

Cancer Research Table of Contents

ACR
American Association
for Cancer Research

December 15, 2014 • Volume 74 • Number 24

BREAKING ADVANCES

7159 Highlights from Recent Cancer Literature

REVIEWS

7161 MDM2–p53 Pathway in Hepatocellular Carcinoma
Xuan Meng, Derek A. Franklin, Jiahong Dong, and Yanping Zhang

7168 Trafficking of T Cells into Tumors
Clare Y. Slaney, Michael H. Kershaw, and Phillip K. Darcy

7175 When Will Resistance Be Futile?
Katherine L.B. Borden

PERSPECTIVES

7181 Unique Molecular Landscapes in Cancer: Implications for Individualized, Curated Drug Combinations
Jennifer Wheler, J. Jack Lee, and Razelle Kurzrock

7185 Mechanisms of Hypoxia-Mediated Immune Escape in Cancer
Ivraym B. Barsoum, Madhuri Koti, D. Robert Siemens, and Charles H. Graham

PRIORITY REPORTS

7191 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
Précis: Results from studies of oral cancer offer the first definitive establishment of *Dusp1* as a tumor suppressor gene that regulates cancer-associated inflammation.

7198 AKT1 and MYC Induce Distinctive Metabolic Fingerprints in Human Prostate Cancer
Carmen Priolo, Saumyadipta Pyne, Joshua Rose, Erzsébet Ravasz Regan, Giorgia Zadra, Cornelia Photopoulos, Stefano Cacciatore, Denise Schultz, Natalia Scaglia, Jonathan McDunn, Angelo M. De Marzo, and Massimo Loda
Précis: These findings may pave the way for a metabolic classification of prostate tumors that is complementary to genomics and signaling pathway analyses, with implications for the development of metabolic diagnostics and targeted therapeutics.

CLINICAL STUDIES

7205 Chemoradiotherapy-Induced Upregulation of PD-1 Antagonizes Immunity to HPV-Related Oropharyngeal Cancer
Falguni Parikh, Dorothée Duluc, Naoko Imai, Amelia Clark, Krzys Misiukiewicz, Marcello Bonomi, Vishal Gupta, Alexis Patsias, Michael Parides, Elizabeth G. Demicco, David Y. Zhang, Seunghee Kim-Schulze, Johnny Kao, Sacha Gnjjatic, Sangkon Oh, Marshall R. Posner, and Andrew G. Sikora

Précis: Findings from a small clinical study strongly encourage human trials of PD-1–blocking antibodies in combination with standard-of-care therapy for HPV-associated oral cancers, the incidence of which has been rising rapidly.

INTEGRATED SYSTEMS AND TECHNOLOGIES

7217 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, Yian Ann Chen, Uwe Rix, and Eric B. Haura

Précis: This study of cancer cell signaling perturbed by the tyrosine kinase inhibitor dasatinib suggests rational combinations to improve the efficacy of this drug in the subset of lung cancers where it is used.

7229 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

Précis: This study describes a bioengineered platform that allows detailed cellular and molecular characterization of the metastatic microenvironment in vivo, providing a new tool for a better understanding of tumor/stromal interactions at secondary sites.

Table of Contents

MICROENVIRONMENT AND IMMUNOLOGY

- 7239 Adenosine A_{2A} Receptors Intrinsically Regulate CD8⁺ T Cells in the Tumor Microenvironment**
Caglar Cekic and Joel Linden
Précis: Targeted deletion of the adenosine A_{2A} 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 A_{2A} receptor antagonists to enhance cancer immunotherapy.
- 7250 Myeloid Expression of Adenosine A_{2A} 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 IKK β Promotes Antitumor Immunity by Modulating CCL11 and the Innate Immune Response**
Jinming Yang, Oriana E. Hawkins, 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- κ B 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, Leying 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 BRAF^{V600E}-Mutant Metastatic Melanoma**
Lucas Ferrari de Andrade, Shin F. Ngiow, 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**
Bin Hu, Luni Emdad, Manny D. Bacolod, Timothy P. Kegelman, Xue-Ning Shen, Mohammad A. Alzubi, Swadesh K. Das, Devanand Sarkar, and Paul B. Fisher
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.

Table of Contents

- 7333 H3K9 Histone Methyltransferase, KMT1E/SETDB1, Cooperates with the SMAD2/3 Pathway to Suppress Lung Cancer Metastasis**
Pei-Chun Wu, Jeng-Wei Lu, Jer-Yen Yang, I-Hsuan Lin, Da-Liang Ou, Yu-Hsiang Lin, Kuan-Hsien Chou, Wen-Feng Huang, Wan-Ping Wang, Yih-Leih Huang, Chiun Hsu, Liang-In Lin, Yueh-Min Lin, C.-K. James Shen, and Tsai-Yu Tzeng
Précis: These findings provide important mechanistic insights into how TGF β promotes lung cancer metastasis, with possible implications for understanding how to target this broadly important pathway in cancer progression.
- 7344 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, Laurent Schaeffer, Anne Bonnieu, and Damien G. Freyssenet
Précis: Striking preclinical results suggest that targeting a TGF β -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.
- 7357 Homeoprotein Six2 Promotes Breast Cancer Metastasis via Transcriptional and Epigenetic Control of E-Cadherin Expression**
Chu-An Wang, David Drasin, Catherine Pham, Paul Jedlicka, Vadym Zaberezhnyy, Michelle Guney, 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.
- 7371 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.
- 7383 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.
- 7395 PELP1 Overexpression in the Mouse Mammary Gland Results in the Development of Hyperplasia and Carcinoma**
Valerie Cortez, Cathy Samayoa, Andrea Zamora, Lizatte Martinez, 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.
- 7406 Differentiation and Loss of Malignant Character of Spontaneous Pulmonary Metastases in Patient-Derived Breast Cancer Models**
Jessica Bockhorn, Aleix 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.
- 7418 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 Horiike, Shinsuke Iida, and Masafumi Taniwaki
Précis: These findings provide a preclinical rationale for the development of inhibitors of a phosphatidylinositol kinase as a generally effective treatment for deadly multiple myelomas, regardless of their cytogenetic and molecular profiles.

Table of Contents

7430 **Oncogenic KRAS Confers Chemoresistance by Upregulating NRF2**

Shasha Tao, Shue Wang, Seyed Javad Moghaddam, Aikseng Ooi, Eli Chapman, Pak K. Wong, and Donna D. Zhang

Précis: 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

7442 **Plasma Choline Metabolites and Colorectal Cancer Risk in the Women's Health Initiative Observational Study**

Sajin Bae, Cornelia M. Ulrich, Marian L. Neuhouser, Olga Malysheva, 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

Précis: 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

7453 **Endothelin A Receptor/ β -Arrestin Signaling to the Wnt Pathway Renders Ovarian Cancer Cells Resistant to Chemotherapy**

Laura Rosanò, Roberta Cianfrocca, Piera Tocci, Francesca Spinella, Valeriana Di Castro, Valentina Caprara, Elisa Semprucci, Gabriella Ferrandina, Pier Giorgio Natali, and Anna Bagnato

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

7465 **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

Précis: 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.

7475 **Syntheses and Discovery of a Novel Class of Cinnamic Hydroxamates as Histone Deacetylase Inhibitors by Multimodality Molecular Imaging in Living Subjects**

C.T. Chan, J. Qi, W. Smith, R. Paranol, R. Mazitschek, N. West, R. Reeves, G. Chiosis, S.L. Schreiber, J.E. Bradner, R. Paulmurugan, and S.S. Gambhir

Précis: 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.

7487 **FL118 Induces p53-Dependent Senescence in Colorectal Cancer Cells by Promoting Degradation of MdmX**

Xiang Ling, Chao Xu, Chuandong Fan, Kai Zhong, Fengzhi Li, and Xinjiang Wang

Précis: 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.

7498 **Mitochondrial MKP1 Is a Target for Therapy-Resistant HER2-Positive Breast Cancer Cells**

Demet Candas, Chung-Ling Lu, Ming Fan, Frank Y.S. Chuang, Colleen Sweeney, Alexander D. Borowsky, and Jian Jian Li

Précis: 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.

7510 **Harnessing the Fc μ Receptor for Potent and Selective Cytotoxic Therapy of Chronic Lymphocytic Leukemia**

Bérengère Vire, Martin Skarzynski, Joshua D. Thomas, Christopher G. Nelson, Alexandre David, Georg Aue, Terrence R. Burke Jr, Christoph Rader, and Adrian Wiestner

Précis: 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.

7521 **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

Précis: 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.

Table of Contents

7534 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.*

7573 Targeting of miR34a–NOTCH1 Axis Reduced Breast Cancer Stemness and Chemoresistance

Eun Young Park, EunSun Chang, Eun Ji Lee, Hyun-Woo Lee, Hyeok-Gu Kang, Kyung-Hee Chun, Yu Mi Woo, Hyun Kyung Kong, Je Yeong Ko, Hiromu Suzuki, Erwei Song, and Jong Hoon Park

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.*

TUMOR AND STEM CELL BIOLOGY

7546 Targeting the c-Met/FZD8 Signaling 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 Zhiyuan 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.*

7560 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.*

7583 Oncogene Pathway Activation in Mammary Tumors Dictates FDG-PET Uptake

James V. Alvarez, George K. Belka, Tien-Chi Pan, Chien-Chung Chen, Eric Blankemeyer, Abass Alavi, Joel S. Karp, and Lewis A. Chodosh

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.*

LETTER TO THE EDITOR

7599 The Increasing Urgency for Standards in Basic Biologic Research Published Recently in Cancer Research—Letter

Keith Dredge

7600 Acknowledgment to Reviewers

AC icon indicates Author Choice

For more information please visit www.aacrjournals.org

Table of Contents

ABOUT THE COVER

Myostatin gene inactivation drastically reduces the development of polyposis in $Apc^{Min/+}$ mouse. The $Apc^{Min/+}$ 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 $Apc^{Min/+}$ 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.

