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

PRIORİTY 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. Rabinovitz, Chi V. Dung, and Gregory J. Riggins

Précis: IDH1 mutations create a higher dependence of glioma cells on α-ketoglutarate, relative to normal cells, that could be therapeutically exploited by targeting glutamine metabolism.

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

Précis: Findings implicate a chaperone network in controlling mitochondrial permeability transition and apoptosis in cancer cells.

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 Vasmatzis

Précis: The study presents TOP2A as a superior prognostic marker for prostate cancer and shows that its predictive ability is dependent on cancer subtype.

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 Vasilinnin, 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 64Cu-DOTA-Knottin Peptide

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

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.

MICROENVIRONMENT AND IMMUNOLOGY

9053 Multiple Injections of Electroporated Autologous 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 Autologous Tumor Cells Experiencing Immunogenic Death
Roberta Zappasodi, Serenella M. Pupa, Gaia C. Gnedini, 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
Tatsuhiro Shibata, 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-Actin Pathway
Li-hui Wang, Jin Xiang, Min Yan, Yan Zhang, Yan Zhao, Cui-fong 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, Mahmoud Malekpour, Mahmood Youns, Ramesh Omranipour, Fatemeh Malekpour, Stefano Volinia, Carlo M. Croce, Hossein Najmabadi, Sven Diederichs, Özgür Sahin, Doris Mayer, Frank Lyko, Jörg D. Heheisel, 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 Adyabalam S. Balajee

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

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-Lühn, Johannes Gerdes, and Tayyaba Hasan

Précis: A common immunohistopathological marker used for staging of clinical cancers may offer unexpected opportunities as a therapeutic target.

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. Labin, 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.

Prevention and Epidemiology

Therapeutics, Targets, and Chemical Biology
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 Nicolaiow, Estelle Coppolani, Bernard Paule, Laurent Salomon, Stéphane Culin, 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.

Nox2 NADPH Oxidase Promotes Pathologic Cardiac Remodeling Associated with Doxorubicin Chemotherapy
Youyou Zhao, Declan McLaughlin, Emma Robinson, Adam P. Harvey, Michelle B. Hookham, Ajay M. Shah, Barbara J. McDermott, and David J. Grieve

Précis: A major ROS-producing enzyme in the heart is implicated in adverse cardiac remodeling caused by doxorubicin chemotherapy, implying a new therapeutic strategy to reduce doxorubicin cardiotoxicity.

WNT11 Expression Is Induced by Estrogen-Related Receptor α and β-Catenin and Acts in an Autocrine Manner to Increase Cancer Cell Migration
Mary A. Dwyer, James D. Joseph, Hilary E. Wade, Matthew L. Eaton, Rebecca S. Kunder, Dmitri Kazmin, Ching-yi Chang, and Donald P. McDonnell

Précis: Results define an autocrine mechanism controlled by the nuclear receptor ERRα, associated with poor outcomes in several cancers, that influences cancer cell migratory capacity.

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, Chiun 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.
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**TUMOR AND STEM CELL BIOLOGY**

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**Précis:**

- **Voluntary Running Prevents Progressive Memory Decline and Increases Adult Hippocampal Neurogenesis and Growth**
  - 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**
  - 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**
  - 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**
  - 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, Emile 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.
Silencing of Autocrine Motility Factor Induces Mesenchymal-to-Epithelial Transition and Suppression of Osteosarcoma Pulmonary Metastasis

Yasufumi Niinaka, Kiyoshi Harada, Masahiro Fujimuro, Masamitsu Oda, Arayo Haga, Misa Hosoki, Narikazu 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 Kühnencordt, Heidi Förster, Heike Beck, 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


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.