


## BREAKING ADVANCES

- 5169** Highlights from Recent Cancer Literature

## REVIEWS

- 5171** Dependence Receptors and Cancer: Addiction to Trophic Ligands  
Benjamin Gibert and Patrick Mehlen
- 5176** Preclinical Models Provide Scientific Justification and Translational Relevance for Moving Novel Therapeutics into Clinical Trials for Pediatric Cancer  
David M. Langenau, Alejandro Sweet-Cordero, Robert J. Wechsler-Reya, and Michael A. Dyer
- 5187** IL15 and T-cell Stemness in T-cell–Based Cancer Immunotherapy  
Karolina Pilipow, Alessandra Roberto, Mario Roederer, Thomas A. Waldmann, Domenico Mavilio, and Enrico Lugli

## RESOURCE

- 5194**  A Federated Network for Translational Cancer Research Using Clinical Data and Biospecimens  
Rebecca S. Jacobson, Michael J. Becich, Roni J. Bollag, Girish Chavan, Julia Corrigan, Rajiv Dhir, Michael D. Feldman, Carmelo Gaudioso, Elizabeth Legowski, Nita J. Maible, Kevin Mitchell, Monica Murphy, Mayurapriyan Sakthivel, Eugene Tseytlin, and JoEllen Weaver

## PERSPECTIVE

- 5202** Essential Components of Cancer Education  
Danny R. Welch, Toni M. Antalis, Kerry Burnstein, Linda Vona-Davis, Roy A. Jensen, Harikrishna Nakshatri, Anna T. Riegel, Douglas R. Spitz, Dennis K. Watson, and George J. Weiner, The Cancer Biology Training Consortium

## MEETING REPORT

- 5206** The Inescapable Influence of Noncoding RNAs in Cancer  
Brian D. Adams, Eleni Anastasiadou, Manel Esteller, Lin He, and Frank J. Slack

## PRIORITY REPORTS

- 5211** SBI-0640756 Attenuates the Growth of Clinically Unresponsive Melanomas by Disrupting the eIF4F Translation Initiation Complex  
Yongmei Feng, Anthony B. Pinkerton, Laura Hulea, Tongwu Zhang, Michael A. Davies, Stefan Grotegut, Yann Cheli, Hongwei Yin, Eric Lau, Hyungsoo Kim, Surya K. De, Elisa Barile, Maurizio Pellecchia, Marcus Bosenberg, Jian-Liang Li, Brian James, Christian A. Hassig, Kevin M. Brown, Ivan Topisirovic, and Ze'ev A. Ronai  
*Précis:* This study presents work on a first-in-class inhibitor of the translation initiation complex eIF4F, the targeting of which may offer broad therapeutic applications in cancer.
- 5219** Genomic Profiling of Penile Squamous Cell Carcinoma Reveals New Opportunities for Targeted Therapy  
Andrew S. McDaniel, Daniel H. Hovelson, Andi K. Cani, Chia-Jen Liu, Yali Zhai, Yajia Zhang, Alon Z. Weizer, Rohit Mehra, Felix Y. Feng, Ajjai S. Alva, Todd M. Morgan, Jeffrey S. Montgomery, Javed Siddiqui, Seth Sadis, Santhoshi Bandla, Paul D. Williams, Kathleen R. Cho, Daniel R. Rhodes, and Scott A. Tomlins  
*Précis:* By offering a description of the genomic alterations underlying penile squamous cell carcinoma, this study offers the first opportunity to reposition available molecular-targeted drugs for use in this disease, with immediate implications for clinical testing.
- 5228** UV-Associated Mutations Underlie the Etiology of MCV-Negative Merkel Cell Carcinomas  
Stephen Q. Wong, Kelly Waldeck, Ismael A. Vergara, Jan Schröder, Jason Madore, James S. Wilmott, Andrew J. Colebatch, Ricardo De Paoli-Iseppi, Jason Li, Richard Lupat, Timothy Semple, Gisela Mir Arnau, Andrew Fellowes, J. Helen Leonard, George Hruby, Graham J. Mann, John F. Thompson, Carleen Cullinane, Meredith Johnston, Mark Shackleton, Shahneen Sandhu, David D.L. Bowtell, Ricky W. Johnstone, Stephen B. Fox, Grant A. McArthur, Anthony T. Papenfuss, Richard A. Scolyer, Anthony J. Gill, Rodney J. Hicks, and Richard W. Tothill  
*Précis:* These findings suggest how a rare but highly invasive and mainly untreatable sensory cell cancer in the skin might be managed by targeted therapeutic drugs currently available in clinic.

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## MICROENVIRONMENT AND IMMUNOLOGY

**5235** TNF Receptor-2 Facilitates an Immunosuppressive Microenvironment in the Liver to Promote the Colonization and Growth of Hepatic Metastases

Boram Ham, Ni Wang, Zarina D'Costa, Maria Celia Fernandez, France Bourdeau, Patrick Auguste, Martin Illemann, Rikke Loevendahl Eefsen, Gunilla Høyer-Hansen, Ben Vainer, Maximilien Evrard, Zu-Hua Gao, and Pnina Brodt

*Précis:* These findings implicate a targetable TNF receptor in supporting immune escape and metastasis in the liver, suggesting a new strategy to prevent metastatic progression to the liver in colon and other cancers with a preference for that organ.

**5248** Stromal Fibroblasts Induce CCL20 through IL6/C/EBP $\beta$  to Support the Recruitment of Th17 Cells during Cervical Cancer Progression

Barbara Walch-Rückheim, Russalina Mavrova, Melanie Henning, Benjamin Vicinus, Yoo-Jin Kim, Rainer Maria Bohle, Ingolf Juhasz-Böss, Erich-Franz Solomayer, and Sigrun Smola

*Précis:* These results show how cervical cancer cells instruct local stromal fibroblasts to secrete the chemokine CCL20, which supports the recruitment of pro-tumorigenic Th17 cells.

**5260** Bortezomib Improves Adoptive T-cell Therapy by Sensitizing Cancer Cells to FasL Cytotoxicity

Anil Shanker, Samuel T. Pellom Jr, Duafalia F. Dudimah, Menaka C. Thounaojam, Rachel L. de Kluyver, Alan D. Brooks, Hideo Yagita, Daniel W. McVicar, William J. Murphy, Dan L. Longo, and Thomas J. Sayers

*Précis:* These findings offer preclinical proof of concept for a strategy to enhance the use of immunotherapy in patients that may otherwise be unresponsive, with immediate implications for clinical investigation.

**5273** TGF $\beta$  Treatment Enhances Glioblastoma Virotherapy by Inhibiting the Innate Immune Response

Jianfeng Han, Xilin Chen, Jianhong Chu, Bo Xu, Walter H. Meisen, Lichao Chen, Lingling Zhang, Jianying Zhang, Xiaoming He, Qi-En Wang, E. Antonio Chiocca, Balveen Kaur, Michael A. Caligiuri, and Jianhua Yu

*Précis:* These findings offer a preclinical rationale to investigate the clinical application of a single administration of TGF $\beta$  to improve the efficacy of oncolytic viruses being evaluated to treat the most aggressive type of brain cancer.

**5283** CCL9 Induced by TGF $\beta$  Signaling in Myeloid Cells Enhances Tumor Cell Survival in the Premetastatic Organ



Hangyi H. Yan, Jian Jiang, Yanli Pang, B.R. Achyut, Michael Lizardo, Xinhua Liang, Kent Hunter, Chand Khanna, Christine Hollander, and Li Yang

*Précis:* These provocative findings suggest that targeting chemokine CCL9 could engender a broadly effective anti-metastatic treatment to attack aggressive cancers.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

**5299** Nitric Oxide Regulates Gene Expression in Cancers by Controlling Histone Posttranslational Modifications

Divya Vasudevan, Jason R. Hickok, Rhea C. Bovee, Vy Pham, Lin L. Mantell, Neil Bahroos, Pinal Kanabar, Xing-Jun Cao, Mark Maienschein-Cline, Benjamin A. Garcia, and Douglas D. Thomas

*Précis:* While nitric oxide has been recognized as a key contributor to cancer pathophysiology for many years, this seminal study offers a unifying explanation to help understand why nitric oxide exerts such a broad diversity of effects, both positive and negative.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**5309** miR-124 and Androgen Receptor Signaling Inhibitors Repress Prostate Cancer Growth by Downregulating Androgen Receptor Splice Variants, EZH2, and Src

Xu-Bao Shi, Ai-Hong Ma, Lingru Xue, Meimei Li, Hao G. Nguyen, Joy C. Yang, Clifford G. Tepper, Regina Gandour-Edwards, Christopher P. Evans, Hsing-Jien Kung, and Ralph W. deVere White

*Précis:* These findings offer a preclinical proof of concept for miR-124-based therapies to treat advanced prostate cancer.

**5318** Activation of Pim Kinases Is Sufficient to Promote Resistance to MET Small-Molecule Inhibitors

Ningfei An, Ying Xiong, Amanda C. LaRue, Andrew S. Kraft, and Bo Cen

*Précis:* These results rationalize coinhibition of the Pim protein kinases as a strategy to augment responses and blunt acquired resistance to MET inhibitors, which may offer broad applications in human cancer treatment.

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**5329** SLC46A3 Is Required to Transport Catabolites of Noncleavable Antibody Maytansine Conjugates from the Lysosome to the Cytoplasm

Kevin J. Hamblett, Allison P. Jacob, Jesse L. Gurgel, Mark E. Tometsko, Brooke M. Rock, Sonal K. Patel, Robert R. Milburn, Sophia Siu, Seamus P. Ragan, Dan A. Rock, Christopher J. Borths, Jason W. O'Neill, Wesley S. Chang, Margaret F. Weidner, Matthew M. Bio, Kim C. Quon, and William C. Fanslow

*Précis:* This study reports the identification of a lysosome transporter that is essential for the antitumor effects of antibody-drug conjugates containing the cytotoxic compound maytansine, the first of which was approved recently to treat breast cancer.

**5341** Identification of Variant-Specific Functions of PIK3CA by Rapid Phenotyping of Rare Mutations

Turgut Dogruluk, Yiu Huen Tsang, Maribel Espitia, Fengju Chen, Tenghui Chen, Zechen Chong, Vivek Appadurai, Armel Dogruluk, Agna Karina Eterovic, Penelope E. Bonnen, Chad J. Creighton, Ken Chen, Gordon B. Mills, and Kenneth L. Scott

*Précis:* A functional genomics platform integrates high-throughput gene mutagenesis and molecular barcoding technologies with functional screening to rapidly interrogate tumor mutations driving malignant phenotypes.

## TUMOR AND STEM CELL BIOLOGY

**5355** Targeting a Plk1-Controlled Polarity Checkpoint in Therapy-Resistant Glioblastoma-Propagating Cells

Robin G. Lerner, Stefan Grossauer, Banafsheh Kadkhodaei, Ian Meyers, Maxim Sidorov, Katharina Koeck, Rintaro Hashizume, Tomoko Ozawa, Joanna J. Phillips, Mitchel S. Berger, Theodore Nicolaides, C. David James, and Claudia K. Petritsch

*Précis:* This study illuminates how heterogeneous glioblastoma cell subpopulations respond to BRAF/MAPK inhibition, highlighting cell polarity and asymmetric cell division as distinguishing features of therapy-resistant tumor-propagating cells that must be eradicated to prevent disease relapse.

**5367** Disseminated Tumor Cells Persist in the Bone Marrow of Breast Cancer Patients through Sustained Activation of the Unfolded Protein Response

Kai Bartkowiak, Marcel Kwiatkowski, Friedrich Buck, Tobias M. Gorges, Lars Nilse, Volker Assmann, Antje Andreas, Volkmar Müller, Harriet Wikman, Sabine Riethdorf, Hartmut Schlüter, and Klaus Pantel

*Précis:* These findings provide the evidence that the unfolded protein response supports the survival of disseminated tumor cells, which are under acute microenvironmental stress, with implications for defining a general predictive biomarker of metastatic relapse in cancer patients after their initial treatment.

**5378** PIK3CA<sup>H1047R</sup> Accelerates and Enhances KRAS<sup>G12D</sup>-Driven Lung Tumorigenesis

Shon Green, Christy L. Trejo, and Martin McMahon

*Précis:* Activating mutations in the PI3K lipid signaling pathway can act as secondary hits needed to potentiate the oncogenicity of mutant KRAS in the lung, providing mechanistic insights into the sequential steps governing tumor progression.

**5392** Targeted Deletion of p53 in Lgr5-Expressing Intestinal Stem Cells Promotes Colon Tumorigenesis in a Preclinical Model of Colitis-Associated Cancer

Laurie A. Davidson, Evelyn S. Callaway, Eunjoo Kim, Brad R. Weeks, Yang-Yi Fan, Clinton D. Allred, and Robert S. Chapkin

*Précis:* These findings show that p53 deletion in intestinal stem cells will promote colon cancer only if DNA damage and chronic inflammation are also present.

## LETTERS TO THE EDITOR

**5398** Melphalan, Antimelanoma Immunity, and Inflammation—Letter

Anna Martner, Junko Johansson, Ilan Ben-Shabat, and Roger Olofsson Bagge

**5400** Melphalan, Antimelanoma Immunity, and Inflammation—Response

Abhishek D. Garg, Aleksandra M. Dudek-Peric, and Patrizia Agostinis

## CORRECTION

**5402** Correction: Genetic Regulation of Fate Decisions in Therapeutic T Cells to Enhance Tumor Protection and Memory Formation

**5403** Acknowledgment to Reviewers

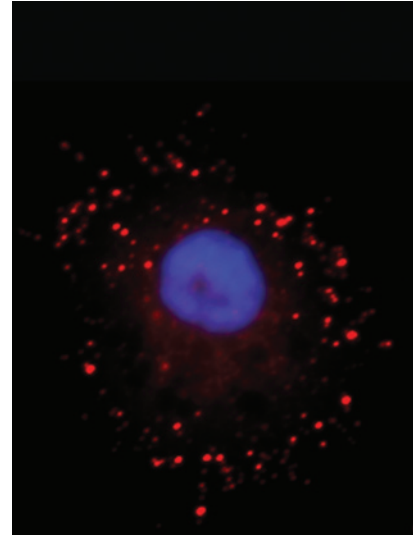
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## ABOUT THE COVER

In CD133-positive tumor-propagating cells from glioblastoma, an intact actin cytoskeleton is required for elevated PLK1 activity, which in turn controls mitotic entry and cell polarity. Taken together, the data suggest a Plk1-driven polarity checkpoint, distinguishing CD133-positive tumor-propagating cells from autologous CD133-negative cells. Elevated PLK1 activity protects CD133-positive tumor-propagating cells from BRAF/MAPK inhibition and sensitizes them to Plk1 inhibition. Using immunocytochemistry, it was found that CD133 failed to localize to the membrane and in a polarized fashion in cells treated with actin polymerization inhibitor Latrunculin A. For details, see article by Lerner and colleagues on page 5355.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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