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 PIK3R1 (p85α) Is Somatically Mutated at High Frequency in Primary Endometrial Cancer
Mary E. Urick, 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 p85α 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 Pierreddon, 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.

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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 immunotherapy.

4085 Targeting Hyaluronidase for Cancer Therapy: Antitumor Activity of Sulfated Hyaluronic Acid in Prostate Cancer Cells
Anaïd Benítez, 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.
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.

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.

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.

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.L. 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.

Intrinsic Anticancer Drug Resistance of Malignant Melanoma Cells Is Abrogated by IFN-β and Valproic Acid
Wynand P. Roos, Eva Jost, Christina Belohlawek, Georg Nagel, Gerhard Fritz, and Bernrd 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.

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 Gharbhi, 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.

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. Vandeuersen, 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.

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, Celine 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.
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. Schrump

Precis: 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.

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 Gyu, and Michael A. Dyer

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

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 Crescenzii, Oriol Casanovas, Ulrike Sattler, Wolfgang Mueller-Klieser, Barbara Riesalski, Oliver Thews, Rossella Canese, Egidio Iorio, Paola Zanovello, Alberto Amadori, and Stefano Indraccolo

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

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

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

IFN-γ Inhibits Gastric Carcinogenesis by Inducing Epithelial Cell Autophagy and T-Cell Apoptosis
Shui Ping Tu, Michael Quante, Govind Bhagat, Shigeo Takaini, Guanglin Cui, Xiang Dong Yang, Sureshkumar Muthuplani, Wataru Shibata, James G. Fox, D. Mark Pritchard, and Timothy C. Wang

Precis: 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.

LIN28B Promotes Colon Cancer Progression and Metastasis
Catrina E. King, Miriam Cuatrecasas, Antonia Castells, Antonia R. Sepulveda, Ju-Seog Lee, and Anil K. Rustgi

Precis: LIN28B is an oncogene that is highly expressed in non-small-cell lung cancer, and its expression levels are associated with tumor aggressiveness. This study provides evidence that LIN28B expression is required for cancer cell survival and metastasis, and identifies potential therapeutic targets.

Nuclear ErbB2 Enhances Translation and Cell Growth by Activating Transcription of Ribosomal RNA Genes
Long-Yuan Li, Hsiu-I Chen, Yi-Hsien Hsieh, Ying-Nai Wang, Hsiao-Ju Chu, Ya-Huey Chen, Hui-Yu Chen, Peng-Ju Chien, Haow-Tzong Ma, Ho-Cheng Tsai, Chien-Chen Lai, Yuh-Ping Sherr, Huang-Chun Lin, Chang-Hai Tsai, and Mien-Chie Hung

Precis: This study identifies a novel role for nuclear ErbB2 in enhancing translation and cell growth by activating transcription of ribosomal RNA genes. These findings suggest that nuclear ErbB2 may be a therapeutic target for cancer treatment.

MMSET Is Highly Expressed and Associated with Aggressiveness in Neuroblastoma
Heidi Bye Hulebusch, Julie Skotte, Eric Santoni-Rugiu, Zarah Glad Zimling, Michael James Lees, Ronald Simon, Guido Sauter, Rossella Rota, Maria Antonietta De Ioris, Micaela Quarto, Jens Vistrup Johansen, Mette Jørgensen, Catherine Rechnitzer, Lisa Leth Maroun, Henrik Schroder, Bodil Laub Petersen, and Kristian Helin

Precis: 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.
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.

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.

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.

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 theranostic target for neuroblastoma.

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 (µmol/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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