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Cancer Research

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BREAKING ADVANCES

- 4053 | **Highlights from Recent Cancer Literature**

REVIEW

- 4055 | **Heterogeneity Maintenance in Glioblastoma: A Social Network**
Rudy Bonavia, Maria-del-Mar Inda, Webster K. Cavenee, and Frank B. Furnari

PRIORITY REPORTS

- 4061 | **PIK3RI (p85 α) Is Somatically Mutated at High Frequency in Primary Endometrial Cancer**
Mary E. Urlick, Meghan L. Rudd, Andrew K. Godwin, Dennis Sgroi, Maria Merino, and Daphne W. Bell

Précis: This study reveals a new mode of PI3K alteration in human endometrial cancer and suggests that the mutational status of the PI3K p85 α subunit might predict clinical outcomes to inhibitors of the PI3K pathway.

- 4068 | **Formation of the eIF4F Translation-Initiation Complex Determines Sensitivity to Anticancer Drugs Targeting the EGFR and HER2 Receptors**
Pierre Zindy, Yann Bergé, Ben Allal, Thomas Filleron, Sandra Pierredon, Anne Cammas, Samantha Beck, Loubna Mhamdi, Li Fan, Gilles Favre, Jean-Pierre Delord, Henri Roché, Florence Dalenc, Magali Lacroix-Triki, and Stéphan Vagner

Précis: The translation initiation factor eIF4E may serve as a marker for therapeutic resistance to anti-HER2 therapies, where combining inhibitors of PI3K/Akt/mTOR may help relieve resistance.

MICROENVIRONMENT AND IMMUNOLOGY

- 4074 | **mTOR Kinase Inhibitor AZD8055 Enhances the Immunotherapeutic Activity of an Agonist CD40 Antibody in Cancer Treatment**
Qun Jiang, Jonathan M. Weiss, Timothy Back, Tim Chan, John R. Ortaldo, Sylvie Guichard, and Robert H. Wiltout

Précis: Findings suggest that the most effective combinations of mTOR inhibitors in clinical trials might be as adjuvants in cancer immunochemotherapy.

- 4085 | **Targeting Hyaluronidase for Cancer Therapy: Antitumor Activity of Sulfated Hyaluronic Acid in Prostate Cancer Cells**
Anaid Benitez, Travis J. Yates, Luis E. Lopez, Wolfgang H. Cerwinka, Ashraf Bakkar, and Vinata B. Lokeshwar

Précis: Findings offer mechanistic insights into the tumor-associated hyaluronidase system along with a preclinical proof-of-concept of the safety and efficacy of targeting this system to control prostate cancer growth and progression.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4096 | **A Novel Function of Junctional Adhesion Molecule-C in Mediating Melanoma Cell Metastasis**
Harald F. Langer, Valeria V. Orlova, Changping Xie, Sunil Kaul, Darius Schneider, Anke S. Lonsdorf, Manuela Fahrleitner, Eun Young Choi, Vanessa Dutoit, Manuela Pellegrini, Sylvia Grossklaus, Peter P. Nawroth, Gustavo Baretton, Sentot Santoso, Sam T. Hwang, Bernd Arnold, and Triantafyllos Chavakis

Précis: Endothelial-specific ablation of a specific cell adhesion function is sufficient to decrease metastasis of melanoma to the lung, suggesting strategies to prevent this type of progression based on disruption of melanoma cell binding to endothelia.

4106

Nonredundant Functions for Akt Isoforms in Astrocyte Growth and Gliomagenesis in an Orthotopic Transplantation Model

Raelene Endersby, Xiaoyan Zhu, Nissim Hay, David W. Ellison, and Suzanne J. Baker

Précis: Findings elucidate the unique functions of Akt isoforms 1-3 in the growth regulation, transformation, and tumorigenesis of gliomas.

4117

Common and Overlapping Oncogenic Pathways Contribute to the Evolution of Acute Myeloid Leukemias

Brynn T. Kvinlaug, Wai-In Chan, Lars Bullinger, Mukundhan Ramaswami, Christopher Sears, Donna Foster, Stanley E. Lazic, Rachel Okabe, Axel Benner, Benjamin H. Lee, Inusha De Silva, Peter J.M. Valk, Ruud Delwel, Scott A. Armstrong, Hartmut Döhner, D. Gary Gilliland, and Brian J.P. Huntly

Précis: Common programs of self-renewal and transformation act downstream of diverse oncogenes in acute myeloid leukemia, suggesting that mechanistically common therapeutic approaches may be possible regardless of the identity of the driver oncogene involved.

4130

Quantitative, Noninvasive Imaging of Radiation-Induced DNA Double-Strand Breaks *In Vivo*

Wenrong Li, Fang Li, Qian Huang, Jingping Shen, Frank Wolf, Yujun He, Xinjian Liu, Y. Angela Hu, Joel S. Bedford, and Chuan-Yuan Li

Précis: This study establishes a novel approach to visualize and quantify DNA double strand breaks in live cells and tissues.

4138

Sirtuin 1 Is Upregulated in a Subset of Hepatocellular Carcinomas where It Is Essential for Telomere Maintenance and Tumor Cell Growth

Juan Chen, Bin Zhang, Nathalie Wong, Anthony W.I. Lo, Ka-Fai To, Anthony W.H. Chan, Margaret H.L. Ng, Cecilia Y.S. Ho, Suk-Hang Cheng, Paul B.S. Lai, Jun Yu, Ho-Keung Ng, Ming-Tat Ling, Ai-Long Huang, Xue-Fei Cai, and Ben C.B. Ko

Précis: Findings offer a preclinical proof-of-concept for the clinical exploration of SIRT1 inhibitors for liver cancer treatment.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4150

Intrinsic Anticancer Drug Resistance of Malignant Melanoma Cells Is Abrogated by IFN- β and Valproic Acid

Wynand P. Roos, Eva Jöst, Christina Belohlavek, Georg Nagel, Gerhard Fritz, and Bernd Kaina

Précis: Resistance arising to the front line chemotherapy for melanoma can be relieved by cotreatment with interferon and an HDAC inhibitor which reactivates effective pathways of cancer cell death.

4161

Identification of Aldo-Keto Reductase AKR1B10 as a Selective Target for Modification and Inhibition by Prostaglandin A₁: Implications for Antitumoral Activity

Beatriz Díez-Dacal, Javier Gayarre, Severine Gharbi, John F. Timms, Claire Coderch, Federico Gago, and Dolores Pérez-Sala

Précis: The anti-inflammatory compound prostaglandin A₁, which selectively inhibits an aldo-keto-reductase, could be exploited to relieve chemoresistance to doxorubicin and perhaps other cancer drugs.

4172

Antihelminth Compound Niclosamide Downregulates Wnt Signaling and Elicits Antitumor Responses in Tumors with Activating APC Mutations

Takuya Osada, Minyong Chen, Xiao Yi Yang, Ivan Spasojevic, Jeffrey B. Vandeusen, David Hsu, Bryan M. Clary, Timothy M. Clay, Wei Chen, Michael A. Morse, and H. Kim Lyerly

Précis: Important preclinical findings suggest that the well-tolerated antihelminth compound niclosamide might be repositioned for clinical treatment of many colorectal cancers.

4183

Enhancement of Cancer Vaccine Therapy by Systemic Delivery of a Tumor-Targeting *Salmonella*-Based STAT3 shRNA Suppresses the Growth of Established Melanoma Tumors

Edwin R. Manuel, Céline A. Blache, Rebecca Paquette, Teodora I. Kaltcheva, Hidenobu Ishizaki, Joshua D.I. Ellenhorn, Michael Hensel, Leonid Metelitsa, and Don J. Diamond

Précis: Correcting a tolerogenic mechanism of immune escape established by cancer cells could greatly enhance the therapeutic efficacy of a bacterial-expressed survivin vaccine in bulky established tumors.

4192

Inhibition of Histone Lysine Methylation Enhances Cancer–Testis Antigen Expression in Lung Cancer Cells: Implications for Adoptive Immunotherapy of Cancer

Mahadev Rao, Nachimuthu Chinnasamy, Julie A. Hong, Yuwei Zhang, Mary Zhang, Sichuan Xi, Fang Liu, Victor E. Marquez, Richard A. Morgan, and David S. Schrupp

Précis: Data presented in this article are the first to demonstrate that modulation of histone lysine methylation enhances the derepression of CT-X genes by DNA demethylating agents. Combining inhibitors of histone lysine methylation such as DZNep with DNA demethylating agents may be a novel strategy to augment cancer-testis antigen expression for cancer immunotherapy.

4205

Targeting the p53 Pathway in Retinoblastoma with Subconjunctival Nutlin-3a

Rachel C. Brennan, Sara Federico, Cori Bradley, Jiakun Zhang, Jacqueline Flores-Otero, Matthew Wilson, Clinton Stewart, Fangyi Zhu, Kip Guy, and Michael A. Dyer

Précis: A locally delivered p53-activating therapy shows both efficacy and reduced toxicity for retinoblastoma treatment compared to current systemic treatments.

4214

Glycolytic Phenotype and AMP Kinase Modify the Pathologic Response of Tumor Xenografts to VEGF Neutralization

Giorgia Nardo, Elena Favaro, Matteo Curtarello, Lidia Moserle, Elisabetta Zulato, Luca Persano, Elisabetta Rossi, Giovanni Esposito, Marika Crescenzi, Oriol Casanovas, Ulrike Sattler, Wolfgang Mueller-Klieser, Barbara Biesalski, Oliver Thews, Rossella Canese, Egidio Iorio, Paola Zanovello, Alberto Amadori, and Stefano Indraccolo

Précis: This study identifies new metabolic and genetic markers useful to predict the therapeutic response of tumors to VEGF neutralization.

4236

Delineation of a Cellular Hierarchy in Lung Cancer Reveals an Oncofetal Antigen Expressed on Tumor-Initiating Cells

Marc Damelin, Kenneth G. Geles, Maximillian T. Follettie, Ping Yuan, Michelle Baxter, Jonathon Golas, John F. DiJoseph, Maha Karnoub, Shuguang Huang, Veronica Diesl, Carmen Behrens, Sung E. Choe, Carol Rios, Janet Gruzaz, Latha Sridharan, Maureen Dougher, Arthur Kunz, Philip R. Hamann, Deborah Evans, Douglas Armellino, Kiran Khandke, Kimberly Marquette, Lioudmila Tchistiakova, Erwin R. Boghaert, Robert T. Abraham, Ignacio I. Wistuba, and Bin-Bing S. Zhou

Précis: This study identifies an oncofetal antigen expressed on undifferentiated lung cancer–initiating cells and shows that its targeting can elicit sustained lung tumor regression.

4247

IFN- γ Inhibits Gastric Carcinogenesis by Inducing Epithelial Cell Autophagy and T-Cell Apoptosis

Shui Ping Tu, Michael Quante, Govind Bhagat, Shigeo Takaishi, Guanglin Cui, Xiang Dong Yang, Sureshkumar Muthuplani, Wataru Shibata, James G. Fox, D. Mark Pritchard, and Timothy C. Wang

Précis: IFN- γ is a proinflammatory cytokine that might be expected to promote carcinogenesis in the setting of gastric inflammation, where bacterial infections have a major role, but instead its dominant action is tumor suppressive, consistent with this role defined in other solid tumor settings.

4260

LIN28B Promotes Colon Cancer Progression and Metastasis

Catrina E. King, Miriam Cuatrecasas, Antoni Castells, Antonia R. Sepulveda, Ju-Seog Lee, and Anil K. Rustgi

Précis: An isoform of the RNA binding protein Lin28 which mediates pluripotent stem cell programming is implicated in this study to promote colon tumor pathogenesis, especially metastasis.

4269

Nuclear ErbB2 Enhances Translation and Cell Growth by Activating Transcription of Ribosomal RNA Genes

Long-Yuan Li, Hsiuyi Chen, Yi-Hsien Hsieh, Ying-Nai Wang, Hsiao-Ju Chu, Ya-Huey Chen, Hui-Yu Chen, Peng-Ju Chien, Haou-Tzong Ma, Ho-Cheng Tsai, Chien-Chen Lai, Yuh-Pyng Sher, Huang-Chun Lien, Chang-Hai Tsai, and Mien-Chie Hung

Précis: Findings elucidate functions of a nuclear localized form of ErbB2/HER2 that may contribute to cancer growth and progression.

TUMOR AND STEM CELL BIOLOGY

4226

MMSET Is Highly Expressed and Associated with Aggressiveness in Neuroblastoma

Heidi Rye Hudlebusch, Julie Skotte, Eric Santoni-Rugiu, Zarah Glad Zimling, Michael James Lees, Ronald Simon, Guido Sauter, Rossella Rota, Maria Antonietta De Ioris, Micaela Quarto, Jens Vilstrup Johansen, Mette Jørgensen, Catherine Rechnitzer, Lisa Leth Maroun, Henrik Schröder, Bodil Laub Petersen, and Kristian Helin

Précis: A histone methyltransferase that has been implicated in an important pathway of DNA damage repair may offer a therapeutic target in aggressive neuroblastomas with poor prognosis.

4280 **Protein Kinase D3 Sensitizes RAF Inhibitor RAF265 in Melanoma Cells by Preventing Reactivation of MAPK Signaling**

Jian Chen, Qiong Shen, Mark Labow, and L. Alex Gaither

Précis: A protein kinase little studied in cancer is implicated as a potentially important mediator of resistance to RAF or MEK inhibitors that is being widely experienced in clinical trials of these drugs.

4292 **FoxM1 in Tumorigenicity of the Neuroblastoma Cells and Renewal of the Neural Progenitors**

Zebin Wang, Hyun Jung Park, Janai R. Carr, Yi-ju Chen, Yu Zheng, Jing li, Angela L. Tyner, Robert H. Costa, Srilata Bagchi, and Pradip Raychaudhuri

Précis: Findings identify an important driver of aggressive neuroblastoma cells which acts by sustaining maintenance of an undifferentiated state.

4303 **MST1 Is a Multifunctional Caspase-Independent Inhibitor of Androgenic Signaling**

Bekir Cinar, Filiz Kisaayak Collak, Delia Lopez, Seckin Akgul, Nishit K. Mukhopadhyay, Murat Kilicarslan, Daniel G. Gioeli, and Michael R. Freeman

Précis: A regulator of the Hippo tumor suppressor pathway is found to be an inhibitor of androgen receptor signaling and a suppressor of prostate cell growth.

4314 **HOXC9 Links Cell-Cycle Exit and Neuronal Differentiation and Is a Prognostic Marker in Neuroblastoma**

Ling Mao, Jane Ding, Yunhong Zha, Liqun Yang, Brian A. McCarthy, William King, Hongjuan Cui, and Han-Fei Ding

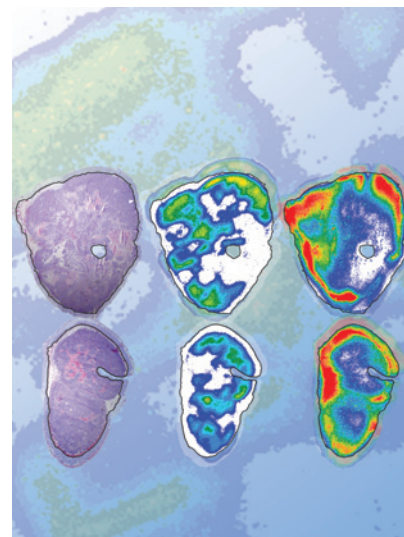
Précis: Findings link a developmentally important gene to the control of neuroblastoma cell proliferation and differentiation, providing an attractive therapeutic target for neuroblastoma.

CORRECTION

4325 **Correction: Online Publication Dates for Cancer Research May 1, 2011 Articles**

ABOUT THE COVER

Metabolic bioluminescence imaging. Induced metabolic bioluminescence imaging allows for quantification and structure-associated assessment of metabolites from cryopreserved samples. This technique was used to measure ATP and glucose concentrations in sequential cryosections from human ovarian tumor cells (IGROV-1) xenografted in nude mice. Hematoxylin & eosin stainings as well as ATP levels were used to discriminate between regions of vital and nonvital tumor and adjacent normal tissue, such as stroma. Color-coded concentrations ($\mu\text{mol/g}$) of both metabolites revealed a reduction in ATP and glucose levels in tumors treated with the anti-VEGF mAb A4.6.1. For details, see the article by Nardo and colleagues on page 4214 of this issue.



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