

September 1, 2016 • Volume 76 • Number 17

BREAKING ADVANCES

- 4911** Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 4913** Commentary on "Humanization of an Anti-VEGF Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders"
Napoleone Ferrara
- 4916** Commentary on "Proteasome Inhibitors: A Novel Class of Potent and Effective Antitumor Agents"
Kenneth D. Tew


REVIEW


- 4918** Somatic Engineering of Oncogenic Chromosomal Rearrangements: A Perspective
Danilo Maddalo and Andrea Ventura

PERSPECTIVE

- 4924** Challenging Roadblocks to Cancer Cure
 Massimo Loda

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4931** Mathematical Modeling of Cancer Immunotherapy and Its Synergy with Radiotherapy
Raphael Serre, Sebastien Benzekry, Laetitia Padovani, Christophe Meille, Nicolas André, Joseph Ciccolini, Fabrice Barlesi, Xavier Muracciole, and Dominique Barbolosi
Précis: This report presents a mathematical algorithm that can model the efficacy of any drug combination in silico before being implemented at bedside.
- 4941** A Simple PSA-Based Computational Approach Predicts the Timing of Cancer Relapse in Prostatectomized Patients
 Ilaria Stura, Domenico Gabriele, and Caterina Guiot
Précis: The mathematical model presented in this report offers a tool to elaborate the follow-up of clinical data in a manner to predict prostate cancer recurrence.

- 4948** Integrated Classification of Prostate Cancer Reveals a Novel Luminal Subtype with Poor Outcome


Sungyong You, Beatrice S. Knudsen, Nicholas Erho, Mohammed Alshalalfa, Mandeep Takhar, Hussam Al-deen Ashab, Elai Davicioni, R. Jeffrey Karnes, Eric A. Klein, Robert B. Den, Ashley E. Ross, Edward M. Schaeffer, Isla P. Garraway, Jayoung Kim, and Michael R. Freeman

Précis: A novel approach to subtyping human prostate cancer provides important diagnostic and prognostic information of potential clinical value at both early and late disease stages.

MICROENVIRONMENT AND IMMUNOLOGY

- 4959** BAFF and APRIL from Activin A–Treated Dendritic Cells Upregulate the Antitumor Efficacy of Dendritic Cells *In Vivo*
Michael R. Shurin, Yang Ma, Anton A. Keskinov, Ruijing Zhao, Anna Lokshin, Marianna Agassandian, and Galina V. Shurin
Précis: A cell fate-determining factor related to TGF β exerts positive effects on tumor immunity and increases the antitumor potential of dendritic cell vaccines.
- 4970** Activation of the c-Met Pathway Mobilizes an Inflammatory Network in the Brain Microenvironment to Promote Brain Metastasis of Breast Cancer
Fei Xing, Yin Liu, Sambad Sharma, Kerui Wu, Michael D. Chan, Hui-Wen Lo, Richard L. Carpenter, Linda J. Metheny-Barlow, Xiaobo Zhou, Shadi A. Qasem, Boris Pasche, and Kounosuke Watabe
Précis: This potentially seminal study identifies c-Met as a master regulator of vascular elements in the brain metastatic niche, also identifying the available natural compound pterostilbene as a chemopreventive for brain metastasis, which can be studied immediately in the clinic.
- 4981** Syndecan-1 (CD138) Suppresses Apoptosis in Multiple Myeloma by Activating IGF1 Receptor: Prevention by Synstatin_{IGF1R} Inhibits Tumor Growth
DeannaLee M. Beauvais, Oisun Jung, Yang Yang, Ralph D. Sanderson, and Alan C. Rapraeger
Précis: These results offer a preclinical proof of concept for exploration of an IGF1 receptor binding peptide as an experimental therapeutic to attack both tumor cells and the tumor vasculature in multiple myeloma.

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MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4994** **TMEM2 Is a SOX4-Regulated Gene That Mediates Metastatic Migration and Invasion in Breast Cancer**
Hyeseung Lee, Hani Goodarzi, Sohail F. Tavazoie, and Claudio R. Alarcón
Précis: These findings identify a little studied transmembrane protein as a direct target gene for the stem cell developmental factor SOX4, which mediates its prometastatic effects.
- 5006** **Metabolic Stress-Induced Phosphorylation of KAP1 Ser473 Blocks Mitochondrial Fusion in Breast Cancer Cells**
Chun-Ting Cheng, Ching-Ying Kuo, Ching Ouyang, Chien-Feng Li, Yiyin Chung, David C. Chan, Hsing-Jien Kung, and David K. Ann
Précis: These results define a mechanism of mitochondrial dynamics regulation that operates in cancer cells under metabolic stress to help preserve their survival, with potential therapeutic implications.
- 5019** **Rebound Effects Caused by Withdrawal of MET Kinase Inhibitor Are Quenched by a MET Therapeutic Antibody**
Emanuela Pupo, Nadia Ducano, Barbara Lupo, Elisa Vigna, Daniele Avanzato, Timothy Perera, Livio Trusolino, Letizia Lanzetti, and Paolo M. Comoglio
Précis: Treatment of cancer cells with a MET kinase inhibitory drug leads to accumulation of the receptor at the plasma membrane, generating a rapid rebound after the drug is discontinued, but this effect can be prevented by adding a MET therapeutic antibody to the initial treatment, with immediate implications for clinic testing.
- 5030** **RPL23 Links Oncogenic RAS Signaling to p53-Mediated Tumor Suppression**
Xuan Meng, Nicole R. Tackmann, Shijie Liu, Jing Yang, Jiahong Dong, Congying Wu, Adrienne D. Cox, and Yanping Zhang
Précis: Oncogenic mutation of RAS activates p53 through the p19ARF-MDM2 pathway, but as this study shows, RAS also induces p53 through a second distinct MDM2 pathway, which assists in the suppression of RAS-induced tumorigenesis.
- 5040** **Activation of Wnt/ β -Catenin in Ewing Sarcoma Cells Antagonizes EWS/ETS Function and Promotes Phenotypic Transition to More Metastatic Cell States**
Elisabeth A. Pedersen, Rajasree Menon, Kelly M. Bailey, Dafydd G. Thomas, Raelene A. Van Noord, Jenny Tran, Hongwei Wang, Ping Ping Qu, Antje Hoering, Eric R. Fearon, Rashmi Chugh, and Elizabeth R. Lawlor
Précis: Activation of Wnt/ β -catenin signaling in Ewing sarcoma is heterogeneous and promotes poor clinical outcomes as a consequence of EWS/ETS transcriptional antagonism and derepression of metastasis programs.
- 5054** **MEF2D Transduces Microenvironment Stimuli to ZEB1 to Promote Epithelial–Mesenchymal Transition and Metastasis in Colorectal Cancer**
Li Su, Yongli Luo, Zhi Yang, Jing Yang, Chao Yao, Feifei Cheng, Juanjuan Shan, Jun Chen, Fangfang Li, Limei Liu, Chungang Liu, Yanmin Xu, Lupin Jiang, Deyu Guo, Jesus Prieto, Matías A. Ávila, Junjie Shen, and Cheng Qian
Précis: These results offer new insights into how microenvironmental signals activate the epithelial–mesenchyme transition in cancer cells, with implications for deeper molecular understanding of the pathophysiology of metastatic colon cancer and its prevention and treatment.
- 5068** **HTLV-1 Viral Factor HBZ Induces CCR4 to Promote T-cell Migration and Proliferation**
Kenji Sugata, Jun-ichirou Yasunaga, Haruka Kinoshita, Yuichi Mitobe, Rie Furuta, Mohamed Mahgoub, Chiho Onishi, Kazutaka Nakashima, Koichi Ohshima, and Masao Matsuoka
Précis: These results offer an explanation for how the human tumor virus HTLV-1 drives T-cell migration and proliferation, two phenomena linked tightly to viral pathogenesis.
- 5080** **Tyrosine Phosphatase PTPRJ/DEP-1 Is an Essential Promoter of Vascular Permeability, Angiogenesis, and Tumor Progression**
Patrick Fournier, Sylvie Dussault, Alfredo Fusco, Alain Rivard, and Isabelle Royal
Précis: This study helps resolve divergent perspectives on the functions of a protein tyrosine phosphatase often depicted as a negative regulator in cancer, but revealed in this study through careful in vivo investigations as a positive stimulus to angiogenesis, permeability, and metastasis.

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- 5092** **The Genomic Landscape of Pancreatic and Periampullary Adenocarcinoma**
Vandana Sandhu, David C. Wedge, Inger Marie Bowitz Lothe, Knut Jørgen Labori, Stefan C. Dentre, Trond Buanes, Martina L. Skrede, Astrid M. Dalsgaard, Else Munthe, Ola Myklebost, Ole Christian Lingjærde, Anne-Lise Børresen-Dale, Tone Ikdahl, Peter Van Loo, Silje Nord, and Elin H. Kure
Précis: This study identifies candidate prognostic markers for periampullary tumors, which arise in the vicinity of the ampulla of Vater, an enlargement of liver and pancreas ducts where they join and enter the small intestine, a class of cancers where genetic characterization has lagged.

PREVENTION AND EPIDEMIOLOGY

- 5103** **Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations**
Gordon Fehring, Peter Kraft, Paul D. Pharoah, on behalf of Ovarian Cancer Association Consortium (OCAC); Rosalind A. Eeles, on behalf of The PRACTICAL Consortium; Nilanjan Chatterjee, Fredrick R. Schumacher, Joellen M. Schildkraut, Sara Lindström, Paul Brennan, Heike Bickeböller, Richard S. Houlston, Maria Teresa Landi, Neil Caporaso, Angela Risch, Ali Amin Al Olama, Sonja I. Berndt, Edward L. Giovannucci, Henrik Grönberg, Zsofia Kote-Jarai, Jing Ma, Kenneth Muir, Meir J. Stampfer, Victoria L. Stevens, Fredrik Wiklund, Walter C. Willett, Ellen L. Goode, Jennifer B. Permuth, Harvey A. Risch, Brett M. Reid, Stéphane Bezieau, Hermann Brenner, Andrew T. Chan, Jenny Chang-Claude, Thomas J. Hudson, Jonathan K. Kocarnik, Polly A. Newcomb, Robert E. Schoen, Martha L. Slattery, Emily White, Muriel A. Adank, on behalf of Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON); Habibul Ahsan, Kristiina Aittomäki, Laura Baglietto, Carl Blomquist, Federico Canzian, Kamila Czene, Isabel dos-Santos-Silva, A. Heather Eliassen, Jonine D. Figueroa, Dieter Flesch-Janys, Olivia Fletcher, Montserrat Garcia-Closas, Mia M. Gaudet, Nichola Johnson, Per Hall, Aditi Hazra, Rebecca Hein, Albert Hofman, John L. Hopper, Astrid Irwanto, Mattias Johansson, Rudolf Kaaks, Muhammad G. Kibriya, Peter Lichtner, Jianjun Liu, Eiliv Lund, Enes Makalic, Alfons Meindl, Bertram Müller-Myhsok, Taru A. Muranen, Heli Nevanlinna, Petra H. Peeters, Julian Peto, Ross L. Prentice, Nazneen Rahman, Maria Jose Sanchez, Daniel F. Schmidt, Rita K. Schmutzler, Melissa C. Southey, Rulla Tamimi, Ruth C. Travis, Clare Turnbull, Andre G. Uitterlinden, Zhaoming Wang, Alice S. Whittemore, Xiaohong R. Yang, Wei Zheng, Daniel D. Buchanan, Graham Casey, David V. Conti, Christopher K. Edlund, Steven Gallinger, Robert W. Haile, Mark Jenkins, Loïc Le Marchand, Li Li, Noralene M. Lindor, Stephanie L. Schmit, Stephen N. Thibodeau, Michael O. Woods, Thorunn Rafnar, Julius Gudmundsson, Simon N. Stacey,

Kari Stefansson, Patrick Sulem, Y. Ann Chen, Jonathan P. Tyrer, David C. Christiani, Yongyue Wei, Hongbing Shen, Zhibin Hu, Xiao-Ou Shu, Kouya Shiraishi, Atsushi Takahashi, Yohan Bossé, Ma'en Obeidat, David Nickle, Wim Timens, Matthew L. Freedman, Qiyuan Li, Daniela Seminara, Stephen J. Chanock, Jian Gong, Ulrike Peters, Stephen B. Gruber, on behalf of Colorectal Transdisciplinary (CORECT) Study; Christopher I. Amos, Thomas A. Sellers, Douglas F. Easton, David J. Hunter, Christopher A. Haiman, on behalf of African American Breast Cancer Consortium (AABC) and African Ancestry Prostate Cancer Consortium (AAPC); Brian E. Henderson, and Rayjean J. Hung

Précis: This study describes the largest investigation of pleiotropy across cancers to date, providing important insights into common carcinogenic mechanisms underlying cancer etiology and susceptibility.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 5115** **Structural Basis for Induction of Peripheral Neuropathy by Microtubule-Targeting Cancer Drugs**
Jennifer A. Smith, Barbara S. Slusher, Krystyna M. Wozniak, Mohamed H. Farah, Gregory S. Smiyun, Leslie Wilson, Stuart Feinstein, and Mary Ann Jordan
Précis: The results of this study indicate that inhibition of anterograde transport in peripheral neurons by microtubule-stabilizing drugs paclitaxel and ixabepilone may be an important cause of the peripheral neuropathy that develops in many patients treated with these drugs.
- 5124** **Multivalent Peptoid Conjugates Which Overcome Enzalutamide Resistance in Prostate Cancer Cells**
Yu Wang, Dilani C. Dehigaspitiya, Paul M. Levine, Adam A. Profit, Michael Haugbro, Keren Imberg-Kazdan, Susan K. Logan, Kent Kirshenbaum, and Michael J. Garabedian
Précis: This report presents a new approach to antagonize the androgen receptor and suppress the proliferation of drug-resistant prostate cancer cells.
- 5133** **The WASF3–NCKAP1–CYFIP1 Complex Is Essential for Breast Cancer Metastasis**
Yong Teng, Haiyan Qin, Abdulaziz Bahassan, N. George Bendzun, Eileen J. Kennedy, and John K. Cowell
Précis: Targeting a protein-protein complex that is critical for the promotion of metastasis by the WASF3 gene suggests a therapeutic approach to suppress metastasis.

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TUMOR AND STEM CELL BIOLOGY

5143 Rapid Reprogramming of Primary Human Astrocytes into Potent Tumor-Initiating Cells with Defined Genetic Factors

Fang Li, Xinjian Liu, John H. Sampson, Darell D. Bigner, and Chuan-Yuan Li

Précis: This study describes a method to rapidly generate tumor-initiating cells from primary human astrocytes, potentially offering an important new tool for studies of glioma biology and therapeutics development.

5151 miR-214 and miR-148b Targeting Inhibits Dissemination of Melanoma and Breast Cancer

Francesca Orso, Lorena Quirico, Federico Virga, Elisa Penna, Daniela Dettori, Daniela Cimino, Roberto Coppo, Elena Grassi, Angela Rita Elia, Davide Brusa, Silvia Deaglio, Maria Felice Brizzi, Michael B. Stadler, Paolo Provero, Michele Caselle, and Daniela Taverna

Précis: These findings define an antagonistic relationship of two microRNAs in determining the dissemination of cancer cells via tumor-endothelial cell interactions, with potential implications for therapeutic intervention.

5163 α v β 6 Integrin Promotes Castrate-Resistant Prostate Cancer through JNK1-Mediated Activation of Androgen Receptor

Huimin Lu, Tao Wang, Jing Li, Carmine Fedele, Qin Liu, Jianzhong Zhang, Zhong Jiang, Dhanpat Jain, Renato V. Iozzo, Shelia M. Violette, Paul H. Weinreb, Roger J. Davis, Daniel Gioeli, Thomas J. FitzGerald, Dario C. Altieri, and Lucia R. Languino

Précis: These results describe a novel pathway that promotes castrate-resistant prostate cancer initiated by PTEN deletion, with potential implications for treatment of this advanced stage disease.

5175 GON4L Drives Cancer Growth through a YY1-Androgen Receptor-CD24 Axis

Neeraj Agarwal, Garrett M. Dancik, Andrew Goodspeed, James C. Costello, Charles Owens, Jason E. Duex, and Dan Theodorescu

Précis: This work identifies a novel oncogene that drives cancer growth via the transcription factor YY1 and the androgen receptor, offering a new platform for biomarker and therapeutic opportunities.

CORRECTION

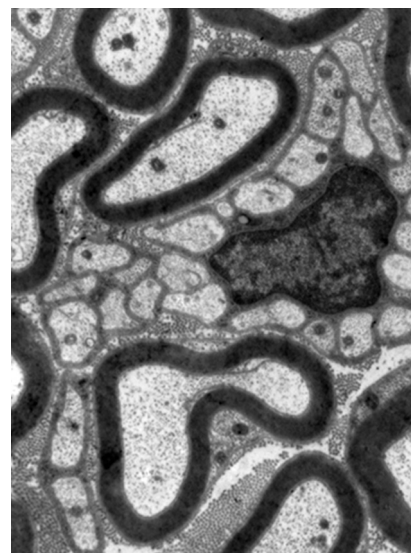
5186 Correction: Combining miR-10b-Targeted Nanotherapy with Low-Dose Doxorubicin Elicits Durable Regressions of Metastatic Breast Cancer

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ABOUT THE COVER

Neurons require transport of ATP-producing mitochondria for survival. Antiproliferative concentrations of the anticancer drugs paclitaxel and ixabepilone that bind along microtubule lengths significantly inhibited anterograde transport of fluorescently labeled mitochondria in human neuroblastoma cells, whereas the microtubule end-binding drugs eribulin and vincristine inhibited transport only at significantly higher concentrations. The electron micrographic image shows a section of a control mouse sciatic nerve in which mitochondria were transported in the absence of drug (a control). Paclitaxel, but not eribulin, inhibited transport in mouse sciatic nerves. For details, see article by Smith and colleagues on page 5115.



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