**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. Maihle, Kevin Mitchell, Monica Murphy, Mayurarupiyiyan Sakthivel, Eugene Tseytlin, and JoEllen Weaver

**Perspective**

5202 Essential Components of Cancer Education

**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, Huyngoo Kim, Surya K. De, Elisa Barile, Maurizio Pellecchia, Marcus Rosenberg, 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
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
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.
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 Hoyer-Hansen, Ben Vainer, Maximilien Evrard, Zu-Hua Gao, and Pnina Brodt

Precis: 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/EBPβ 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

Precis: These results show how cervical cancer cells instruct local stromal fibroblasts to secrete the chemokine CCL20, which supports the recruitment of protumorigenic Th17 cells.

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

Precis: These findings implicate bortezomib in sensitizing cancer cells to FasL, potentially enhancing adoptive T-cell therapy.

5273 TGFβ 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

Precis: These findings offer a preclinical rationale to investigate the clinical application of TGFβ to improve the efficacy of oncolytic viruses being evaluated to treat the most aggressive type of brain cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

5283 CCL9 Induced by TGFβ Signaling in Myeloid Cells Enhances Tumor Cell Survival in the Premetastatic Organ
Hangri H. Yan, Jian Jiang, Yanli Pang, B.R. Achyut, Michael Lizardo, Xinhua Liang, Kent Hunter, Chand Khanna, Christine Hollander, and Li Yang

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

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, Xingjun Cao, Mark Mainschein-Cline, Benjamin A. Garcia, and Douglas D. Thomas

Precis: 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.

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, Lingrui Xue, Meimei Li, Hao C. Nguyen, Joy C. Yang, Cliford G. Tepper, Regina Gandour-Edwards, Christopher P. Evans, Hsing-Jien Kung, and Ralph W. deVere White

Precis: 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

Precis: These results rationalize co-inhibition 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.
SLC46A3 Is Required to Transport Catabolites of Noncleavable Antibody Maytansine Conjugates from the Lysosome to the Cytoplasm


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.

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


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.

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


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.

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

Kai Barkowid, Marcel Roviankowski, Friedrich Buck, Tobias M. Gogges, Lars Nilse, Volker Ansmann, Anje Andreas, Volkmar Müller, Harriet Wilmann, Sabine Riethdorf, Hartmut Schüller, 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.

PIK3CAH1047R Accelerates and Enhances KRASG12D-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.

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.

Melphalan, Antimelanoma Immunity, and Inflammation—Letter

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

Melphalan, Antimelanoma Immunity, and Inflammation—Response

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

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

ACKNOWLEDGMENT TO REVIEWERS
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.
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