BREAKING ADVANCES

8971 Highlights from Recent Cancer Literature

REVIEWS

8973 Breast Cancer Stem Cells: Something Out of Notching?
Hannah Harrison, Gillian Farnie, Keith R. Brennan, and Robert B. Clarke

8977 Turning on a Fuel Switch of Cancer: hnRNP Proteins Regulate Alternative Splicing of Pyruvate Kinase mRNA
Mo Chen, Jian Zhang, and James L. Manley

PRIORİTİ REPORTS

8981 Inhibition of Glutaminase Preferentially Slows Growth of Glioma Cells with Mutant IDH1
Meghan J. Seltzer, Bryson D. Bennett, Avadhut D. Joshi, Ping Gao, Ajit G. Thomas, Dana V. Ferraris, Takashi Tsukamoto, Camilo J. Rojas, Barbara S. Slusher, Joshua D. Rabiniowitz, Chi V. Dung, and Gregory J. Riggins

8988 Heat Shock Protein 60 Regulation of the Mitochondrial Permeability Transition Pore in Tumor Cells
Jagadish C. Ghosh, Markus D. Siegelin, Takehiko Dohi, and Dario C. Altieri

CLINICAL STUDIES

8994 The Ability of Biomarkers to Predict Systemic Progression in Men with High-Risk Prostate Cancer Treated Surgically Is Dependent on ERG Status
R. Jeffrey Karnes, John C. Cheville, Cristiane M. Ida, Thomas J. Sebo, Asha A. Nair, Hui Tang, Jan-Marie Munz, Farhad Kosari, and George Vasmatsiz

9003 Repeat Dose Study of the Cancer Chemopreventive Agent Resveratrol in Healthy Volunteers: Safety, Pharmacokinetics, and Effect on the Insulin-like Growth Factor Axis
Victoria A. Brown, Ketan R. Patel, Maria Viskaduraki, James A. Crowell, Marjorie Perloff, Tristan D. Booth, Grygoriy Vaslinin, Ananda Sen, Anna Maria Schinas, Gianfranca Piccirilli, Karen Brown, William P. Steward, Andreas J. Gescher, and Dean E. Brenner

Précis: This study defines suitable doses, accompanying blood levels, and potential efficacy biomarkers which might help to optimize future cancer chemoprevention intervention studies of the red wine constituent resveratrol.
INTEGRATED SYSTEMS AND TECHNOLOGIES

9012 | Multimodal Mass Spectrometric Imaging of Small Molecules Reveals Distinct Spatio-Molecular Signatures in Differentially Metastatic Breast Tumor Models

Précis: Mass spectrometry imaging techniques can identify different tissue microenvironments in breast tumors, possibly improving their clinicopathological assessment in the future.

9022 | PET Imaging of Tumor Neovascularization in a Transgenic Mouse Model with a Novel $^{64}$Cu-DOTA-Knottin Peptide

Précis: Methods that improve PET imaging in cancer offer opportunities for improved detection and management.

MICROENVIRONMENT AND IMMUNOLOGY

9031 | Intranodal Vaccination with Naked Antigen-Encoding RNA Elicits Potent Prophylactic and Therapeutic Antitumoral Immunity
Sebastian Kreiter, Abderraouf Selmi, Mustafa Diken, Michael Koslowski, Cedrik M. Britten, Christoph Huber, Özlem Türeci, and Ugur Sahin

Précis: Findings define methods to achieve strong antigen-specific immunity and cancer cures using antigen-encoding RNA in preclinical animal models.

9041 | A Therapeutic OX40 Agonist Dynamically Alters Dendritic, Endothelial, and T Cell Subsets within the Established Tumor Microenvironment
Angela D. Pardee, Dustin McCurry, Sean Alber, Peisheng Hu, Alan L. Epstein, and Walter J. Storkus

Précis: Correcting tumoral immune escape exerts therapeutic effects against established tumors by improving the delivery of antitumor T cells into the tumor microenvironment.

9053 | Multiple Injections of Electroporated Allogeneic T Cells Expressing a Chimeric Antigen Receptor Mediate Regression of Human Disseminated Tumor
Yangbing Zhao, Edmund Moon, Carmine Carpenito, Chrysal M. Paulos, Xiaojun Liu, Andrea L. Brennan, Anne Chew, Richard G. Carroll, John Scholler, Bruce L. Levine, Steven M. Albelda, and Carl H. June

Précis: Findings offer preclinical proof-of-concept for a novel adoptive T-cell transfer approach for cancer treatment that can potentiate antitumor effects and complement approaches using retroviral and lentiviral engineered T-cell therapies.

9062 | Improved Clinical Outcome in Indolent B-Cell Lymphoma Patients Vaccinated with Allogeneic Tumor Cells Experiencing Immunogenic Death
Roberta Zappasodi, Serenella M. Pupa, Gaia C. Ghedin, Italia Bongarzone, Michele Magni, Antonello D. Cabras, Mario P. Colombo, Carmelo Carlo-Stella, Alessandro M. Gianni, and Massimo Di Nicola

Précis: Clinical findings confirm expectations of a stringent correlation between the therapeutic efficacy of a dendritic cell vaccine and the extent of immunogenic death induced in the tumor cells used to load the dendritic cells before vaccination.

9073 | High-Throughput Characterization of 10 New Minor Histocompatibility Antigens by Whole Genome Association Scanning

Précis: In this study, efficient T-cell selection was combined with SNP genotyping to discover a significant number of new minor histocompatibility antigens that can be targeted by cellular immunotherapy of cancer.
Critical Roles of DMP1 in Human Epidermal Growth Factor Receptor 2/neu-Arf-p53 Signaling and Breast Cancer Development

Pankaj Taneja, Dejan Maglic, Fumitake Kai, Takayuki Sugiyama, Robert D. Kendig, Donna P. Frazier, Mark C. Willingham, and Kazushi Inoue

Précis: Mechanistic findings define a transcriptional cascade that plays a critical role in quenching HER2/neu oncogenic signals known to promote breast cancer.

Global Downstream Pathway Analysis Reveals a Dependence of Oncogenic NF-E2–Related Factor 2 Mutation on the mTOR Growth Signaling Pathway

Tatsuhiko Shihata, Shigeru Saito, Akiko Kokubu, Takafumi Suzuki, Masayuki Yamamoto, and Setsuo Hirohashi

Précis: Findings offer a rationale to target a master transcriptional regulator of antioxidant genes and phase II detoxifying enzymes as an anticancer strategy, also suggesting it as a novel theranostic biomarker.

Insulin-Like Growth Factor I Suppresses Bone Morphogenetic Protein Signaling in Prostate Cancer Cells by Activating mTOR Signaling

Reema S. Wahdan-Alaswad, Kyung Song, Tracy L. Krebs, Dorjee T.N. Shola, Jose A. Gomez, Shigemi Matsuyama, and David Danielpour

Précis: Findings elucidate how a key growth factor in prostate cancer acts at several levels to shut down a central pathway of epithelial cell function in the prostate, with important therapeutic implications for prostate cancer management.

The Mitotic Kinase Aurora-A Induces Mammary Cell Migration and Breast Cancer Metastasis by Activating the Cofilin-F-actin Pathway

Li-hui Wang, Jin Xiang, Min Yan, Yan Zhang, Yan Zhao, Cui-feng Yue, Jie Xu, Fei-meng Zheng, Jin-na Chen, Zhuang Kang, Tong-sheng Chen, Da Xing, and Quentin Liu

Précis: An important mitotic kinase that is targeted by small molecule inhibitors currently in clinical testing is found to have an important role in supporting metastasis.

Metabolic Profiling Detects Field Effects in Nondysplastic Tissue from Esophageal Cancer Patients

Danny Yakoub, Hector C. Keun, Robert Goldin, and George B. Hanna

Précis: Esophageal cancer can be detected by metabolic profiling of adjacent histologically normal mucosa.

Dysregulation of the Mitogen Granulin in Human Cancer through the miR-15/107 microRNA Gene Group

Wang-xia Wang, Natasha Kyprianou, Xiaowei Wang, and Peter T. Nelson

Précis: Findings elucidate microRNA-mediated control of a common mitogen in a variety of human cancers, the regulation of which had been previously obscure, with implications for microRNA-based therapeutic targeting.

Mammalian Target of Rapamycin–Dependent Acinar Cell Neoplasia after Inactivation of Apc and Pten in the Mouse Salivary Gland: Implications for Human Acinic Cell Carcinoma

Cassandra R. Diegel, Kathleen R. Cho, Adel K. El-Naggar, Bart O. Williams, and Charlotte Lindvall

Précis: Findings report a novel preclinical model and a rationale to evaluate rapamycin therapy for salivary gland acinic cell carcinoma, a low grade neoplasm but one that tends to recur.

Expression Profiling in Progressive Stages of Fumarate-Hydratase Deficiency: The Contribution of Metabolic Changes to Tumorigenesis


Précis: Fumarate hydratase deficiency compels cells to prematurely adopt a metabolic phenotype that predisposes them to cell proliferation and growth and ultimately to cancer.
Acquired TNFRSF14 Mutations in Follicular Lymphoma Are Associated with Worse Prognosis

Précis: Findings identify a candidate genetic marker of prognosis in follicular lymphoma, which may provide an explanation as to why its treatment with rituximab provides less benefit in some patients.

Epigenetically Deregulated microRNA-375 Is Involved in a Positive Feedback Loop with Estrogen Receptor α in Breast Cancer Cells
Pedro de Souza Rocha Simonini, Achim Breiling, Nibedita Gupta, Mahdi Malekpour, Mahmoud Youns, Ramesh Omranipour, Fatemeh Malekpour, Stefano Volland, Carlo M. Croce, Hossein Najmabadi, Sven Diederichs, Özgür Sahin, Doris Mayer, Frank Lyko, Jörg D. Hehese, and Yasser Riazalhosseini

Précis: Findings offer significant new insights into how the estrogen receptor is deregulated in breast cancer.

Alternative Splicing of Caspase 9 Is Modulated by the Phosphoinositide 3-Kinase/Akt Pathway via Phosphorylation of SRp30a

Précis: Findings define a functionally important alternative splicing mechanism in lung adenocarcinoma that offers a novel approach to therapeutic development.

Upregulation of DLX5 Promotes Ovarian Cancer Cell Proliferation by Enhancing IRS-2-AKT Signaling
Yinfei Tan, Mitchell Cheung, Jianming Pei, Craig W. Menges, Andrew K. Godwin, and Joseph R. Testa

Précis: Findings define a homeobox protein that positively modifies a variety of oncogenic signals in ovarian cancer, with potential prognostic applications.

Human RecQL4 Helicase Plays Critical Roles in Prostate Carcinogenesis
Yanrong Su, Jarah A. Meador, Gloria M. Calaf, Luca Proietti De Santis, Yongliang Zhao, Vilhelm A. Bohr, and Adayabalam S. Balajee

Précis: Study implicates a DNA helicase regulated by Rb-E2F as an important driver of metastatic progression of prostate cancer.

Serum Vitamin D and Risk of Bladder Cancer
Alison M. Mondul, Stephanie J. Weinstein, Satu Männistö, Kirk Snyder, Ronald L. Horst, Jarmo Virtamo, and Demetrius Albanes

Précis: Accumulating evidence argues that serum levels of vitamin D exert a profound influence on cancer risk, as illustrated in this study of bladder cancer.

Pesticide Use Modifies the Association Between Genetic Variants on Chromosome 8q24 and Prostate Cancer
Stella Koutros, Laura E. Beane Freeman, Sonja I. Berndt, Gabriella Andreotti, Jay H. Lubin, Dale P. Sandler, Jane A. Hoppin, Kai Yu, Qizhai Li, Laura A. Burdette, Jeffrey Yuenger, Meredith Yeager, and Michael C.R. Alavanja

Précis: Study offers an excellent illustration of how an environmental modifier can radically alter the impact of a genetic risk marker on a patient’s susceptibility to disease.

Ki-67 as a Molecular Target for Therapy in an In vitro Three-Dimensional Model for Ovarian Cancer
Ramtin Rahmanzadeh, Prakash Rai, Jonathan P. Celli, Imran Rizvi, Bettina Baron-Lühr, Johannes Gerdes, and Tayyaba Hasan

Précis: A common immunohistopathological marker used for staging of clinical cancers may offer unexpected opportunities as a therapeutic target.
MGMT-Independent Temozolomide Resistance in Pediatric Glioblastoma Cells Associated with a PI3-Kinase–Mediated HOX/Stem Cell Gene Signature
Nathalie Gaspar, Lynley Marshall, Lara Perryman, Dorine A. Bax, Suzanne E. Little, Marta Viana-Pereira, Swee Y. Sharp, Gilles Vassal, Andrew D.J. Pearson, Rui M. Reis, Darren Hargrave, Paul Workman, and Chris Jones

Précis: Findings identify a reversible novel mechanism of resistance to the alkylating agent temozolomide in pediatric glioblastoma model systems and patient samples.

Class III β-Tubulin Expression Predicts Prostate Tumor Aggressiveness and Patient Response to Docetaxel-Based Chemotherapy
Guillaume Ploussard, Stéphane Terry, Pascale Maillé, Yves Allory, Nanor Sirab, Laurence Kheuang, Pascale Soyeux, Nathalie Nicolaeiv, Estelle Coppolani, Bernard Paulie, Laurent Salomon, Stéphane Culine, Ralph Buttyan, Francis Vacherot, and Alexandre de la Taille

Précis: Findings suggest a novel theranostic molecule in advanced prostate cancer to predict responses to taxane therapy and improve treatment of taxane-resistant disease.

Deubiquitinase Inhibition by Small-Molecule WP1130 Triggers Aggresome Formation and Tumor Cell Apoptosis
Vaibhav Kapuria, Luke F. Peterson, Dexing Fang, William G. Bornmann, Moshe Talpaz, and Nicholas J. Donato

Précis: An antitumor compound previously found to block signaling by Jak2 kinase is found to target deubiquitinases that are commonly overexpressed in cancer cells.

Selective Killing of Tumor Neovasculature Paradoxically Improves Chemotherapy Delivery to Tumors
Freddy E. Escorcia, Erik Henke, Michael R. McDevitt, Carlos H. Villa, Peter Smith-Jones, Ronald G. Blasberg, Robert Benezra, and David A. Scheinberg

Précis: A novel approach to remodel the tumor vasculature has strongly positive pharmacokinetic consequences on cancer drug delivery in a preclinical model, resulting in better therapy and survival outcomes.

Induction of DNA Damage-Inducible Gene GADD45β Contributes to Sorafenib-Induced Apoptosis in Hepatocellular Carcinoma Cells
Da-Liang Ou, Ying-Chun Shen, Sung-Liang Yu, Kuen-Feng Chen, Pei-Yen Yeh, Hsiang-Hsuan Fan, Wen-Chi Feng, Ching-Tzu Wang, Liang-In Lin, Chiu Hsu, and Ann-Lii Cheng

Précis: Mechanistic findings suggest a potential surrogate marker that could be useful to predict the efficacy of Sorafenib in liver cancer.

Synergistic Enhancement of Carboplatin Efficacy with Photodynamic Therapy in a Three-Dimensional Model for Micrometastatic Ovarian Cancer
Imran Rizvi, Jonathan P. Celli, Conor L. Evans, Adnan O. Abu-Yousif, Alona Muzikansky, Brian W. Pogue, Dianne Finkelstein, and Tayyaba Hasan

Précis: A 3D model for ovarian micrometastases is introduced as a high-throughput platform to report treatment response, exemplified in this study to show how photodynamic therapy synergistically enhances carboplatin efficacy.
Voluntary Running Prevents Progressive Memory Decline and Increases Adult Hippocampal Neurogenesis and Growth after Whole-Brain Irradiation

Sarah J.E. Wong-Goodrich, Madeline L. Pfau, Catherine T. Flores, Jennifer A. Fraser, Christina L. Williams, and Lee W. Jones

Précis: Studies in mice suggest that voluntary exercise can alleviate progressive memory loss after cranial irradiation, strongly prompting studies in clinical settings.

Telomerase-Dependent Oncolytic Adenovirus Sensitizes Human Cancer Cells to Ionizing Radiation via Inhibition of DNA Repair Machinery

Shinji Kuroda, Toshiya Fujiwara, Yasuhiro Shirakawa, Yasumoto Yamasaki, Shuya Yano, Futoshi Uno, Hiroshi Tazawa, Yuuri Hashimoto, Yuichi Watanabe, Kazuhiro Noma, Yasuo Urata, Shunsuke Kagawa, and Toshiyoshi Fujiwara

Précis: Results illustrate the potential of combining engineered oncolytic virotherapy and ionizing radiation as a strategy to improve the management of human cancer.

Brick1 Is an Essential Regulator of Actin Cytoskeleton Required for Embryonic Development and Cell Transformation

Beatriz Escobar, Guillermo de Cárcer, Gonzalo Fernández-Miranda, Alberto CASCÓN, José J. Bravo-Cordero, María C. Montoya, Mercedes Robledo, Marta Cañamero, and Marcos Malumbres

Précis: Genetic ablation of Brick1, a component of the Wave/Scar actin regulatory complex, appears to exert a protective effect against malignant development in renal cancer and other cancers where loss occurs.

mTOR Complex Component Rictor Interacts with PKCζ and Regulates Cancer Cell Metastasis

Fei Zhang, Xiaofang Zhang, Menghui Li, Peng Chen, Bin Zhang, Hua Guo, Wenfeng Cao, Xiyang Wei, Xuchen Cao, Xishan Hao, and Ning Zhang

Précis: Findings illuminate understanding of how EGF activates the mTORC2 growth regulatory complex to drive breast cancer metastasis, with implications for clinical studies of mTOR inhibitors.
ANCCA/ATAD2 Overexpression Identifies Breast Cancer Patients with Poor Prognosis, Acting to Drive Proliferation and Survival of Triple-Negative Cells through Control of B-Myb and EZH2
Ekaterina V. Kalashnikova, Alexey S. Revenko, Abigail T. Gemo, Nicolas P. Andrews, Clifford G. Tepper, June X. Zou, Robert D. Cardiff, Alexander D. Borowsky, and Hong-Wu Chen

Précis: Findings suggest that the prognostic significance of a chromatin coregulator for hormone receptors in breast cancer is based on its role in integrating multiple oncogenic programs, with particular importance to aggressive triple-negative tumors.

Quantitative In vivo Imaging of the Effects of Inhibiting Integrin Signaling via Src and FAK on Cancer Cell Movement: Effects on E-cadherin Dynamics
Marta Canel, Alan Serrels, Derek Miller, Paul Timpson, Bryan Serrels, Margaret C. Frame, and Valerie G. Brunton

Précis: Results identify a novel role for FAK and Src in regulating tumor cell movement in vivo using fluorescence based microscopy.

Hepatocyte Nuclear Factor-4α Promotes Gut Neoplasia in Mice and Protects against the Production of Reactive Oxygen Species
Mathieu Darsigny, Jean-Philippe Babeu, Ernest G. Seidman, Fernand-Pierre Gendron, Émile Levy, Julie Carrier, Nathalie Perreault, and François Boudreau

Précis: Findings point to the nuclear receptor HNF4α as a potential therapeutic target to modify epithelial cell resistance to ROS production during intestinal tumorigenesis.

Clld7, A Candidate Tumor Suppressor on Chromosome 13q14, Regulates Pathways of DNA Damage/Repair and Apoptosis
Xiaobo Zhou and Karl Münger

Précis: Findings support the definition of a new tumor suppressor located at chromosome 13q14 and suggest its possible utility in predicting cancer chemosensitivity.

Tumor-Initiating Function of Nucleostemin-Enriched Mammary Tumor Cells
Tao Lin, Lingjun Meng, Yi Li, and Robert Y.L. Tsai

Précis: Studies of a stem cell marker in breast cancer cells suggest its potential as a therapeutic target.

Aberrant Activation of Fatty Acid Synthesis Suppresses Primary Cilium Formation and Distorts Tissue Development
Nicolas Willemarck, Evelien Rysman, Koen Brusselmans, Griet Van Immschoot, Frank Vanderhydencoe, Katrien Moerloose, Evelyne Lerut, Guido Verhoeven, Frans van Roy, Kris Vleminckx, and Johannes V. Swinnen

Précis: Findings suggest that characteristic elevations in lipogenesis in cancer cells contribute to tumor growth not by improving membrane biosynthesis, as commonly believed, but by modifying fundamental developmental signaling and cell polarity.

Double-Negative Feedback Loop between Reprogramming Factor LIN28 and microRNA let-7 Regulates Aldehyde Dehydrogenase 1–Positive Cancer Stem Cells
Xiaojun Yang, Xiaojuan Lin, Xiaomin Zhong, Sippy Kaur, Ning Li, Shun Liang, Heini Lassus, Liping Wang, Dionyssios Katsaros, Kathleen Montone, Xia Zhao, Youcheng Zhang, Ralf Büttzow, George Coukos, and Lin Zhang

Précis: Findings offer evidence that cancer stem cells may arise through cellular reprogramming-like mechanisms.

MicroRNA miR-302 Inhibits the Tumorigenicity of Human Pluripotent Stem Cells by Coordinate Suppression of the CDK2 and CDK4/6 Cell Cycle Pathways
Shi-Lung Lin, Donald C. Chang, Shao-Yao Ying, Davey Leu, and David T.S. Wu

Précis: As the most abundant tumor suppressor microRNA in human embryonic stem cells, miR-302 offers an appealing focus for the development of a universal cancer therapeutic.
Silencing of Autocrine Motility Factor Induces Mesenchymal-to-Epithelial Transition and Suppression of Osteosarcoma Pulmonary Metastasis
Yasufumi Nitaka, Kiyoshi Harada, Masahiro Fujimuro, Masamitsu Oda, Arayo Haga, Misa Hosoki, Norikazu Uzawa, Naoya Arai, Satoshi Yamaguchi, Masashi Yamashiro, and Avraham Raz

Précis: An enzyme that functions inside cells in glycolysis and gluconeogenesis has a second extracellular function that in cancer provides a critical support for invasive cell motility, EMT, and metastasis.

The Telomerase Inhibitor Imetelstat Depletes Cancer Stem Cells in Breast and Pancreatic Cancer Cell Lines
Immanuel Joseph, Robert Tressler, Ekaterina Bassett, Calvin Harley, Christen M. Buseman, Preeti Pattamatta, Woodring E. Wright, Jerry W. Shay, and Ning F. Go

Précis: Findings offer preclinical proof-of-concept for a highly tractable and attractive new approach to target cancer stem cells in cancer therapy.

Loss of Thioredoxin Reductase 1 Renders Tumors Highly Susceptible to Pharmacologic Glutathione Deprivation
Pankaj Kumar Mandal, Manuela Schneider, Pirkko Kölle, Peter Kuhlencordt, Heidi Förster, Heike Beek, Georg W. Bornkamm, and Marcus Conrad

Précis: Findings offer preclinical proof-of-concept that simultaneous inhibition of more than one cellular antioxidant system could be highly effective in killing tumor cells via redox modifiers.

Induction of Human Epithelial Stem/Progenitor Expansion by FOXM1
Emilios Gemenetzidis, Daniela Elena-Costea, Eric K. Parkinson, Ahmad Waseem, Hong Wan, and Muy-Teck Teh

Précis: Results identify a transcription factor in the FOXM1 family that can hijack adult human stem cells to jump start cancer initiation.

Correction: Curcumin Blocks RON Tyrosine Kinase–Mediated Invasion of Breast Carcinoma Cells

Correction: RG7204 (PLX4032), a Selective BRAFV600E Inhibitor, Displays Potent Antitumor Activity in Preclinical Melanoma Models

Correction: Immunotherapeutic Potential of B7-DC (PD-L2) Cross-Linking Antibody In Conferring Antitumor Immunity

Retraction: An Effective Vaccine Strategy Protective against Antigenically Distinct Tumor Variants

Retraction: CTL Activation Using the Natural Low-Affinity Epitope 222-229 from Tyrosinase-Related Protein 1 Leads to Tumor Rejection

ABOUT THE COVER
Selective antibody-mediated, α-particle–directed killing of LS174T human colon cancer neovascular endothelium using 225Ac-E4G10 “normalizes” vessels. Animals were treated 15 days before sacrifice and tumors were stained for endothelium (green), pericytes (red), and nuclei (blue). This is a representative cross-section of vessels of 225Ac-E4G10 treated tumors. More pericytes were associated with endothelial cells when compared with chemotherapy-treated or saline-treated controls. Boxes are 6-μm square. For details, see the article by Escorcia and colleagues on page 9277 of this issue.