

BREAKING ADVANCES

- 8253 | **Highlights from Recent Cancer Literature**

REVIEW

- 8255 | **Cancer Stem Cells in the Central Nervous System – A Critical Review**
Lars Prestegarden and Per Øyvind Enger

PRIORITY REPORTS

- 8259 | **Functional MicroRNA Is Transferred between Glioma Cells**
Mark Katakowski, Benjamin Buller, Xinli Wang, Thomas Rogers, and Michael Chopp

Précis: miRNA that is transcribed in one cancer cell can be transported by innate mechanisms to a neighboring cell where it can regulate translation, providing direct evidence that RNA can act as a signaling molecule.

- 8264 | **Definition of Ubiquitination Modulator COPI as a Novel Therapeutic Target in Human Hepatocellular Carcinoma**
Yun-Han Lee, Jesper B. Andersen, Ho-Taek Song, Adam D. Judge, Daekwan Seo, Tsuyoshi Ishikawa, Jens U. Marquardt, Mitsuteru Kitade, Marian E. Durkin, Chiara Raggi, Hyun Goo Woo, Elizabeth A. Conner, Itzhak Avital, Ian MacLachlan, Valentina M. Factor, and Snorri S. Thorgeirsson

Précis: A tractable new approach to treat liver cancer by targeting a specific p53 ubiquitination pathway is demonstrated using an application of SNALP nanoparticle technology.

- 8270 | **DLC1 Negatively Regulates Angiogenesis in a Paracrine Fashion**
Yi-Ping Shih, Yi-Chun Liao, Yuan Lin, and Su Hao Lo

Précis: Attenuation of a Rho GTPase regulatory protein in prostate cancers may drive cancer progression by promoting VEGF-mediated angiogenesis.

- 8276 | **Transcriptome Analysis Reveals that p53 and β -Catenin Alterations Occur in a Group of Aggressive Adrenocortical Cancers**
Bruno Ragazzon, Rossella Libé, Sébastien Gaujoux, Guillaume Assié, Amato Fratticci, Pierre Launay, Eric Clouser, Xavier Bertagna, Frédérique Tissier, Aurélien de Reyniès, and Jérôme Bertherat

Précis: Study reveals important respective roles of p53 and β -catenin in adrenocortical carcinoma development, delineating distinct tumor subgroups and outcomes.

- 8282 | **Transcriptional Activation by pRB and Its Coordination with SWI/SNF Recruitment**
Stephen Flowers, George R. Beck, Jr., and Elizabeth Moran

Précis: Findings reveal the essential role for recruitment of a specific chromatin-remodeling complex by the retinoblastoma protein in transactivation.

CLINICAL STUDIES

- 8288 | **MicroRNA Expression and Clinical Outcomes in Patients Treated with Adjuvant Chemotherapy after Complete Resection of Non-Small Cell Lung Carcinoma**
Johannes Voortman, Akiteru Goto, Jean Mendiboure, Jane J. Sohn, Aaron J. Schetter, Motonobu Saito, Ariane Dunant, Trung C. Pham, Iacopo Petrini, Alan Lee, Mohammed A. Khan, Pierre Hainaut, Jean-Pierre Pignon, Elisabeth Brambilla, Helmut H. Popper, Martin Filipits, Curtis C. Harris, and Giuseppe Giaccone

Précis: No positive correlations were found between expression patterns of a panel of cancer-associated miRNAs and clinical outcomes in the largest study conducted to date of patients receiving adjuvant chemotherapy after radical resection of primary non-small cell lung carcinoma.

INTEGRATED SYSTEMS AND TECHNOLOGIES

8299 **Integrated Microfluidic and Imaging Platform for a Kinase Activity Radioassay to Analyze Minute Patient Cancer Samples**

Cong Fang, Yanju Wang, Nam T. Vu, Wei-Yu Lin, Yao-Te Hsieh, Liudmilla Rubbi, Michael E. Phelps, Markus Müschen, Yong-Mi Kim, Arion F. Chatziioannou, Hsian-Rong Tseng, and Thomas G. Graeber

Précis: Rapid and sensitive pharmacodynamic assays that can handle very small patient samples are needed to assist the clinical development of targeted therapeutics.

8309 **Early Detection of Recurrent Breast Cancer Using Metabolite Profiling**

Vincent M. Asiago, Leiddy Z. Alvarado, Narasimhamurthy Shanaiah, G.A. Nagana Gowda, Kwadwo Owusu-Sarfo, Robert A. Ballas, and Daniel Raftery

Précis: Metabolic profiling of blood serum by NMR and mass spectroscopy can detect breast cancer relapse before it occurs, opening a window of opportunity for patients and oncologists to improve treatment.

MICROENVIRONMENT AND IMMUNOLOGY

8319 **Angiotensin-(1-7) Reduces Fibrosis in Orthotopic Breast Tumors**

Katherine L. Cook, Linda J. Metheny-Barlow, E. Ann Tallant, and Patricia E. Gallagher

Précis: An endogenous peptide hormone of the renin-angiotensin system reduces fibrosis in the tumor microenvironment, thereby decreasing proliferation of cancer-associated fibroblasts that contribute to malignant progression.

8329 **Heparanase Enhances Local and Systemic Osteolysis in Multiple Myeloma by Upregulating the Expression and Secretion of RANKL**

Yang Yang, Yongsheng Ren, Vishnu C. Ramani, Li Nan, Larry J. Suva, and Ralph D. Sanderson

Précis: Study provides important mechanistic insights into the action of a key driver of bone metastasis.

8339 **Peptide Vaccination after T-Cell Transfer Causes Massive Clonal Expansion, Tumor Eradication, and Manageable Cytokine Storm**

Long V. Ly, Marjolein Sluijter, Mieke Versluis, Gre P.M. Luyten, Sjoerd H. van der Burg, Cornelis J.M. Melief, Martine J. Jager, and Thorbald van Hall

Précis: Study describes refinements to active immunotherapy by adoptive T-cell transfer that can heighten effective antitumor T-cell responses in non-lymphodepleted hosts, prompting clinical investigations.

8347 **Cdc42-Interacting Protein 4 Promotes Breast Cancer Cell Invasion and Formation of Invadopodia through Activation of N-WASp**

Christina S. Pichot, Constadina Arvanitis, Sean M. Hartig, Samuel A. Jensen, John Bechill, Saad Marzouk, Jindan Yu, Jeffrey A. Frost, and Seth J. Corey

Précis: Cell membrane remodeling proteins containing BAR domains are a functionally unique class of proteins being found to contribute to cell migration and invadopodia formation in invasive breast cancers.

8357 **Differential Effects of VEGFR-1 and VEGFR-2 Inhibition on Tumor Metastases Based on Host Organ Environment**

Yoon-Jin Lee, Daniel L. Karl, Ugwuji N. Maduekwe, Courtney Rothrock, Sandra Ryeom, Patricia A. D'Amore, and Sam S. Yoon

Précis: VEGF promotes tumor angiogenesis primarily through activation of VEGFR-2, but vascularization of liver metastases is dependent on VEGFR-1 activation.

8368 **CD4⁺ T-Cell Help in the Tumor Milieu Is Required for Recruitment and Cytolytic Function of CD8⁺ T Lymphocytes**

Rinke Bos and Linda A. Sherman

Précis: Antitumor efficacy of tumor-specific CD8 T cells relies upon two T-cell helper functions that must be delivered within the tumor microenvironment.

8378 **Tumor-Reactive CD8⁺ Early Effector T Cells Identified at Tumor Site in Primary and Metastatic Melanoma**

Andrea Anichini, Alessandra Molla, Claudia Vegetti, Ilaria Bersani, Roberta Zappasodi, Flavio Arienti, Fernando Ravagnani, Andrea Maurichi, Roberto Patuzzo, Mario Santinami, Hanspeter Pircher, Massimo Di Nicola, and Roberta Mortarini

Précis: Findings suggest development of early phases of antitumor immunity even in advanced cancers, with definition of an “early effector” subset of T cells that may be a useful tool to monitor immunity at the tumor site.

8388 **Antibodies to Merkel Cell Polyomavirus T Antigen Oncoproteins Reflect Tumor Burden in Merkel Cell Carcinoma Patients**

Kelly G. Paulson, Joseph J. Carter, Lisa G. Johnson, Kevin W. Cahill, Jayasri G. Iyer, David Schrama, Juergen C. Becker, Margaret M. Madeleine, Paul Nghiem, and Denise A. Galloway

Précis: Antibodies that are rare in population controls but common in Merkel cell carcinoma patients can be used to monitor the burden of disease in patients.

8417 **Ablation of TAK1 Upregulates Reactive Oxygen Species and Selectively Kills Tumor Cells**

Emily Omori, Kunihiro Matsumoto, Songyun Zhu, Robert C. Smart, and Jun Ninomiya-Tsuji

Précis: A potential strategy to trigger selective cancer cell killing in many tumor types is suggested by the discovery that inhibition of TAK1 kinase can elicit tumor regression without affecting normal tissues.

8426 **Metabolic Aggressiveness in Benign Meningiomas with Chromosomal Instabilities**

Daniel Monleón, José Manuel Morales, Ana Gonzalez-Segura, José Manuel Gonzalez-Darder, Rosario Gil-Benso, Miguel Cerdá-Nicolás, and Concepción López-Ginés

Précis: Measuring the metabolic phenotype of intact meningioma biopsies at the same time as histopathologic analysis may allow early identification of clinically aggressive disease among histologically benign tumors.

8435 **K-ras Mutation Targeted to Gastric Tissue Progenitor Cells Results in Chronic Inflammation, an Altered Microenvironment, and Progression to Intraepithelial Neoplasia**

Tomoyuki Okumura, Russell E. Ericksen, Shigeo Takaishi, Sophie S.W. Wang, Zinaida Dubeykovskiy, Wataru Shibata, Kelly S. Betz, Sureshkuma Muthupalani, Arlin B. Rogers, James G. Fox, Anil K. Rustgi, and Timothy C. Wang

Précis: Findings argue that K-ras activation supports the development of epithelial cancers by strongly supporting the generation of a chronic inflammatory environment.

8446 **High Levels of Hsp90 Cochaperone p23 Promote Tumor Progression and Poor Prognosis in Breast Cancer by Increasing Lymph Node Metastases and Drug Resistance**

Natalie E. Simpson, W. Marcus Lambert, Renecia Watkins, Shah Giashuddin, S. Joseph Huang, Ellinor Oxelmark, Rezina Arju, Tsvia Hochman, Judith D. Goldberg, Robert J. Schneider, Luiz Fernando Lima Reiz, Fernando Augusto Soares, Susan K. Logan, and Michael J. Garabedian

Précis: Findings identify an important modifier of hormone regulated gene expression that drives metastasis and predicts poor prognosis in breast cancer patients.

MOLECULAR AND CELLULAR PATHOBIOLOGY

8398 **Identification of Susceptibility Loci in a Mouse Model of KRAS^{G12D}-Driven Pancreatic Cancer**

Tonia C. Jorgenson, Bret R. Williams, Allyson Wendland, Andrea Bilger, Eric P. Sandgren, and Norman R. Drinkwater

Précis: Genetic linkage analysis identifies loci that modify the development of pancreatic neoplasms initiated by an oncogenic KRAS allele.

8407 **Regulation of DNA Polymerase POLD4 Influences Genomic Instability in Lung Cancer**

Qin Miao Huang, Shuta Tomida, Yuji Masuda, Chinatsu Arima, Ke Cao, Taka-aki Kasahara, Hirota Osada, Yasushi Yatabe, Tomohiro Akashi, Kenji Kamiya, Takashi Takahashi, and Motoshi Suzuki

Précis: Findings suggest that the frequent occurrence of reduced expression of POLD4, a core DNA replication protein, may play a role in promoting genomic instability in lung cancer.

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Précis: Findings identify an important modifier of hormone regulated gene expression that drives metastasis and predicts poor prognosis in breast cancer patients.

- 8457 **The Oncoprotein c-Ski Functions as a Direct Antagonist of the Transforming Growth Factor- β Type I Receptor**
Nathalie Ferrand, Azeddine Atfi, and Céline Prunier
Précis: The concept that oncoproteins or tumor suppressor proteins are “cytosolic” or “nuclear” in function is increasingly untenable, with an increasing number found to exert distinct functions in different cellular compartments where they can be found.
- 8467 **RAP80 Acts Independently of BRCA1 in Repair of Topoisomerase II Poison-Induced DNA Damage**
Junko Iijima, Zhihong Zeng, Shunichi Takeda, and Yoshihito Taniguchi
Précis: Findings define a critical function in the resistance of cancer to the widely employed DNA damaging anticancer agent etoposide.
- 8475 **BRAF Inactivation Drives Aneuploidy by Deregulating CRAF**
Tamihito Kamata, Jahan Hussain, Susan Giblett, Robert Hayward, Richard Marais, and Catrin Pritchard
Précis: Study defines a new function for the c-RAF kinase in supporting cancer development.
- 8487 **Transforming Properties of 8p11-12 Amplified Genes in Human Breast Cancer**
Zeng-Quan Yang, Gang Liu, Aliccia Bollig-Fischer, Craig N. Giroux, and Stephen P. Ethier
Précis: Results offer new possible strategies to address the eventual acquisition of hormone independence in 8p11-12 amplified, estrogen receptor positive, luminal B type breast cancers, a significant clinical problem.
- 8498 **Evidence of an Adaptive Response Targeting DNA Nonhomologous End Joining and Its Transmission to Bystander Cells**
Holger Klammer, Munira Kadhim, and George Iliakis
Précis: Study elucidates mechanisms underlying adaptive response and bystander effects in cells exposed to low doses of radiation, with the promise of improved strategies for radiation treatment of human tumors.
- 8507 **Overexpression of Transcription Factor Sp2 Inhibits Epidermal Differentiation and Increases Susceptibility to Wound- and Carcinogen-Induced Tumorigenesis**
Tae-Hyung Kim, Shannon L. Chiera, Keith E. Linder, Carol S. Trempus, Robert C. Smart, and Jonathan M. Horowitz
Précis: Findings argue that overexpression of Sp transcription factor Sp2 occurring in a variety of human cancers is likely to have significant functional impact.
- 8517 **Hippo Pathway Effector Yap Is an Ovarian Cancer Oncogene**
Chad A. Hall, Runsheng Wang, Jiangyong Miao, Esther Oliva, Xiaoyun Shen, Thomas Wheeler, Susan G. Hilsenbeck, Sandra Orsulic, and Scott Goode
Précis: Cumulative findings on the role of the Hippo pathway regulated transcription factor Yap in human ovarian cancer suggest a major role for this pathway in ovarian cancer progression.
- 8526 **Activation of Forkhead Box O Transcription Factors by Oncogenic BRAF Promotes p21^{cip1}-Dependent Senescence**
Peter L.J. de Keizer, Leisl M. Packer, Anna A. Szypowska, Paulien E. Riedl-Polderman, Niels J.F. van den Broek, Alain de Bruin, Tobias B. Dansen, Richard Marais, Arjan B. Brenkman, and Boudewijn M.T. Burgering
Précis: Study defines key mechanisms by which a central oncogenic driver in melanoma can trigger cell senescence, with implications for understanding the relationships between cancer and aging.
- 8537 **A Major Role of p95/611-CTF, a Carboxy-Terminal Fragment of HER2, in the Down-modulation of the Estrogen Receptor in HER2-Positive Breast Cancers**
Josep Lluís Parra-Palau, Kim Pedersen, Vicente Peg, Maurizio Scaltriti, Pier Davide Angelini, Marta Escorihuela, Sandra Mancilla, Alexandre Sánchez Pla, Santiago Ramón y Cajal, José Baselga, and Joaquín Arribas
Précis: Discovery of a new mechanism of ER regulation mediated by HER2 fragments suggests a new strategy to improve patient responses to endocrine therapy in breast cancer.

8547 **The miR-17-92 Cluster of MicroRNAs Confers Tumorigenicity by Inhibiting Oncogene-Induced Senescence**

Lixin Hong, Maoyi Lai, Michelle Chen, Changchuan Xie, Rong Liao, Young Jun Kang, Changchun Xiao, Wen-Yuan Hu, Jiahuai Han, and Peiqing Sun

Précis: Study defines a mechanistic basis to understand the pro-oncogenic role of an important microRNA gene cluster in cancer.

8587 **Serum 25-Hydroxyvitamin D and Cancer Mortality in the NHANES III Study (1988–2006)**

D. Michal Freedman, Anne C. Looker, Christian C. Abnet, Martha S. Linet, and Barry I. Graubard

Précis: In this prospective study in NHANES III, overall cancer mortality risks were unrelated to baseline vitamin D status.

8598 **Detection of Elevated Plasma Levels of Epidermal Growth Factor Receptor Before Breast Cancer Diagnosis among Hormone Therapy Users**

Sharon J. Pitteri, Lynn M. Amon, Tina Busald Buson, Yuzheng Zhang, Melissa M. Johnson, Alice Chin, Jacob Kennedy, Chee-Hong Wong, Qing Zhang, Hong Wang, Paul D. Lampe, Ross L. Prentice, Martin W. McIntosh, Samir M. Hanash, and Christopher I. Li

Précis: Findings suggest a marker that may make it possible to predict the emergence of breast cancer, particularly among women treated with menopausal hormone therapy.

PREVENTION AND EPIDEMIOLOGY

8558 **Danger Signaling Protein HMGB1 Induces a Distinct Form of Cell Death Accompanied by Formation of Giant Mitochondria**

Georg Gdynia, Martina Keith, Jürgen Kopitz, Marion Bergmann, Anne Fassl, Alexander N.R. Weber, Julie George, Tim Kees, Hans-Walter Zentgraf, Otmar D. Wiestler, Peter Schirmacher, and Wilfried Roth

Précis: When released into the tissue environment by damaged cells, the DNA binding protein HMGB1 stimulates an inflammatory response from innate immune cells and a distinct necrosis-like form of cancer cell death with therapeutic potential.

8569 **Human Papillomavirus Infection and Reinfection in Adult Women: the Role of Sexual Activity and Natural Immunity**

Helen Trottier, Silvaneide Ferreira, Patricia Thomann, Maria C. Costa, Joao S. Sobrinho, José Carlos M. Prado, Thomas E. Rohan, Luisa L. Villa, and Eduardo L. Franco

Précis: This study has important public health implications concerning vaccination of adult women to prevent cervical cancer.

8578 **Hierarchical Clustering of Human Papilloma Virus Genotype Patterns in the ASCUS-LSIL Triage Study**

Nicolas Wentzensen, Lauren E. Wilson, Cosette M. Wheeler, Joseph D. Carreon, Patti E. Gravitt, Mark Schiffman, and Philip E. Castle

Précis: Findings suggest a novel approach to complex HPV genotype patterns in cervical disease that can address disease misclassification and HPV genotype distributions in different populations.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

8607 **Zoledronic Acid Reduces Bone Loss and Tumor Growth in an Orthotopic Xenograft Model of Osteolytic Oral Squamous Cell Carcinoma**

Chelsea K. Martin, Jillian L. Werbeck, Nanda K. Thudi, Lisa G. Lanigan, Tobie D. Wolfe, Ramiro E. Toribio, and Thomas J. Rosol

Précis: A combination of noninvasive imaging methods reveals inhibitory effects of the clinical drug zoledronic acid on bone resorption in oral squamous cell carcinoma.

8617 **A New Paradigm for Aptamer Therapeutic AS1411 Action: Uptake by Macropinocytosis and Its Stimulation by a Nucleolin-Dependent Mechanism**

E. Merit Reyes-Reyes, Yun Teng, and Paula J. Bates

Précis: Results suggest a new model to understand the activity of a quadruplex-forming oligonucleotide therapeutic in phase II clinical trials, which may be generally relevant to drug delivery and gene therapy strategies.

- 8630 **DNA Damage Recognition via Activated ATM and p53 Pathway in Nonproliferating Human Prostate Tissue**
Sari Jäämaa, Taija M. af Hällström, Anna Sankila, Ville Rantanen, Hannu Koistinen, Ulf-Håkan Stenman, Zhewei Zhang, Zhiming Yang, Angelo M. De Marzo, Kimmo Taari, Mirja Ruutu, Leif C. Andersson, and Marikki Laiho
Précis: Human prostate tissue shows unexpected activation of DNA damage response signaling pathway markers implicating susceptibility of the luminal cells to DNA damage.
- 8642 **Heat Shock Protein 90 Inhibition Depletes LATS1 and LATS2, Two Regulators of the Mammalian Hippo Tumor Suppressor Pathway**
Catherine J. Huntoon, Monica D. Nye, Liyi Geng, Kevin L. Peterson, Karen S. Flatten, Paul Haluska, Scott H. Kaufmann, and Larry M. Karnitz
Précis: Findings identify an important mechanism by which HSP90 inhibitors currently being tested in clinical trials may disable a tumor suppressor pathway and promote tumorigenesis.
- 8651 **FTY720 (Fingolimod) Sensitizes Prostate Cancer Cells to Radiotherapy by Inhibition of Sphingosine Kinase-1**
Dmitri Pchejetski, Torsten Bohler, Leyre Brizuela, Lysann Sauer, Nicolas Doumerc, Muriel Golzio, Vishal Salunkhe, Justin Teissié, Bernard Malavaud, Jonathan Waxman, and Olivier Cuvillier
Précis: Radiosensitizing properties of a sphingolipid analogue FTY720 (Fingolimod) in clinical testing for multiple sclerosis offer a rationale for its application in prostate cancer treatment.
- 8662 **Cediranib/AZD2171 Inhibits Bone and Brain Metastasis in a Preclinical Model of Advanced Prostate Cancer**
Juan Juan Yin, Luhua Zhang, Jeeva Munasinghe, R. Ilona Linnoila, and Kathleen Kelly
Précis: Findings support the utility of applying antiangiogenic therapies to treat advanced cancer patients with metastasis.
- 8674 **F3-Targeted Cisplatin-Hydrogel Nanoparticles as an Effective Therapeutic That Targets Both Murine and Human Ovarian Tumor Endothelial Cells *In vivo***
Ira Winer, Shouyan Wang, Youg-Eun Koo Lee, Wenzhe Fan, Yusong Gong, Daniela Burgos-Ojeda, Greg Spahlinger, R. Kopelman, and Ronald J. Buckanovich
Précis: Ovarian cancers may be highly responsive to strategies that target the tumor vasculature, increasing interest in focusing on such strategies to improve therapeutic outcomes.
- 8684 **Telomerase Inhibition Potentiates the Effects of Genotoxic Agents in Breast and Colorectal Cancer Cells in a Cell Cycle-Specific Manner**
Raina A. Tamakawa, Helen B. Fleisig, and Judy M.Y. Wong
Précis: Results suggest that the protective role of telomerase in cell cycle-restricted DNA damage repair can be exploited for combined anticancer chemotherapy.
- 8695 **γ -Tocotrienol Inhibits Pancreatic Tumors and Sensitizes Them to Gemcitabine Treatment by Modulating the Inflammatory Microenvironment**
Ajaikumar B. Kunnumakkara, Bokyoung Sung, Jayaraj Ravindran, Parmeswaran Diagaradjane, Amit Deorukhkar, Sanjit Dey, Cemile Koca, Vivek R. Yadav, Zhimin Tong, Juri G. Gelovani, Sushovan Guha, Sunil Krishnan, and Bharat B. Aggarwal
Précis: Preclinical findings strongly encourage clinical evaluation of a novel derivative of vitamin E as an adjuvant treatment with standard of care chemotherapy in pancreatic cancer patients.
- 8706 **Targeted Radiosensitization of Cells Expressing Truncated DNA Polymerase β**
Sari Neijenhuis, Manon Verwijs-Janssen, Lenie J. van den Broek, Adrian C. Begg, and Conchita Vens
Précis: This study demonstrates the feasibility of tumor-targeted radiosensitization in tumor cells exhibiting BER/SSBR deficiencies.

- 8715 **Loss of PTEN Expression by Blocking Nuclear Translocation of EGR1 in Gefitinib-Resistant Lung Cancer Cells Harboring Epidermal Growth Factor Receptor–Activating Mutations**
Chizuko Yamamoto, Yuji Basaki, Akihiko Kawahara, Kazutaka Nakashima, Masayoshi Kage, Hiroto Izumi, Kimitoshi Kohno, Hidetaka Uramoto, Kosei Yasumoto, Michihiko Kuwano, and Mayumi Ono
- Précis:* Results reinforce the therapeutic importance of PTEN expression in treatment of lung adenocarcinoma with EGFR targeting drugs.
- 8726 **Histone Methyltransferase MLL1 Regulates MDR1 Transcription and Chemoresistance**
Hairong Huo, Pellegrino G. Magro, E. Christy Pietsch, Brijesh B. Patel, and Kathleen W. Scott
- Précis:* Findings suggest an approach to attack drug resistance in acute lymphoblastic leukemias and other cancers where oncogenic activations of MLL1 occur.
- 8736 **Basal and Treatment-Induced Activation of AKT Mediates Resistance to Cell Death by AZD6244 (ARRY-142886) in *Braf*-Mutant Human Cutaneous Melanoma Cells**
Y.N. Vashisht Gopal, Wanleng Deng, Scott E. Woodman, Kakajan Komurov, Prahlad Ram, Paul D. Smith, and Michael A. Davies
- Précis:* Findings offer a rationale for combining an MEK inhibitor with a PI3K-AKT pathway inhibitor to improve the treatment of malignant melanomas with a *Braf* mutation.
- 8748 **Tumor Cell Kill by c-MYC Depletion: Role of MYC-Regulated Genes that Control DNA Double-Strand Break Repair**
Kaisa R. Luoto, Alice X. Meng, Amanda R. Wasylishen, Helen Zhao, Carla L. Coackley, Linda Z. Penn, and Robert G. Bristow
- Précis:* Findings suggest that anti-MYC agents may prevent genetic instability but may not be useful for radiosensitization or chemosensitization of cancer cells.
- 8760 **Phosphorylation of RalB Is Important for Bladder Cancer Cell Growth and Metastasis**
Hong Wang, Charles Owens, Nidhi Chandra, Mark R. Conaway, David L. Brautigam, and Dan Theodorescu
- Précis:* Mechanistic findings suggest specific tactics to blunt Ral GTPase signaling that could offer an effective approach to treat metastatic bladder cancer.
- 8770 **Synthetic Lethality Screens Reveal RPS6 and MST1R as Modifiers of Insulin-like Growth Factor-1 Receptor Inhibitor Activity in Childhood Sarcomas**
Jenny C. Potratz, Darren N. Saunders, Daniel H. Wai, Tony L. Ng, Steven E. McKinney, Joan M. Carboni, Marco M. Gottardis, Timothy J. Triche, Heribert Jürgens, Michael N. Pollak, Samuel A. Aparicio, and Poul H.B. Sorensen
- Précis:* Probing of the IGF-1 receptor axis in childhood sarcomas reveals resistance mechanisms through activation of alternative tyrosine kinases.
- 8782 **BRCA1-IRIS Overexpression Promotes Cisplatin Resistance in Ovarian Cancer Cells**
Kerri L. Chock, Jamie M.S. Allison, Yoshiko Shimizu, and Wael M. ElShamy
- Précis:* Mechanistic study suggests novel strategies to defeat therapeutic resistance in ovarian cancer, which persists as a top priority to improve clinical treatment of this disease.

TUMOR AND STEM CELL BIOLOGY

- 8792 **PML-RAR α and Dnmt3a1 Cooperate *in vivo* to Promote Acute Promyelocytic Leukemia**
Deepa Subramanyam, Cassandra D. Belair, Keegan Q. Barry-Holson, Haijiang Lin, Scott C. Kogan, Emmanuelle Passegué, and Robert Blelloch

Précis: Findings argue that levels of a DNA methyltransferase are rate limiting for progression of acute promyelocytic leukemias.

- 8802 **Alternative Cyclin D1 Splice Forms Differentially Regulate the DNA Damage Response**
Zhiping Li, Xuanmao Jiao, Chenguang Wang, L. Andrew Shirley, Hany Elsahel, Olav Dahl, Min Wang, Evi Soutoglou, Erik S. Knudsen, and Richard G. Pestell

Précis: Expression of splice isoform cyclin D1a increases the DNA damage response as compared with cyclin D1b.

- 8812 **Nuclear Receptor COUP-TFII Controls Pancreatic Islet Tumor Angiogenesis by Regulating Vascular Endothelial Growth Factor/Vascular Endothelial Growth Factor Receptor-2 Signaling**
Jun Qin, Xinpu Chen, Li-yuan Yu-Lee, Ming-Jer Tsai, and Sophia Y. Tsai

Précis: Findings reveal a master transcriptional regulator of VEGF signaling in endothelial cells that is crucial to support tumor angiogenesis.

- 8822 **EGFR Promotes Lung Tumorigenesis by Activating miR-7 through a Ras/ERK/Myc Pathway That Targets the Ets2 Transcriptional Repressor ERF**
Yu-Ting Chou, Hua-Heng Lin, Yung-Chang Lien, Yuan-Hung Wang, Chun-Fu Hong, Yu-Rung Kao, Sheng-Chieh Lin, Ying-Che Chang, Shu-Yu Lin, Shu-Jen Chen, Hua-Chien Chen, Shaoh-Der Yeh, and Cheng-Wen Wu
- Précis:* Findings identify the microRNA miR-7 as a modulator of EGFR-mediated oncogenesis with important potential applications as a theranostic target in lung cancer.
- 8832 **Characterization of a Candidate Tumor Suppressor Gene Uroplakin 1A in Esophageal Squamous Cell Carcinoma**
Kar Lok Kong, Dora L. Kwong, Li Fu, Tim Hon Man Chan, Leilei Chen, Haibo Liu, Yan Li, Ying-Hui Zhu, Jiong Bi, Yan-Ru Qin, Simon Ying Kit Law, and Xin-Yuan Guan
- Précis:* A tetraspanin cell surface receptor represents an important new theranostic marker in esophageal cancer, a deadly disease with a rising incidence in developed countries.
- 8842 **In vivo Imaging of Inflammation- and Tumor-Induced Lymph Node Lymphangiogenesis by Immuno-Positron Emission Tomography**
Viviane Mumprecht, Michael Honer, Benjamin Vigil, Steven T. Proulx, Eveline Trachsel, Manuela Kaspar, Nadja E. Banziger-Tobler, Roger Schibli, Dario Neri, and Michael Detmar
- Précis:* Proof-of-concept for a strategy of noninvasive imaging of lymph node lymphangiogenesis could permit early detection of metastasis in cancer patients.
- 8852 **Prognostic and Therapeutic Implications of Distinct Kinase Expression Patterns in Different Subtypes of Breast Cancer**
Giampaolo Bianchini, Takayuki Iwamoto, Yuan Qi, Charles Coutant, Christine Y. Shiang, Bailang Wang, Libero Santarpia, Vicente Valero, Gabriel N. Hortobagyi, W. Fraser Symmans, Luca Gianni, and Lajos Pusztai
- Précis:* Study findings indicate that kinases regulating mitosis and immune functions convey distinct prognostic information that varies by clinical subtype, suggesting strategies to combine kinase inhibitors for therapeutic benefit.
- 8863 **Maternal Embryonic Leucine Zipper Kinase Is Upregulated and Required in Mammary Tumor-Initiating Cells In vivo**
Lionel W. Hebbard, Jochen Maurer, Amber Miller, Jacqueline Lesperance, John Hassell, Robert G. Oshima, and Alexey V. Terskikh
- Précis:* Results offer preclinical proof-of-concept for targeting a little-studied kinase as a therapeutic strategy to destroy breast cancer-initiating cells.
- 8874 **Tumorigenic and Metastatic Activity of Human Thyroid Cancer Stem Cells**
Matilde Todaro, Flora Iovino, Vincenzo Eterno, Patrizia Cammareri, Guido Gambarà, Virginia Espina, Gaspare Gulotta, Francesco Dieli, Silvia Giordano, Ruggero De Maria, and Giorgio Stassi
- Précis:* Aldehyde dehydrogenase overexpression identifies thyroid cancer stem cells that could promote the development of novel approaches for thyroid malignancy.
- 8886 **Ionizing Radiation Activates the Nrf2 Antioxidant Response**
J. Tyson McDonald, Kwanghee Kim, Andrew J. Norris, Erina Vlashi, Tiffany M. Phillips, Chann Lagadec, Lorenza Della Donna, Josephine Ratikan, Heather Szelag, Lynn Hlatky, and William H. McBride
- Précis:* A delayed adaptive mechanism of radioprotection is described that might be manipulated to mitigate complications of radiotherapy in normal tissues which arise late after radiation exposure.
- 8896 **Protein Tyrosine Phosphatase Receptor Type γ Is a Functional Tumor Suppressor Gene Specifically Downregulated in Chronic Myeloid Leukemia**
Marco Della Peruta, Giovanni Martinelli, Elisabetta Moratti, Davide Pintani, Marzia Vezzalini, Andrea Mafficini, Tiziana Grafone, Ilaria Iacobucci, Simona Soverini, Marco Murineddu, Fabrizio Vinante, Cristina Tecchio, Giovanna Piras, Attilio Gabbas, Maria Monne, and Claudio Sorio
- Précis:* Findings identify a novel clinically relevant tumor suppressor gene in chronic myelogenous leukemia.

8907 **Enhanced Genetic Instability and Dasatinib Sensitivity in Mammary Tumor Cells Lacking NEDD9**
Mahendra K. Singh, Eugene Izumchenko, Andres J. Klein-Szanto, Brian L. Egleston, Marina Wolfson, and Erica A. Golemis

Précis: Although *Nedd9* overexpression may act as a driver and biomarker for tumor aggressiveness, genetic deficiency in *Nedd9* in mice selects for development of hyperaggressive mammary tumors.

8917 **Gprc5a Deletion Enhances the Transformed Phenotype in Normal and Malignant Lung Epithelial Cells by Eliciting Persistent Stat3 Signaling Induced by Autocrine Leukemia Inhibitory Factor**
Yulong Chen, Jiong Deng, Junya Fujimoto, Humam Kadara, Taoyan Men, Dafna Lotan, and Reuben Lotan

Précis: Findings reveal a mechanistic basis for understanding the tumor suppressor function of a G protein-coupled receptor expressed in normal lung epithelial cells.

8927 **Tissue-Specific Pathways for Estrogen Regulation of Ovarian Cancer Growth and Metastasis**
Monique A. Spillman, Nicole G. Manning, Wendy W. Dye, Carol A. Sartorius, Miriam D. Post, Joshua Chuck Harrell, Britta M. Jacobsen, and Kathryn B. Horwitz

Précis: Estrogen regulates unique genes in ovarian cancers that promote lymph node metastasis.

8937 **Tuberous Sclerosis Complex 1: An Epithelial Tumor Suppressor Essential to Prevent Spontaneous Prostate Cancer in Aged Mice**
Raleigh D. Kladney, Robert D. Cardiff, David J. Kwiatkowski, Gary G. Chiang, Jason D. Weber, Jeffrey M. Arbeit, and Zhi Hong Lu

Précis: Findings suggest that maintaining control of the nodal growth regulatory mTOR complexes during aging is crucial to prevent prostate cancer, the most common cancer in men.

8948 **Cell Signaling by Urokinase-type Plasminogen Activator Receptor Induces Stem Cell-like Properties in Breast Cancer Cells**
Minji Jo, Boryana M. Eastman, Drue L. Webb, Konstantin Stoletov, Richard Klemke, and Steven L. Gonias

Précis: Plasminogen activators and their receptors are well known to be involved in cancer cell migration and invasion, but this is the first study to show that they also induce cancer stem cell-like properties.

8959 **Overexpression of the Protein Tyrosine Phosphatase PRL-2 Correlates with Breast Tumor Formation and Progression**
Serge Hardy, Nau Nau Wong, William J. Muller, Morag Park, and Michel L. Tremblay

Précis: Evidence garnered from clinical specimens and mouse models defines an important new driver of breast cancer invasion and metastasis.

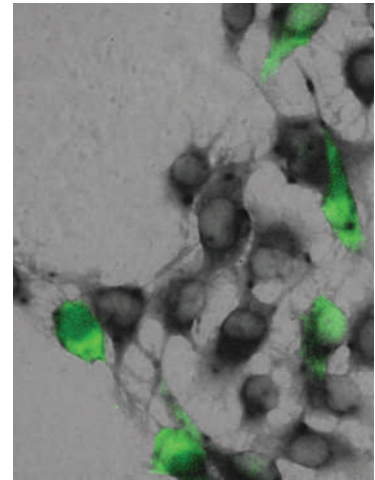
CORRECTIONS

8968 **Correction: Colorectal Tumors Are Effectively Eradicated by Combined Inhibition of β -Catenin, KRAS, and the Oncogenic Transcription Factor ITF2**

8969 **Correction: Activation of Murine Double Minute 2 by Akt in Mammary Epithelium Delays Mammary Involution and Accelerates Mammary Tumorigenesis**

ABOUT THE COVER

9L gliosarcoma cells expressing cel-miR-67 transfer cel-miR-67 to naïve 9L cells. Coculture of cel-miR-67-expressing 9L cells with those that expressed a luciferase reporter containing a complementary sequence to cel-miR-67 results in suppression of luciferase protein expression in the acceptor cells. This image reveals colocalization of cel-miR-67 (dark dots, *in situ* hybridization signal) with eGFP in 9L cells that do not express cel-miR-67. These findings indicate that glioma cells can transfer functional miRNA from one cell to another. Thus, miRNA serves as an intercellular signaling molecule in glioma. For details, see the article by Katakowski and colleagues on page 8259 of this issue.



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