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  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, Tongyu Zhang, Michael A. Davies, Stefan Grotegut, Yann Cheli, Hongwei Yin, Eric Lau, Huynggoo 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 repurpose 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

7043 TNF Receptor-2 Facilitates an Immunosuppressive Microenvironment in the Liver to Promote the Colonization and Growth of Hepatic Metastases

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/EBPβ to Support the Recruitment of Th17 Cells during Cervical Cancer Progression

Précis: 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

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 TGFβ Treatment Enhances Glioblastoma Virotherapy by Inhibiting the Innate Immune Response

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

5283 CCL9 Induced by TGFβ Signaling in Myeloid Cells Enhances Tumor Cell Survival in the Premetastatic Organ

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

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.

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

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

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.
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 Barkowiak, Marcel Rviantkowski, Friedrich Buck, Tobias M. Goges, Lars Nilse, Volker Ansmann, Anjie Andreas, Volkmar Müller, Harriet Wilman, Sabine Riethdorf, Hartmut Slützer, and Klaus Pantel

Précis: These findings provide 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.
Cancer Research

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