Cancer Research
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8288 MicroRNA Expression and Clinical Outcomes in Patients Treated with Adjuvant Chemotherapy after Complete Resection of Non–Small Cell Lung Carcinoma

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.

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

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

**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.

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

Vincent M. Asiago, Leiddy Z. Alvarado, Narasimhamurthy Shanaiah, G.A. Nagana Gowda, Kwaadwo 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

**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.

**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.

**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.

**Cdc42-Interacting Protein 4 Promotes Breast Cancer Cell Invasion and Formation of Invadopodia**

Christina S. Pichot, Constandina 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.

**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.

**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.
MOLECULAR AND CELLULAR PATHOBIOLOGY

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.

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. Cuhill, 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.

Identification of Susceptibility Loci in a Mouse Model of KrasG12D-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.

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, Hirotaka 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.

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.

Metabolic Aggressiveness in Benign Meningiomas with Chromosomal Instabilities

Daniel Monleón, José Manuel Morales, Ana González-Segura, José Manuel González-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.

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.

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


Précis: Findings identify an important modifier of hormone regulated gene expression that drives metastasis and predicts poor prognosis in breast cancer patients.
The Oncoprotein c-Ski Functions as a Direct Antagonist of the Transforming Growth Factor-β Type I Receptor
Nathalie Fernand, Azeddine Atfi, and Céline Prunier

Precis: 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.

RAP80 Acts Independently of BRCA1 in Repair of Topoisomerase II Poison-Induced DNA Damage
Junko Iijima, Zhihong Zeng, Shunichi Takeda, and Yoshihito Taniguchi

Precis: Findings define a critical function in the resistance of cancer to the widely employed DNA damaging anticancer agent etoposide.

BRAF Inactivation Drives Aneuploidy by Deregulating CRAF
Tamihiro Kamata, Jahan Hussain, Susan Giblett, Robert Hayward, Richard Marais, and Catrin Pritchard

Precis: Study defines a new function for the c-RAF kinase in supporting cancer development.

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

Precis: 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.

Evidence of an Adaptive Response Targeting DNA Nonhomologous End Joining and Its Transmission to Bystander Cells
Holger Klammer, Munira Kadhim, and George Iliaikis

Precis: 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.

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

Precis: Findings argue that overexpression of Sp transcription factor Sp2 occurring in a variety of human cancers is likely to have significant functional impact.

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

Precis: 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.

Activation of Forkhead Box O Transcription Factors by Oncogenic BRAF Promotes p21cip1-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

Precis: 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.

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

Precis: 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.
**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, Jiahui Han, and Peiqing Sun

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

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**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.

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**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.

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**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.

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**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.

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**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.

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

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

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**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.
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.

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.

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.

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.

F3-Targeted Cisplatin-Hydrogel Nanoparticles as an Effective Therapeutic That Targets Both Murine and Human Ovarian Tumor Endothelial Cells In vivo
Ira Winer, Shouyuan Wang, Youg-Eun Koo Lee, Wenzhe Fan, Yusong Gong, Daniela Burgos-Ojeda, Greg Spahnling, 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.

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.

γ-Tocotrienol Inhibits Pancreatic Tumors and Sensitizes Them to Gemcitabine Treatment by Modulating the Inflammatory Microenvironment
Ajaikumar B. Kunnumakkara, Bokyung Sung, Jayaraj Ravindran, Parmeswaran Diagaradjane, Amit Deorukhar, Sanjit Dey, Cemile Koca, Vivek R. Yadav, Zhiming 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.

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.
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<td>Précis: Findings suggest that anti-MYC agents may prevent genetic instability but may not be useful for radiosensitization or chemosensitization of cancer cells.</td>
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<td>Hong Wang, Charles Owens, Nidhi Chandra, Mark R. Conaway, David L. Brautigan, and Dan Theodorescu</td>
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<td>BRCA1-IRIS Overexpression Promotes Cisplatin Resistance in Ovarian Cancer Cells</td>
<td>Kerri L. Chock, Jamie M.S. Allison, Yoshiko Shimizu, and Wael M. ElShamy</td>
<td>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.</td>
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**TUMOR AND STEM CELL BIOLOGY**

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<td>Précis: Findings argue that levels of a DNA methyltransferase are rate limiting for progression of acute promyelocytic leukemias.</td>
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<td>Précis: Expression of splice isoform cyclin D1α increases the DNA damage response as compared with cyclin D1β.</td>
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<td>8927</td>
<td>Tissue-Specific Pathways for Estrogen Regulation of Ovarian Cancer Growth and Metastasis</td>
<td>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</td>
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<td>8937</td>
<td>Tuberous Sclerosis Complex 1: An Epithelial Tumor Suppressor Essential to Prevent Spontaneous Prostate Cancer in Aged Mice</td>
<td>Raleigh D. Kladney, Robert D. Cardiff, David J. Kwiatkowski, Gary G. Chiang, Jason D. Weber, Jeffrey M. Arbeit, and Zhi Hong Lu</td>
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<td>8959</td>
<td>Overexpression of the Protein Tyrosine Phosphatase PRL-2 Correlates with Breast Tumor Formation and Progression</td>
<td>Serge Hardy, Nau Nau Wong, William J. Muller, Morag Park, and Michel L. Tremblay</td>
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**CORRECTIONS**

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