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# Cancer Research

September 1, 2012 • Volume 72 • Number 17

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- 4304 | **Therapeutic Administration of a Synthetic CpG Oligodeoxynucleotide Triggers Formation of Anti-CpG Antibodies**  
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- Précis:* Given the large number of clinical studies using CpG oligodeoxynucleotides as an immune adjuvant, this report that anti-CpG antibodies arise in human subjects treated with CpG may advance understanding of their effects on clinical outcome.

- 4311 | **Strain-Specific Variation in Murine Natural Killer Gene Complex Contributes to Differences in Immunosurveillance for Urethane-Induced Lung Cancer**  
Daniel Kreisel, Andrew E. Gelman, Ryuji Higashikubo, Xue Lin, Haris G. Vikis, J. Michael White, Kelsey A. Toth, Charuhas Deshpande, Beatriz M. Carreno, Ming You, Samantha M. Taffner, Wayne M. Yokoyama, Jack D. Bui, Robert D. Schreiber, and Alexander S. Krupnick
- Précis:* This study identifies for the first time that inherited differences in the immune system of mammals, specifically in a population of cells called natural killer cells, can affect the development of lung cancer.

## CLINICAL STUDIES

- 4318 | **Baseline Tumor Oxygen Saturation Correlates with a Pathologic Complete Response in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy**  
Shigeto Ueda, Darren Roblyer, Albert Cerussi, Amanda Durkin, Anais Leproux, Ylenia Santoro, Shanshan Xu, Thomas D. O'Sullivan, David Hsiang, Rita Mehta, John Butler, and Bruce J. Tromberg
- Précis:* This important study shows how visualizing tumor oxygenation prior to treatment correlates with postsurgical responses to neoadjuvant chemotherapy, potentially offering a noninvasive tool to predict outcomes of individual patients to treatment.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4329 | **Global Quantitative Phosphoproteome Analysis of Human Tumor Xenografts Treated with a CD44 Antagonist**  
Stefan Weigand, Frank Herting, Daniela Maisel, Adam Nopora, Edgar Voss, Christoph Schaab, Martin Klammer, and Andreas Tebbe
- Précis:* The use of phosphoproteomics for ex vivo analysis of tumor xenografts identifies key downstream targets of a therapeutic antibody that recognizes an important stem cell antigen in cancer pathophysiology.



## MICROENVIRONMENT AND IMMUNOLOGY

4340 **Transcription Factor NFATc2 Controls the Emergence of Colon Cancer Associated with IL-6–Dependent Colitis**

Katharina Gerlach, Carolin Daniel, Hans A. Lehr, Alexei Nikolaev, Thomas Gerlach, Raja Atreya, Stefan Rose-John, Markus F. Neurath, and Benno Weigmann

*Précis:* Findings define a transcriptional program of colitis-associated inflammation that is associated with elevated risks of colon cancer in humans, as directed by the pivotal proinflammatory cytokine IL-6.

4351 **CXCR3<sup>+</sup> T Regulatory Cells Selectively Accumulate in Human Ovarian Carcinomas to Limit Type I Immunity**

Nassima Redjimi, Caroline Raffin, Isabelle Raimbaud, Pascale Pignon, Junko Matsuzaki, Kunle Odunsi, Danila Valmori, and Maha Ayyoub

*Précis:* A recently described subset of immunosuppressive T-regulatory cells is found to accumulate in ovarian carcinomas, potentially affecting immune targeting approaches that are now in development to improve clinical outcomes.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

4361 **Expression of the PTTG1 Oncogene Is Associated with Aggressive Clear Cell Renal Cell Carcinoma**

Bill Wondergem, Zhongfa Zhang, Dachuan Huang, Choon Kiat Ong, Julie Koeman, David Van't Hof, David Petillo, Aikseng Ooi, John Anema, Brian Lane, Richard J. Kahnoski, Kyle A. Furge, and Bin Tean Teh

*Précis:* This study offers evidence that the PTTG1 oncogene, which resides in a chromosomal region that is often amplified in renal cancer, is a key driver of progression in this disease.

4372 **Activation of Thermogenesis in Brown Adipose Tissue and Dysregulated Lipid Metabolism Associated with Cancer Cachexia in Mice**

Maria Tsoli, Melissa Moore, Dominic Burg, Arran Painter, Ryland Taylor, Sarah H. Lockie, Nigel Turner, Alessandra Warren, Greg Cooney, Brian Oldfield, Stephen Clarke, and Graham Robertson

*Précis:* This study demonstrates how activation of brown adipose tissue by tumors causes cachexia, a wasting disease characterized by severe weight loss that causes the death of many cancer patients.

4383

**Gastrointestinal Adenocarcinomas of the Esophagus, Stomach, and Colon Exhibit Distinct Patterns of Genome Instability and Oncogenesis**

Austin M. Dulak, Steven E. Schumacher, Jasper van Lieshout, Yu Imamura, Cameron Fox, Byoungyong Shim, Alex H. Ramos, Gordon Saksena, Sylvan C. Baca, Jose Baselga, Josep Tabernero, Jordi Barretina, Peter C. Enzinger, Giovanni Corso, Franco Roviello, Lin Lin, Santhoshi Bandla, James D. Luketich, Arjun Pennathur, Matthew Meyerson, Shuji Ogino, Ramesh A. Shivdasani, David G. Beer, Tony E. Godfrey, Rameen Beroukhim, and Adam J. Bass

*Précis:* This large-scale genomic study provides insight into the spectrum of alterations present in gastrointestinal cancers, especially gastric and esophageal adenocarcinomas, in which there is a great need for targeted therapeutic development.

4394

**AMPK Promotes p53 Acetylation via Phosphorylation and Inactivation of SIRT1 in Liver Cancer Cells**

Chi-Wai Lee, Leo Lap-Yan Wong, Edith Yuk-Ting Tse, Heong-Fai Liu, Veronica Yee-Law Leong, Joyce Man-Fong Lee, D. Grahame Hardie, Irene Oi-Lin Ng, and Yick-Pang Ching

*Précis:* These findings are persuasive in showing that the biologic energy sensor AMPK functions as a tumor suppressor in hepatocellular carcinoma via phosphorylation and inactivation of SIRT1, challenging expectations about how AMPK may contribute to cancer.

4405

**Functional Interaction of Tumor Suppressor DLC1 and Caveolin-1 in Cancer Cells**

Xiaoli Du, Xiaolan Qian, Alex Papageorge, Aaron J. Schetter, William C. Vass, Xi Liu, Richard Braverman, Ana I. Robles, and Douglas R. Lowy

*Précis:* This study identifies a mechanism by which cancer cell growth is blocked by the tumor suppressor gene DLC1, which is frequently mutated in lung cancers and other solid tumors.

4417

**Concomitant Targeting of Tumor Cells and Induction of T-cell Response Synergizes to Effectively Inhibit Trastuzumab-Resistant Breast Cancer**

Qingfei Wang, Shau-Hsuan Li, Hai Wang, Yi Xiao, Ozgur Sahin, Samuel W. Brady, Ping Li, Hailiang Ge, Elizabeth M. Jaffee, William J. Muller, Gabriel N. Hortobagyi, and Dihua Yu

*Précis:* Breast cancers resistant to anti-HER2 therapy can be destroyed by blocking the AKT pathway and degrading immune tolerance, thereby effectively restoring T-cell-mediated antitumor immunity.

4429 **Pharmacological Inhibition of LIM Kinase Stabilizes Microtubules and Inhibits Neoplastic Growth**  
Renaud Prudent, Emilie Vassal-Stermann, Chi-Hung Nguyen, Catherine Pillet, Anne Martinez, Chloé Prunier, Caroline Barette, Emmanuelle Soleilhac, Odile Filhol, Anne Beghin, Glaucio Valdameri, Stéphane Honoré, Samia Aci-Sèche, David Grierson, Juliana Antonipillai, Rong Li, Attilio Di Pietro, Charles Dumontet, Diane Braguer, Jean-Claude Florent, Stefan Knapp, Ora Bernard, and Laurence Lafanechère

*Précis: Inhibition of an actin-associated modifier of microtubule dynamics blocks neoplastic growth and evades the multidrug resistance mechanisms that impede the action of conventional microtubule-targeting drugs.*

4440 **Stat3 Inhibition Augments the Immunogenicity of B-cell Lymphoma Cells, Leading to Effective Antitumor Immunity**  
Fengdong Cheng, Hongwei Wang, Pedro Horna, Zi Wang, Bijal Shah, Eva Sahakian, Karrune V. Woan, Alejandro Villagra, Javier Pinilla-Ibarz, Said Sebti, Mitchell Smith, Jianguo Tao, and Eduardo M. Sotomayor

*Précis: A particularly aggressive form of B-cell lymphoma may benefit strongly from treatment with agents that block Stat3 signaling.*

4449 **Hedgehog Signaling Regulates Bladder Cancer Growth and Tumorigenicity**  
Dennis Liang Fei, Avencia Sanchez-Mejias, Zhiqiang Wang, Colin Flaveny, Jun Long, Samer Singh, Jezabel Rodriguez-Blanco, Robert Tokhunts, Camilla Giambelli, Karoline J. Briegel, Wolfgang A. Schulz, A. Jay Gandolfi, Margaret Karagas, Teresa A. Zimmers, Merce Jorda, Pablo Bejarano, Anthony J. Capobianco, and David J. Robbins

*Précis: This study provides direct evidence that Hedgehog signaling plays a critical role in bladder cancer, a finding that previously had been controversial.*

4459 **Acyclic Retinoid Targets Platelet-Derived Growth Factor Signaling in the Prevention of Hepatic Fibrosis and Hepatocellular Carcinoma Development**

Hikari Okada, Masao Honda, Jean S. Campbell, Yoshio Sakai, Taro Yamashita, Yuuki Takebuchi, Kazuhiro Hada, Takayoshi Shirasaki, Riuta Takabatake, Mikiko Nakamura, Hajime Sunagozaka, Takuji Tanaka, Nelson Fausto, and Shuichi Kaneko

*Précis: This study suggests uses for an oral retinoid compound in blocking the development of liver fibrosis and liver cancer and elucidates a molecular basis for understanding the action of this potential treatment.*

4472 **Targeting eNOS in Pancreatic Cancer**  
Benjamin L. Lampson, S. DiSean Kendall, Brooke B. Ancrile, Meghan M. Morrison, Michael J. Shealy, Katharine S. Barrientos, Matthew S. Crowe, David F. Kashatus, Rebekah R. White, Susan B. Gurley, Diana M. Cardona, and Christopher M. Counter

*Précis: The results of this preclinical study suggest that an experimental drug being evaluated clinically for treatment of septic shock could be repurposed for use with pancreatic cancers and perhaps other cancers driven by oncogenic Ras.*

4483 **Dual Targeting of the Akt/mTOR Signaling Pathway Inhibits Castration-Resistant Prostate Cancer in a Genetically Engineered Mouse Model**  
Nicolas Floc'h, Carolyn Waugh Kinkade, Takashi Kobayashi, Alvaro Aytes, Celine Lefebvre, Antonina Mitrofanova, Robert D. Cardiff, Andrea Califano, Michael M. Shen, and Cory Abate-Shen

*Précis: Findings provide preclinical proof that dual targeting of the AKT-mTOR signaling pathway is effective for the treatment of advanced prostate cancers, for which clinical treatment remains problematic.*

4494 **Targeting the EWSR1-FLI1 Oncogene-Induced Protein Kinase PKC-β Abolishes Ewing Sarcoma Growth**  
Didier Surdez, Magdalena Benetkiewicz, Virginie Perrin, Zhi-Yan Han, Gaëlle Pierron, Stelly Ballet, François Lamoureux, Françoise Rédini, Anne-Valérie Decouvelaere, Estelle Daudigeos-Dubus, Birgit Georger, Gonzague de Pinieux, Olivier Delattre, and Franck Tirode

*Précis: Findings offer a preclinical proof-of-concept for the protein kinase PKC-β as a promising therapeutic target for treatment of an aggressive pediatric cancer.*

4504 **Regulation of ERBB2 Receptor by t-DARPP Mediates Trastuzumab Resistance in Human Esophageal Adenocarcinoma**

Jun Hong, Ahmed Katsha, Pengcheng Lu, Yu Shyr, Abbes Belkhiri, and Wael El-Rifai

*Précis:* HER2 antibody therapy is being tested against esophageal cancer, where resistance mechanisms have yet to be explored.

4515 **PDGF Receptor Alpha Is an Alternative Mediator of Rapamycin-Induced Akt Activation: Implications for Combination Targeted Therapy of Synovial Sarcoma**

Alan L. Ho, Shyamprasad Deraje Vasudeva, Marick Laé, Tsuyoshi Saito, Violetta Barbashina, Cristina R. Antonescu, Marc Ladanyi, and Gary K. Schwartz

*Précis:* This study shows that distinct mechanisms of resistance to mTOR-targeted therapy in sarcoma are driven by disease-specific biology that will require individualized approaches for targeted therapies in these patients.

4526 **Glutamine Deprivation Enhances Antitumor Activity of 3-Bromopyruvate through the Stabilization of Monocarboxylate Transporter-1**

Simone Cardaci, Salvatore Rizza, Giuseppe Filomeni, Roberta Bernardini, Fabio Bertocchi, Maurizio Mattei, Maurizio Paci, Giuseppe Rotilio, and Maria Rosa Ciriolo

*Précis:* Findings offer a preclinical proof-of-concept for the use of monocarboxylate-based drugs to enhance the capability of glutamine deprivation to sensitize tumors to chemotherapy.

4562 **Cell Death via DR5, but not DR4, Is Regulated by p53 in Myeloma Cells**

Sylvanie Surget, David Chiron, Patricia Gomez-Bougie, Géraldine Descamps, Emmanuelle Ménoret, Régis Bataille, Philippe Moreau, Steven Le Gouill, Martine Amiot, and Catherine Pellat-Deceunynck

*Précis:* TRAIL receptors are differentially regulated by p53, and this study establishes a rationale to specifically target the TRAIL receptor DR5 with drugs that activate p53.

4574 **Differentially Expressed Genes Regulating the Progression of Ductal Carcinoma In Situ to Invasive Breast Cancer**

Sangjun Lee, Sheila Stewart, Iris Nagtegaal, Jingqin Luo, Yun Wu, Graham Colditz, Dan Medina, and D. Craig Allred

*Précis:* Gene expression profiling combined with in vivo functional studies identifies novel genes that regulate the progression of ductal carcinoma in situ to invasive breast cancer, with implications for prevention, detection, and therapy of early breast cancer.

4587 **NLRR1 Enhances EGF-Mediated MYCN Induction in Neuroblastoma and Accelerates Tumor Growth In Vivo**

Shamim Hossain, Atsushi Takatori, Yohko Nakamura, Yusuke Suenaga, Takehiko Kamijo, and Akira Nakagawara

*Précis:* A positive feedback loop between the transmembrane protein NLRR1 and the N-Myc oncoprotein can explain the aggressiveness of neuroblastoma, conceivably offering an attractive new therapeutic target in this deadly disease.

4597 **SOX4 Induces Epithelial-Mesenchymal Transition and Contributes to Breast Cancer Progression**

Jianchao Zhang, Qian Liang, Yang Lei, Min Yao, Lili Li, Xiaoge Gao, Jingxin Feng, Yu Zhang, Hongwen Gao, Dong-Xu Liu, Jun Lu, and Baiqu Huang

*Précis:* Findings define an important function for the transcription factor SOX4 in EMT and breast cancer progression, also implicating it as a marker of poor prognosis.

## TUMOR AND STEM CELL BIOLOGY

4537 **The MET Oncogene Is a Functional Marker of a Glioblastoma Stem Cell Subtype**

Francesca De Bacco, Elena Casanova, Enzo Medico, Serena Pellegatta, Francesca Orzan, Raffaella Albano, Paolo Luraghi, Gigliola Reato, Antonio D'Ambrosio, Paola Porrati, Monica Patanè, Emanuela Maderna, Bianca Pollo, Paolo M. Comoglio, Gaetano Finocchiaro, and Carla Boccaccio

*Précis:* This report is one of two in the current issue that define a marker of cancer stem-like function that might be exploited immediately for molecular diagnosis and targeted therapy in aggressive forms of brain cancer.

4551 **HSP90 Inhibitor 17-AAG Selectively Eradicates Lymphoma Stem Cells**

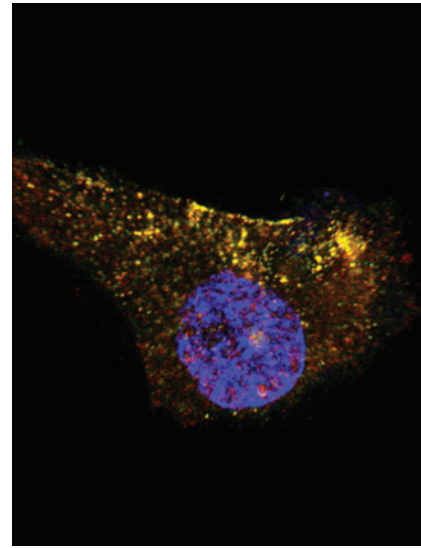
Bryan Newman, Yan Liu, Hsiu-Fang Lee, Duxin Sun, and Yin Wang

*Précis:* An HSP90 inhibitor in clinical trials may have especially useful applications to eliminate lymphoma stem cells.

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## ABOUT THE COVER

Deleted in liver cancer 1 (DLC1), a tumor suppressor gene frequently inactivated in non-small cell lung cancer (NSCLC) and other malignancies, encodes a multidomain protein with a RhoGTPase-activating domain and a StAR-related lipid transfer (START) domain. By using immunofluorescence, DLC1 was found to colocalize with caveolin 1 (CAV-1), the principal structural component and marker of caveolae in NSCLC cell lines. The interaction between DLC1 and CAV-1 was mapped to the DLC1 START domain and was shown to be necessary for the tumor suppressor activity of DLC1. For details, see article by Du and colleagues on page 4405.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

## 72 (17)

*Cancer Res* 2012;72:4287-4608.

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