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# Cancer Research

March 15, 2011 • Volume 71 • Number 6

## BREAKING ADVANCES

- 2025 | **Highlights from Recent Cancer Literature**

## FROM THE EDITOR'S CHAIR

- 2027 | **Perspectives on Emerging Trends in Cancer Research**  
George C. Prendergast

## REVIEWS

- 2029 | **Calcineurin Signaling as a Negative Determinant of Keratinocyte Cancer Stem Cell Potential and Carcinogenesis**  
G. Paolo Dotto
- 2034 | **MYC and Metastasis**  
Anita Wolfer and Sridhar Ramaswamy

## PRIORITY REPORT

- 2038 | **Spontaneous Cytotoxic T-Cell Reactivity against Indoleamine 2,3-Dioxygenase-2**  
Rikke Bæk Sørensen, Tania Køllgaard, Rikke Sick Andersen, Joost Huibert van den Berg, Inge Marie Svane, Per thor Straten, and Mads Hald Andersen
- Précis:* IDO2-specific T cells are present among peripheral blood lymphocytes in cancer patients and are able to recognize and kill cancer cells.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2045 | **Genome-Wide Analysis of Alternative Splicing in Medulloblastoma Identifies Splicing Patterns Characteristic of Normal Cerebellar Development**  
Francesca Menghi, Thomas S. Jacques, Martino Barenco, Ed C. Schwalbe, Steven C. Clifford, Mike Hubank, and Jonathan Ham
- Précis:* Increasing evidence points to a critical role for dysregulated patterns of alternate splicing in driving tumorigenesis, here illustrated by implications of a failure of differentiation pathways in a little understood but deadly childhood tumor.

## MICROENVIRONMENT AND IMMUNOLOGY

- 2056 | **CCL11-CCR3 Interactions Promote Survival of Anaplastic Large Cell Lymphoma Cells via ERK1/2 Activation**  
Tomomitsu Miyagaki, Makoto Sugaya, Takashi Murakami, Yoshihide Asano, Yayoi Tada, Takafumi Kadono, Hitoshi Okochi, Kunihiko Tamaki, and Shinichi Sato
- Précis:* Findings prompt a novel therapeutic approach to treat relapses of an aggressive form of lymphoma based on the discovery that a cell surface marker of disease functions as a critical autocrine growth receptor.
- 2066 | **Cancer Immunotherapy Using a Bispecific NK Receptor Fusion Protein that Engages both T Cells and Tumor Cells**  
Tong Zhang and Charles L. Sentman
- Précis:* This study offers preclinical proof-of-concept for an interesting new biologic agent that stimulates effective host antitumor immunity, in support of clinical evaluation.
- 2077 | **Anti-IL-23 Monoclonal Antibody Synergizes in Combination with Targeted Therapies or IL-2 to Suppress Tumor Growth and Metastases**  
Michele W.L. Teng, Bianca von Scheidt, Helene Duret, Jennifer E. Towne, and Mark J. Smyth
- Précis:* This study offers the first description of therapeutic activity for anti-IL-23 antibody in preclinical mouse models of cancer.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 2087 | **Protein Kinase C  $\delta$  Is a Downstream Effector of Oncogenic K-ras in Lung Tumors**  
Jennifer M. Symonds, Angela M. Ohm, Cristan J. Carter, Lynn E. Heasley, Theresa A. Boyle, Wilbur A. Franklin, and Mary E. Reyland
- Précis:* A protein kinase C isoform implicated in apoptosis has a differential effect on cancer cell growth depending on the involvement of oncogenic KRAS in proliferation and survival, with potential implications on how to improve therapeutic targeting of mutant KRAS-driven tumors.

- 2098 ***Shmt1* Heterozygosity Impairs Folate-Dependent Thymidylate Synthesis Capacity and Modifies Risk of *Apc<sup>min</sup>*-Mediated Intestinal Cancer Risk**  
Amanda J. MacFarlane, Cheryll A. Perry, Michael F. McEntee, David M. Lin, and Patrick J. Stover  
*Précis:* Folate-dependent thymidylate synthesis capacity modifies susceptibility to intestinal cancer, independent of cellular methylation potential.
- 2108 **Intragenic Rearrangement and Altered RNA Splicing of the Androgen Receptor in a Cell-Based Model of Prostate Cancer Progression**  
Yingming Li, Majid Alsagabi, Danhua Fan, G. Steven Bova, Ahmed H. Tewfik, and Scott M. Dehm  
*Précis:* This study describes a novel genomic aberration in prostate cancer cells that is associated with aberrant RNA splicing of the androgen receptor, leading to synthesis of truncated receptors that drive resistance to androgen depletion therapy.
- 2118 **CARMI Is an Important Determinant of ER $\alpha$ -Dependent Breast Cancer Cell Differentiation and Proliferation in Breast Cancer Cells**  
Mariam Al-Dhaheri, Jiakai Wu, Georgios P. Skliris, Jun Li, Ken Higashimoto, Yidan Wang, Kevin P. White, Paul Lambert, Yuerong Zhu, Leigh Murphy, and Wei Xu  
*Précis:* Results define a histone arginine methyltransferase as a candidate theranostic target in ER-positive breast cancers, with implications to improve the diagnosis of well-differentiated tumors and potentially to improve the chance for cures.
- 2129 **Cep63 Recruits Cdk1 to the Centrosome: Implications for Regulation of Mitotic Entry, Centrosome Amplification, and Genome Maintenance**  
Harald Löffler, Anne Fechter, Marc Matuszewska, Rainer Saffrich, Martin Mistrik, Joachim Marhold, Christin Hornung, Frank Westermann, Jiri Bartek, and Alwin Krämer  
*Précis:* The discovery how Cdk1 kinase is recruited to centrosomes advances understanding of how mitosis is controlled and why centrosome amplification and chromosomal breakage occur so commonly in cancer cells.
- 2140 **Oncogenic Synergism between ErbB1, Nucleolin, and Mutant Ras**  
Keren Farin, Sari Schokoroy, Roni Haklai, Ifat Cohen-Or, Galit Elad-Sfadia, Merit E. Reyes-Reyes, Paula J. Bates, Adrienne D. Cox, Yoel Kloog, and Ronit Pinkas-Kramarski  
*Précis:* This study describes a fascinating protein complex that might be targeted as a general approach to attack the many human cancers driven by EGF family receptors and Ras small GTPases.
- 2152 **HSulf-1 Modulates FGF2- and Hypoxia-Mediated Migration and Invasion of Breast Cancer Cells**  
Ashwani Khurana, Peng Liu, Pasquale Mellone, Laura Lorenzon, Bruno Vincenzi, Kaustubh Datta, Bo Yang, Robert J. Linhardt, Wilma Lingle, Jeremy Chien, Alfonso Baldi, and Viji Shridhar  
*Précis:* This study describes regulation of heparan sulfatase-1 by hypoxia leading to increased cell migration and invasion in breast cancer cells.
- 2162 **Identification of a Tumor Suppressor Relay between the FOXP3 and the Hippo Pathways in Breast and Prostate Cancers**  
Weiyan Li, Lizhong Wang, Hiroto Katoh, Runhua Liu, Pan Zheng, and Yang Liu  
*Précis:* Findings define a functional connection between two important tumor suppressor pathways in cancer, with potential theranostic implications.
- 2172 **IMP-1 Displays Cross-Talk with K-Ras and Modulates Colon Cancer Cell Survival through the Novel Proapoptotic Protein CYFIP2**  
Perry S. Mongroo, Felicite K. Noubissi, Miriam Cuatrecasas, Jiri Kalabis, Catrina E. King, Cameron N. Johnstone, Mark J. Bowser, Antoni Castells, Vladimir S. Spiegelman, and Anil K. Rustgi  
*Précis:* Findings indicate that the Myc-interacting protein IMP-1 acts upstream of K-Ras to promote survival through a novel mechanism that may be important in colon cancer pathogenesis.
- 2183 **CARMA3 is Crucial for EGFR-Induced Activation of NF- $\kappa$ B and Tumor Progression**  
Tang Jiang, Brian Grabiner, Yifan Zhu, Changying Jiang, Hongxiu Li, Yun You, Jingyu Lang, Mien-Chie Hung, and Xin Lin  
*Précis:* Results elucidate how EGFR signaling leads to NF- $\kappa$ B activation and its role in tumor progression.

2193

**PrlZ Protects Prostate Cancer Cells from Apoptosis Induced by Androgen Deprivation via the Activation of Stat3/Bcl-2 Pathway**

Dong Zhang, Dalin He, Yan Xue, Ruoxiang Wang, Kaijie Wu, Hongjun Xie, Jin Zeng, Xinyang Wang, Haiyen E. Zhau, Leland W.K. Chung, Luke S. Chang, and Lei Li

*Précis:* A novel antiapoptotic gene that is specifically activated in prostate cancer cells escaping androgen deprivation may offer an appealing therapeutic target to prevent or treat advanced prostate malignancy.

2203

**The Adaptor Protein AMOT Promotes the Proliferation of Mammary Epithelial Cells via the Prolonged Activation of the Extracellular Signal-Regulated Kinases**

William P. Ranahan, Zhang Han, Whitney Smith-Kinnaman, Sarah C. Nabinger, Brigitte Heller, Britney-Shea Herbert, Rebecca Chan, and Clark D. Wells

*Précis:* This study identifies a novel mechanism whereby the adaptor protein Amot mediates ERK1/2 dependent proliferation of breast cancer cells.

2212

**Interaction between MYC and MCL1 in the Genesis and Outcome of Non-Small-Cell Lung Cancer**

Thaddeus D. Allen, Chang Qi Zhu, Kirk D. Jones, Naoki Yanagawa, Ming-Sound Tsao, and J. Michael Bishop

*Précis:* Findings offer an excellent illustration of how studies in clinically relevant mouse models can lead to a re-examination of clinical findings, here linking two important oncogenes as prognostic biomarkers in the most common type of human lung cancer.

## PREVENTION AND EPIDEMIOLOGY

2222

**Contribution of Inherited Mutations in the BRCA2-Interacting Protein PALB2 to Familial Breast Cancer**

Silvia Casadei, Barbara M. Norquist, Tom Walsh, Sunday Stray, Jessica B. Mandell, Ming K. Lee, John A. Stamatoyannopoulos, and Mary-Claire King

*Précis:* This study characterizes the mutational spectrum of the tumor suppressor gene PALB2, which is mutated in a fraction of familial breast cancer patients and is particularly strongly associated with male breast cancer and pancreatic cancer.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2230

**Targeted Signal-Amplifying Enzymes Enhance MRI of EGFR Expression in an Orthotopic Model of Human Glioma**

Mohammed S. Shazeeb, Christopher H. Sotak, Michael DeLeo III, and Alexei Bogdanov Jr.

*Précis:* Findings define a signal amplification and contrast agent retention strategy for in vivo imaging of gliomas expressing EGFRvIII variants that are best suited to treatment with therapeutic EGFR antibodies.

2240

**Heavy Chain Ferritin siRNA Delivered by Cationic Liposomes Increases Sensitivity of Cancer Cells to Chemotherapeutic Agents**

Xiaoli Liu, A.B. Madhankumar, Becky Slagle-Webb, Jonas M. Sheehan, Nodar Surguladze, and James R. Connor

*Précis:* Findings provide preclinical demonstration of a siRNA-based targeting and delivery approach that can be used to sensitize brain tumor cells to chemotherapy.

2250

**Influence of Affinity and Antigen Internalization on the Uptake and Penetration of Anti-HER2 Antibodies in Solid Tumors**

Stephen I. Rudnick, Jianlong Lou, Calvin C. Shaller, Yong Tang, Andres J.P. Klein-Szanto, Louis M. Weiner, James D. Marks, and Gregory P. Adams

*Précis:* Determining the factors that influence how effectively a therapeutic antibody can penetrate tumors is important for optimizing efficacious effects in cancer treatment.

2260

**NRF2 Blockade Suppresses Colon Tumor Angiogenesis by Inhibiting Hypoxia-Induced Activation of HIF-1 $\alpha$**

Tae-Hyoung Kim, Eu-gene Hur, Su-Jin Kang, Jung-Ae Kim, Dinesh Thapa, You Mie Lee, Sae Kwang Ku, Yunjin Jung, and Mi-Kyoung Kwak

*Précis:* Findings show how blocking the NRF2 system, an important modifier of oxidative stress signaling in cells, could be an effective way to control tumor growth and angiogenesis.

2276

**Suppression of Glucosylceramide Synthase Restores p53-Dependent Apoptosis in Mutant p53 Cancer Cells**

Yong-Yu Liu, Gauri A. Patwardhan, Kaustubh Bhinge, Vineet Gupta, Xin Gu, and S. Michal Jazwinski

*Précis:* This study suggests that wild-type p53 function can be resuscitated in p53 mutant cancer cells by disrupting ceramide glycosylation, suggesting a tractable new strategy to treat p53 mutant cancers.

2286 **MYC Phosphorylation, Activation, and Tumorigenic Potential in Hepatocellular Carcinoma Are Regulated by HMG-CoA Reductase**

Zhongwei Cao, Hua Fan-Minogue, David I. Bellovin, Aleksey Yevtodiyenko, Julia Arzeno, Qiwei Yang, Sanjiv Sam Gambhir, and Dean W. Felsher

*Précis:* The ability of statins to suppress MYC oncogenic activity suggests their evaluation as novel adjuvant modalities in cancer therapy.

2298 **Human CD59 Inhibitor Sensitizes Rituximab-Resistant Lymphoma Cells to Complement-Mediated Cytolysis**

Weiguo Hu, Xiaowen Ge, Tao You, Ting Xu, Jinyan Zhang, Gongxiong Wu, Zhihai Peng, Michael Chorev, Bertal H. Aktas, Jose A. Halperin, Jennifer R. Brown, and Xuebin Qin

*Précis:* Findings rationalize a tractable method to reduce or abolish resistance to rituximab, a monoclonal antibody therapy used widely to treat certain common blood malignancies.

2308 **Overcoming Temozolomide Resistance in Glioblastoma via Dual Inhibition of NAD<sup>+</sup> Biosynthesis and Base Excision Repair**

Eva M. Goellner, Bradford Grimme, Ashley R. Brown, Ying-Chih Lin, Xiao-Hong Wang, Kelsey F. Sugrue, Leah Mitchell, Ram N. Trivedi, Jiang-bo Tang, and Robert W. Sobol

*Précis:* Temozolomide resistance in glioblastoma can be overcome by dual inhibition of NAD<sup>+</sup> biosynthesis and base excision repair.

2318 **Genetic Ablation of PKC Epsilon Inhibits Prostate Cancer Development and Metastasis in Transgenic Mouse Model of Prostate Adenocarcinoma**

Bilal Bin Hafeez, Weixiong Zhong, Jamey Weichert, Nancy E. Dreckschmidt, Mohammad Sarwar Jamal, and Ajit K. Verma

*Précis:* Findings provide first genetic evidence of the role of PKC epsilon in prostate cancer development and metastasis, suggesting novel preventive and therapeutic strategies.

## TUMOR AND STEM CELL BIOLOGY

2328 **DCAMKL-1 Regulates Epithelial–Mesenchymal Transition in Human Pancreatic Cells through a miR-200a–Dependent Mechanism**

Sripathi M. Sureban, Randal May, Stan A. Lightfoot, Aimee B. Hoskins, Megan Lerner, Daniel J. Brackett, Russell G. Postier, Rama Ramanujam, Altaf Mohammed, Chinthalapally V. Rao, James H. Wyche, Shrikant Anant, and Courtney W. Houchen

*Précis:* Findings indicate that a microtubule associated kinase previously identified as a pancreatic stem cell marker can serve as an effective therapeutic target in pancreatic cancer treatment.

2339 **Outgrowth of Drug-Resistant Carcinomas Expressing Markers of Tumor Aggression after Long-term T $\beta$ RI/II Kinase Inhibition with LY2109761**

Erin C. Connolly, Elise F. Saunier, David Quigley, Minh Thu Luu, Angela De Sapio, Byron Hann, Jonathan M. Yingling, and Rosemary J. Akhurst

*Précis:* Long-term pharmacological TGF- $\beta$  receptor inhibition potentiates chemically-induced skin cancer progression and promotes outgrowth of a tumor type with molecular features which contrasts with short-term effects of TGF- $\beta$  inhibition.

2350 **Zyxin Is a Critical Regulator of the Apoptotic HIPK2-p53 Signaling Axis**

Johanna Crone, Carolina Glas, Kathrin Schultheiss, Jutta Moehlenbrink, Eva Krieghoff-Henning, and Thomas G. Hofmann

*Précis:* Findings identify Zyxin as novel regulator of DNA damage-induced cell death through controlling the HIPK2-p53 signaling axis.

2360 **Histone Methyltransferase EZH2 Induces Akt-Dependent Genomic Instability and BRCA1 Inhibition in Breast Cancer**

Maria E. Gonzalez, Matthew L. DuPrie, Heather Krueger, Sofia D. Merajver, Alejandra C. Ventura, Kathy A. Toy, and Celina G. Kleer

*Précis:* Findings offer mechanistic insight into how elevated activity of an important chromatin modifier drives breast cancer progression.

2371 **Activation of the Aryl Hydrocarbon Receptor AhR Promotes Retinoic Acid–Induced Differentiation of Myeloblastic Leukemia Cells by Restricting Expression of the Stem Cell Transcription Factor Oct4**

Rodica P. Bunaciu and Andrew Yen

*Précis: Findings suggest a mechanism-based rationale to enhance the therapeutic effects of retinoic acid, which is used to treat certain cancers, through co-treatment with activators of AhR signaling.*

2381 **miR-218 Suppresses Nasopharyngeal Cancer Progression through Downregulation of Survivin and the SLIT2-ROBO1 Pathway**

Nehad M. Alajez, Michelle Lenarduzzi, Emma Ito, Angela B.Y. Hui, Wei Shi, Jeff Bruce, Shijun Yue, Shao H. Huang, Wei Xu, John Waldron, Brian O'Sullivan, and Fei-Fei Liu

*Précis: Findings suggest a tumor suppressor function for the microRNA mi-218 that integrates control of two important cell survival and migratory mechanisms.*

2392 **MAP Kinase-Interacting Kinase 1 Regulates SMAD2-Dependent TGF- $\beta$  Signaling Pathway in Human Glioblastoma**

Michal Grzmil, Pier Jr Morin, Maria Maddalena Lino, Adrian Merlo, Stephan Frank, Yuhua Wang, Gerald Moncayo, and Brian A. Hemmings

*Précis: Findings identify a pathway that controls translation of key cancer-related RNAs including SMAD2, a key component of the TGF- $\beta$ -signaling pathway, with implications for targeting deadly brain tumors more effectively.*

## LETTER TO THE EDITOR

2403 **Essential Requirement for PP2A Inhibition by the Oncogenic Receptor c-KIT Suggests PP2A Reactivation as a Strategy to Treat c-KIT<sup>+</sup> Cancers — Letter**

Amaury G. Dumont, David G. Reynoso, and Jonathan C. Trent

2404 **Essential Requirement for PP2A Inhibition by the Oncogenic Receptor c-KIT Suggests PP2A Reactivation as a Strategy to Treat c-KIT<sup>+</sup> Cancers — Response**

Kathryn G. Roberts, Fiona McDougall, and Nicole M. Verrills

## CORRECTIONS

2405 **Correction: Glioblastoma Recurrence after Cediranib Therapy in Patients: Lack of "Rebound" Revascularization as Mode of Escape**

2406 **Correction: Phospholipase D Meets Wnt Signaling: A New Target for Cancer Therapy**

2407 **Correction: Breast Cancer Stem Cells Are Regulated by Mesenchymal Stem Cells through Cytokine Networks**

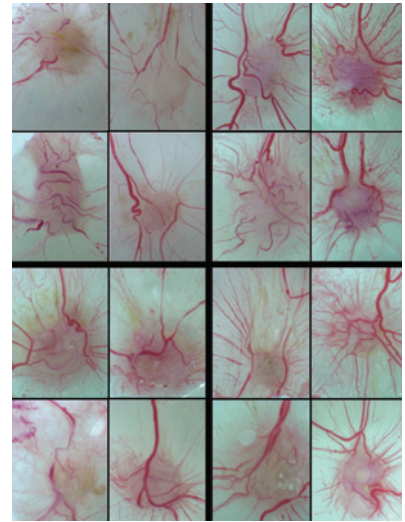
2408 **Correction: Online Publication Dates for Cancer Research January 15, 2011 Articles**



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## ABOUT THE COVER

Diminished angiogenesis in NRF2 knockdown colon cancer cells. Matrigel-loaded colon cancer cells (HCT116 and HT29) with stable expression of interfering RNA of NRF2 (NRF2i) were inoculated on the CAM of 10-day-old chicken embryos and the branch points of formed blood vessels were counted as a marker of angiogenesis. NRF2 knockdown cancer cells developed fewer blood vessels; the numbers of vessel branch points in HCT-NRF2i and HT-NRF2i cells reduced to 73% and 58% of those in the control cells (SCi). The data represent means  $\pm$  SD of at least 8 embryos. For details, see the article by Kim and colleagues on page 2260 of this issue.



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