BREAKING ADVANCES

Highlights from Recent Cancer Literature

REVIEWS

MDM2–p53 Pathway in Hepatocellular Carcinoma
Xuan Meng, Derek A. Franklin, Jiahong Dong, and Yanping Zhang

Trafficking of T Cells into Tumors
Clare Y. Slaney, Michael H. Kershaw, and Phillip K. Darcy

When Will Resistance Be Futile?
Katherine L.B. Borden

PERSPECTIVES

Unique Molecular Landscapes in Cancer: Implications for Individualized, Curated Drug Combinations
Jennifer Wheler, J. Jack Lee, and Razelle Kurzrock

Mechanisms of Hypoxia-Mediated Immune Escape in Cancer
Ivraym B. Barsoum, Madhuri Koti, D. Robert Siemens, and Charles H. Graham

PRIORITY REPORTS

DUSP1 Phosphatase Regulates the Proinflammatory Milieu in Head and Neck Squamous Cell Carcinoma
Xiaoyi Zhang, J. Madison Hyer, Hong Yu, Nisha J. D’Silva, and Keith L. Kirkwood

AKT1 and MYC Induce Distinctive Metabolic Fingerprints in Human Prostate Cancer
Carmen Priolo, Saumyadipta Pyne, Joshua Rose, Erzsébet Ravasz Regan, Giorgia Zadra, Cornelia Photopoulou, Stefano Cacciatore, Denise Schultz, Natalia Scaglia, Jonathan McDunn, Angelo M. De Marzo, and Massimo Loda

CLINICAL STUDIES

Chemoradiotherapy-Induced Upregulation of PD-1 Antagonizes Immunity to HPV-Related Oropharyngeal Cancer

Mechanisms of Hypoxia-Mediated Immune Escape in Cancer
Ivraym B. Barsoum, Madhuri Koti, D. Robert Siemens, and Charles H. Graham

INTEGRATED SYSTEMS AND TECHNOLOGIES

Adaptive Responses to Dasatinib-Treated Lung Squamous Cell Cancer Cells Harboring DDR2 Mutations
Yun Bai, Jae-Young Kim, January M. Watters, Bin Fang, Fumi Kinose, Lanxi Song, John M. Koomen, Jamie K. Teer, Kate Fisher, Yan Ann Chen, Uwe Rix, and Eric B. Haura

Bioengineered Implantable Scaffolds as a Tool to Study Stromal-Derived Factors in Metastatic Cancer Models
Francesca Bersani, Jungwoo Lee, Min Yu, Robert Morris, Rushil Desai, Sridhar Ramaswamy, Mehmet Toner, Daniel A. Haber, and Biju Parekkadan
MICROENVIRONMENT AND IMMUNOLOGY

7239 Adenosine A2A Receptors Intrinsically Regulate CD8 T Cells in the Tumor Microenvironment
Caglar Cekic and Joel Linden
Précis: Targeted deletion of the adenosine A2A receptor, an important inhibitory receptor on T cells, paradoxically enhances the growth rate of solid tumors by impairing tumor-associated T-cell maintenance and effector/memory differentiation, with implications for clinical testing of A2A receptor antagonists to enhance cancer immunotherapy.

7250 Myeloid Expression of Adenosine A2A Receptor Suppresses T and NK Cell Responses in the Solid Tumor Microenvironment
Caglar Cekic, Yuan-Ji Day, Duygu Sag, and Joel Linden
Précis: This study provides a mechanistic rationale to reposition inhibitors of a certain class of cell surface adenosine receptors to block an important pathway of immune escape that is commonly activated in solid tumors, with immediate implications for clinical evaluation.

7260 Cellular Factors Promoting Resistance to Effective Treatment of Glioma with Oncolytic Myxoma Virus
Franz J. Zemp, Brienne A. McKenzie, Xueqing Lun, Karlyne M. Reilly, Grant McFadden, V. Wee Yong, and Peter A. Forsyth
Précis: This study identifies specific leukocyte classes that are responsible for conferring resistance to oncolytic viral therapy in a syngeneic orthotopic model of glioma, demonstrating the importance of immunocompetency in preclinical models of this type of therapy and suggesting immune-based strategies to improve its efficacy.

7274 Myeloid IKKβ Promotes Antitumor Immunity by Modulating CCL11 and the Innate Immune Response
Jinming Yang, Oriana E. Hawkings, Whitney Barham, Pavlo Gilchuk, Mark Boothby, Gregory D. Ayers, Sebastian Joyce, Michael Karin, Fiona E. Yull, and Ann Richmond
Précis: The importance of maintaining NF-κB in myeloid cells to optimize the host antitumor response is illustrated in melanoma tumor models, illuminating mechanisms relevant to therapeutics affecting this pathway.

7285 RAGE Expression in Tumor-Associated Macrophages Promotes Angiogenesis in Glioma
Xuebo Chen, Leyeing Zhang, Ian Y. Zhang, Junling Liang, Huaqing Wang, Mao Ouyang, Shihua Wu, Anna Carolina Carvalho da Fonseca, LiHong Weng, Yasuhiko Yamamoto, Hiroshi Yamamoto, Rama Natarajan, and Behnam Badie
Précis: Signaling by a proinflammatory receptor in glioma-associated microglial and macrophages drives angiogenesis in the tumor microenvironment, reinforcing interest in this receptor as a therapeutic target in glioma.

7298 Natural Killer Cells Are Essential for the Ability of BRAF Inhibitors to Control BRAFV600E-Mutant Metastatic Melanoma
Lucas Ferrari de Andrade, Shin F. Ngio, Kimberley Stannard, Sylvie Rusakiewicz, Murugan Kalimutho, Kum Kum Khanna, Siok-Keen Tey, Kazuyoshi Takeda, Laurence Zitvogel, Ludovic Martinet, and Mark J. Smyth
Précis: This seminal study shows that, like imatinib, inhibitors of mutant BRAF must engage the immune system to elicit their profound antitumor effects, offering further encouragement to the concept that immunotherapeutic responses form the foundation of any effective cancer therapy.

7309 ISG15 Is a Critical Microenvironmental Factor for Pancreatic Cancer Stem Cells
Bruno Sainz Jr, Beatriz Martín, Marianthi Tatari, Christopher Heeschen, and Susana Guerra
Précis: This study highlights the role of a previously unrecognized support factor in the tumor microenvironment for cancer stem cells in pancreatic cancer, with implications for tractable new strategies to attack this deadly disease.

MOLECULAR AND CELLULAR PATHOBIOLOGY

7321 Astrocyte Elevated Gene-1 Interacts with Akt Isoform 2 to Control Glioma Growth, Survival, and Pathogenesis
Précis: These results illuminate a central mechanism of glioma progression and provide a rationale to target this mechanism as a novel treatment in this setting.
H3K9 Histone Methyltransferase, KMT1E/SETDB1, Cooperates with the SMAD2/3 Pathway to Suppress Lung Cancer Metastasis


Précis: These findings provide important mechanistic insights into how TGFβ promotes lung cancer metastasis, with possible implications for understanding how to target this broadly important pathway in cancer progression.

Myostatin Gene Inactivation Prevents Skeletal Muscle Wasting in Cancer

Yann S. Gallot, Anne-Cécile Durieux, Josiane Castells, Marine M. Desgeorges, Barbara Vernus, Léa Plantureux, Didier Rémond, Vanessa E. Jahnke, Etienne Lefai, Dominique Dardevet, Georges Nemoz, Laurence Schaeffer, Anne Bonnieu, and Damien G. Freyssenet

Précis: Striking preclinical results suggest that targeting a TGFβ-related protein that inhibits muscle differentiation may not only impede muscle wasting (cachexia) in patients with advanced cancer, but also limit malignant growth and increase survival.

Homeoprotein Six2 Promotes Breast Cancer Metastasis via Transcriptional and Epigenetic Control of E-Cadherin Expression

Chu-An Wang, David Drasin, Catherine Pham, Paul Jedlicka, Vadyom Zaberezhnyy, Michelle Gurney, Howard Li, Raphael Nemenoff, James C. Costello, Aik-Choon Tan, and Heide L. Ford

Précis: A transcription factor that regulates normal kidney development is found to be switched on in aggressive breast cancers, where it drives metastasis in part by downregulating E-cadherin.

Mig-6 Suppresses Endometrial Cancer Associated with Pten Deficiency and ERK Activation

Tae Hoon Kim, Jung-Yoon Yoo, Hong Im Kim, Jenifer Gilbert, Bon Jeong Ku, Jane Li, Gordon B. Mills, Russell R. Broaddus, John P. Lydon, Jeong Mook Lim, Ho-Geun Yoon, and Jae-Wook Jeong

Précis: These findings provide a mechanistic rationale for the evaluation of ERK1/2 inhibitors as a therapeutic treatment in human endometrial cancer.

Combined Genome and Transcriptome Analysis of Single Disseminated Cancer Cells from Bone Marrow of Prostate Cancer Patients Reveals Unexpected Transcriptomes

Miodrag Gužvić, Bernhard Braun, Roman Ganzer, Maximilian Burger, Michael Nerlich, Sebastian Winkler, Melanie Werner-Klein, Zbigniew T. Czyż, Bernhard Polzer, and Christoph A. Klein

Précis: Provocative indications of unexpected transcriptome plasticity in disseminated cancer cells challenge transcriptional criteria to identify these cells in blood as early harbingers of metastatic disease.

PELP1 Overexpression in the Mouse Mammary Gland Results in the Development of Hyperplasia and Carcinoma

Valerie Cortez, Cathy Samaya, Andrea Zamora, Lizatte Martínez, Rajeshwar R. Tekmal, and Ratna K. Vadlamudi

Précis: A transcriptional coactivator of estrogen receptor target genes acts as an oncogene in breast tumorigenesis, with possible implications in understanding the etiology and pathogenesis of estrogen receptor–positive breast cancers.

Differentiation and Loss of Malignant Character of Spontaneous Pulmonary Metastases in Patient-Derived Breast Cancer Models

Jessica Bockhorn, Alex Prat, Ya-Fang Chang, Xia Liu, Simo Huang, Meng Shang, Chika Nwachukwu, Maria J. Gomez-Vega, J. Chuck Harrell, Olufunmilayo I. Olopade, Charles M. Perou, and Huiping Liu

Précis: microRNAs contribute to the phenotypic regulation of homed metastatic cells, loss of the mesenchymal state and malignancy but gain of luminal epithelial differentiation, compared with the parental tumor cells in the primary site.

Phosphoinositide Protein Kinase PDPK1 Is a Crucial Cell Signaling Mediator in Multiple Myeloma

Yoshiaki Chinen, Junya Kuroda, Yuji Shimura, Hisao Nagoshi, Miki Kiyota, Mio Yamamoto-Sugitani, Shinsuke Mizutani, Natsumi Sakamoto, Masaki Ri, Eri Kawata, Tsutomu Kobayashi, Yosuke Matsumoto, Shigeo Horii, Shinsuke Iida, and Masafumi Taniwaki

Précis: These findings provide a preclinical rationale for the development of inhibitors of a phosphotidylinositol kinase as a generally effective treatment for deadly multiple myelomas, regardless of their cytogenetic and molecular profiles.
**Oncogenic KRAS Confers Chemoresistance by Upregulating NRF2**
Shasha Tao, Shue Wang, Seyed Javad Moghaddam, Alkensg Ooi, Eli Chapman, Pak K. Wong, and Donna D. Zhang

Precis: Although strategies to attack KRAS in tumors have remained elusive, despite decades of research, this study shows how it may be possible to ablate the most damaging effect of KRAS mutations in conferring therapeutic resistance, an exciting prospect with immediate clinical implications.

**PREVENTION AND EPIDEMIOLOGY**

**Plasma Choline Metabolites and Colorectal Cancer Risk in the Women’s Health Initiative Observational Study**
Sajin Bae, Cornelia M. Ulrich, Marian L. Neuhausen, Olga Malyshева, Lynn B. Bailey, Liren Xiao, Elissa C. Brown, Kara L. Cushing-Haugen, Yingye Zheng, Ting-Yuan David Cheng, Joshua W. Miller, Ralph Green, Dorothy S. Lane, Shirley A.A. Beresford, and Marie A. Caudill

Precis: These results suggest that alterations in gut choline metabolism may drive a higher risk of colon cancer, possibly connected to changes in the gut microbiome.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**Endothelin A Receptor/β-Arrestin Signaling to the Wnt Pathway Renders Ovarian Cancer Cells Resistant to Chemotherapy**
Laura Rosano, Roberta Cianfrocca, Piera Tocci, Francesca Spinella, Valeriana Di Castro, Valentina Caprara, Elisa Semprucci, Gabriella Ferrandina, Pier Giorgio Natali, and Anna Bagnato

Precis: By linking endothelin signaling to chemoresistance in ovarian cancer, this study suggests new strategies to improve treatment outcomes in this disease setting.

**Quantitative In Vivo Immunohistochemistry of Epidermal Growth Factor Receptor Using a Receptor Concentration Imaging Approach**
Kimberley S. Samkoe, Kenneth M. Tichauer, Jason R. Gunn, Wendy A. Wells, Tayyaba Hasan, and Brian W. Pogue

Precis: This study reports a robust in vivo measure of receptor expression that is equivalent to ex vivo immunostaining, with implications for use in noninvasive monitoring of therapy or therapeutic guidance during surgery.

**Syntheses and Discovery of a Novel Class of Cinnamic Hydroxamates as Histone Deacetylase Inhibitors by Multimodality Molecular Imaging in Living Subjects**

Precis: This study offers a preclinical proof of concept for the selectivity and anticancer efficacy of a novel hydroxamate-based class of small molecule HDAC inhibitors.

**FL118 Induces p53-Dependent Senescence in Colorectal Cancer Cells by Promoting Degradation of MdmX**
Xiang Ling, Chao Xu, Chuandong Fan, Kai Zhong, Fengbei Li, and Xinjiang Wang

Precis: The study defines a mechanism of action for an experimental camptothecin-like agent, which exhibits a superior preclinical antitumor activity related to its ability to stimulate p53-dependent senescence.

**Mitochondrial MKP1 Is a Target for Therapy-Resistant HER2-Positive Breast Cancer Cells**
Demet Candas, Chung-Ling Lu, Frank Y.S. Chuang, Colleen Sweeney, Alexander D. Borovsky, and Jian Jian Li

Precis: This study identifies a potential mechanism of resistance in breast tumors and reveals the MAPK phosphatase MKP1 as a therapeutic target to sensitize resistant tumors and improve the efficacy of anticancer therapy.

**Harnessing the Fcγ Receptor for Potent and Selective Cytotoxic Therapy of Chronic Lymphocytic Leukemia**
Berengere Vire, Martin Skarzynski, Joshua D. Thomas, Christopher G. Nelson, Alexandre David, Georg Aue, Terrence R. Burke Jr, Christoph Rader, and Adrian Wiestner

Precis: These findings offer a basis to exploit an intrinsic feature of chronic lymphocytic leukemia to improve the selective delivery and efficacy of cytotoxic drugs to eradicate this cancer.

**Serine Deprivation Enhances Antineoplastic Activity of Biguanides**
Simon-Pierre Gravel, Laura Hulea, Nader Toban, Elena Birman, Marie-José Blouin, Mahvash Zakikhani, Yunhua Zhao, Ivan Topisirovic, Julie St-Pierre, and Michael Pollak

Precis: While more than 100 clinical trials are under way to evaluate metformin and other biguanides in cancer treatment, careful attention to nutritional and metabolic factors that influence antineoplastic activity is needed to optimize clinical trial designs.
Identification of ATR–Chk1 Pathway Inhibitors That Selectively Target p53-Deficient Cells without Directly Suppressing ATR Catalytic Activity
Masaoki Kawasumi, James E. Bradner, Nicola Tolliday, Renee Thibodeau, Heather Sloan, Kay M. Brummond, and Paul Nghiem

Précis: These results highlight a set of new molecular probes that act in a mechanistically novel manner to inhibit the ATR-Chk1 checkpoint pathway and improve the therapeutic responses produced by DNA damaging drugs.

TARGETING THE c-MET/FZD8 SIGNALLING AXIS ELIMINATES PATIENT-DERIVED CANCER STEM–LIKE CELLS IN HEAD AND NECK SQUAMOUS CARCINOMAS
Shuyang Sun, Suling Liu, Sheng Zhong Duan, Lei Zhang, Henghua Zhou, Yongjie Hu, Xianghui Zhou, Chaoji Shi, Rong Zhou, and Zhuyuan Zhang

Précis: These results offer a preclinical proof of concept to target the MET receptor kinase to improve the treatment of head and neck squamous cancers, with immediate clinical implications for repositioning MET inhibitors in human trials.

DOWNREGULATED miR329 AND miR410 PROMOTE THE PROLIFERATION AND INVASION OF ORAL SQUAMOUS CELL CARCINOMA BY TARGETING Wnt-7b
Shine-Gwo Shiah, Jenn-Ren Hsiao, Wei-Min Chang, Ya-Wen Chen, Ying-Tai Jin, Tung-Yiu Wong, Jehn-Shyun Huang, Sen-Tien Tsai, Yuan-Ming Hsu, Sung-Tau Chou, Yi-Chen Yen, Shih Sheng Jiang, Yi-Shing Shieh, I-Shou Chang, Michael Hsiao, and Jang-Yang Chang

Précis: These findings offer insight into the carcinogenic properties of betel quid, a botanical that is sometimes mixed with tobacco for use as an oral stimulant in the Indian subcontinent and other regions of Asia.

Targeting of miR34a–NOTCH1 Axis Reduced Breast Cancer Stemness and Chemoresistance

Précis: Downregulation of a tumor suppressor miRNA appears to be important in generating stem-like properties and doxorubicin resistance in a well-established model of estrogen-dependent breast cancer.

ONCOGENE PATHWAY ACTIVATION IN MAMMARY TUMORS DICTATES FDG-PET UPTAKE

Précis: PET scans are used commonly in the clinic to image tumors on the basis of their elevated glucose uptake, but the parameters underlying uptake of the imaging probe have not been well understood, as explored by this study.

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ABOUT THE COVER

Myostatin gene inactivation drastically reduces the development of polyposis in Apc\textsuperscript{Min/þ} mouse. The Apc\textsuperscript{Min/þ} mouse has a mutation in the adenomatous polyposis coli (Apc) tumor suppressor gene, which is responsible for the development of colorectal cancer and cachexia. Myostatin is a master negative regulator of skeletal muscle mass. It was found that inactivation of the myostatin gene on the Apc\textsuperscript{Min/þ} genetic background, a condition that completely prevents cancer cachexia, strikingly reduced the number and size of intestinal polyps. For details see article by Gallot and colleagues on page 7344.
Cancer Research

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