph, Chris Tran, Samedy Ouk, Anna Dihlas, Yu Chen, Kate Grillot, Eric D. Bischoff, Ling Cai, Anna Aparicio, Steven Dorow, Vivek Azora, Gang Shao, Jing Qian, Hong Zhao, Guangbin Yang, Chunyan Cao, John Sensintaffar, Teresa Wasielewska, Mark R. Herbert, Celine Bonnefous, Beatrice Darimont, Howard L Scher, Peter Smith-Jones, Mark Klang, Nicholas D. Smith, Elisa De Stanchina, Nian Wu, Ouazzek Ouerfelli, Peter J. Rix, Richard A. Heyman, Michael E. Jung, Charles L. Sawyers, and Jeffrey H. Hager

Precis: 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.

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

Precis: 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-Portoles, 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  
kinease 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-1α Promotes the Growth of  
ErbB2/Neu–Induced Mammary  
Tumors by Regulating Nutrient  
Supply  
Eva Klimcakova, Valérie Chénard,  
Shawn McGuirk, David Germain,  
Daina Avizonis, William J. Muller, and  
Julie St-Pierre  
Précis: Findings suggest that breast cancer  
patients with HER2-positive tumors might benefit  
most from treatment with antiangiogenic  
drugs, addressing an important question of great  
current interest.

1547  
Differential WNT Activity in Colorectal  
Cancer Confer Limited Tumorigenic  
Potential and Is Regulated by MAPK  
Signaling  
David Horst, Justina Chen, Tepppei 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.

CORRECTION

1557  
KrasG12D and p53 Mutation Cause  
Primary Intrahepatic  
Cholangiocarcinoma  
Michael R. O’Dell, Jing Li Huang,  
Christa L. Whitney-Miller, Vikram Deshpande,  
Paul Rothberg, Valerie Grove, 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 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. Earn, 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/GSK3β 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  
kine BMK1 inhibits EMT and suppresses tumor  
metastasis.

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.