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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

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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. Rabkinowitz, 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
Jagdish C. Ghosh, Markus D. Siegelin, 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 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

_Pricip:_ 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

_Pricip:_ 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, Christoph Huber, Özlem Türeci, and Ugur Sahin

_Pricip:_ 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

_Pricip:_ 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 Antalogous 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

_Pricip:_ 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. Ghedini, Italia Bongarzone, Michele Magni, Antonello D. Cabras, Mario P. Colombo, Carmelo Carlo-Stella, Alessandro M. Gianni, and Massimo Di Nicola

_Pricip:_ 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

_Pricip:_ 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 Sugiyma, 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-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 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 Volinia, Carlo M. Croce, Hossein Najmahabadi, Sven Diederichs, Özgür Sahin, Doris Mayer, Frank Lyko, Jörg D. Hoheisel, 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, Yongjiang 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 Alavanja

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 Nicolaiew, Estelle Coppolani, Bernard Paule, Laurent Salomon, Stéphane Culine, Ralph Buttayan, 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-и Chang, and Donald P. McDonnell

Précis: Results define an autocrine mechanism controlled by the nuclear receptor ERα, 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, 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, Yuichi Watanabe, 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, Maria 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, Xiying 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.

Surface-Immobilized Aptamers for Cancer Cell Isolation and Microscopic Cytology

Yuan Wan, Young-tae Kim, Na Li, Steve K. Cho, Robert Bachoo, Andrew D. Ellington, and Samir M. Iqbal

Précis: More sensitive and specific tumor detection technologies are needed to rapidly assess surgical resection margins and to monitor residual tumor cells that may persist in blood after disease treatment.

Intrinsic Cooperation between p16INK4a and p21WAF1/Cip1 in the Onset of Cellular Senescence and Tumor Suppression In vivo

Shinji Takeuchi, Akiko Takahashi, Noriko Motoi, Shin Yoshimoto, Tomoko Tajima, Kimi Yamakoshi, Atsushi Hirao, Shigeru Yanagi, Kiyoko Fukami, Yuichi Ishikawa, Saburo Sone, Eiji Hara, and Naoko Ohtani

Précis: Expectations that mice lacking both the p16INK4a and p21WAF1 tumor suppressor genes would be highly susceptible to carcinogenesis is experimentally confirmed and mechanistically dissected in this study.

Tyrosine Phosphorylation Profiling Reveals the Signaling Network Characteristics of Basal Breast Cancer Cells

Falko Hochgräfe, Luxi Zhang, Sandra A. O’Toole, Brigid C. Browne, Mark Pinese, Ana Porta Cubas, Gillian M. Lehrbach, David R. Croucher, Danny Rickwood, Alice Boughourjian, Robert Shearer, Radhika Nair, Alexander Swarbrick, Dana Faratian, Peter Mullen, David J. Harrison, Andrew V. Biankin, Robert L. Sutherland, Mark J. Raftery, and Roger J. Daly

Précis: Phosphoproteomic profiling reveals that basal breast cancer cells are characterized by an extensive Src family kinase signalling network, highlighting candidate theranostic targets for this aggressive subtype of breast cancers.
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<td>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.</td>
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<td>Précis: Results identify a novel role for FAK and Src in regulating tumor cell movement in vivo using fluorescence based microscopy.</td>
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<td>Mathieu Darsigny, Jean-Philippe Babeu, Ernest G. Seidman, Fernand-Pierre Gendron, Emile Levy, Julie Carrier, Nathalie Perreault, and François Boudreau</td>
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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 Haqa, 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.

Corrections
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

Retractions
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 ^225^Ac-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 ^225^Ac-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.
Cancer Research

70 (22)

Cancer Res 2010;70:8971-9529.

Updated version
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