

CANCER RESEARCH

TABLE OF CONTENTS

BREAKING INSIGHTS

- 4869** Highlights from Recent Cancer Literature

REVIEWS

- 4871** Relationships between Breast Feeding and Breast Cancer Subtypes: Lessons Learned from Studies in Humans and in Mice
Christine B. Ambrosone and Michael J. Higgins
- 4878** Junctional Adhesion Molecules in Cancer: A Paradigm for the Diverse Functions of Cell-Cell Interactions in Tumor Progression
Adam Lauko, Zhaomei Mu, David H. Gutmann, Ulhas P. Naik, and Justin D. Lathia

CANCER RESEARCH HIGHLIGHTS

- 4886** Fats and Mets, KRAS-Driven Lipid Dysregulation Affects Metastatic Potential in Pancreatic Cancer
Jennifer Man, Marina Pajic, and Anthony M. Joshua
See related article, p. 4932

CONTROVERSY AND CONSENSUS

- 4888** Field Carcinogenesis in Cancer Evolution: What the Cell Is Going On?
Ansam Sinjab, Guangchun Han, Linghua Wang, and Humam Kadara

GENOME AND EPIGENOME

- 4892** Morphology-Predicted Large-Scale Transition Number in Circulating Tumor Cells Identifies a Chromosomal Instability Biomarker Associated with Poor Outcome in Castration-Resistant Prostate Cancer
Joseph D. Schonhoft, Jimmy L. Zhao, Adam Jendrisak, Emily A. Carbone, Ethan S. Barnett, Melanie A. Hullings, Audrey Gill, Ramsay Sutton, Jerry Lee, Angel E. Dago, Mark Landers, Samuel F. Bakhoun, Yipeng Wang, Mithat Gonen, Ryan Dittamore, and Howard I. Scher
A rapidly assessable biomarker of chromosomal instability in CTC is associated with poor outcomes when detected in men with progressing mCRPC.

- 4904** Protein Arginine Methyltransferase 5 Promotes pICln-Dependent Androgen Receptor Transcription in Castration-Resistant Prostate Cancer
Elena Beketova, Shuyi Fang, Jake L. Owens, Sheng Liu, Xufeng Chen, Qingfu Zhang, Andrew M. Asberry, Xuehong Deng, Jonathan Malola, Jiaoti Huang, Chenglong Li, Roberto Pili, Bennett D. Elzey, Timothy L. Ratliff, Jun Wan, and Chang-Deng Hu
This study provides evidence that targeting PRMT5 can eliminate expression of AR and can be explored as a novel therapeutic approach to treat metastatic hormone-naïve and castration-resistant prostate cancer.

- 4918** Chromothripsis in Human Breast Cancer
Michiel Bolkestein, John K.L. Wong, Verena Thewes, Verena Körber, Mario Hlevnjak, Shaymaa Elgaafary, Markus Schulze, Felix K.F. Kommoss, Hans-Peter Sinn, Tobias Anzeneder, Steffen Hirsch, Frauke Devens, Petra Schröter, Thomas Höfer, Andreas Schneeweiss, Peter Lichter, Marc Zapatka, and Aurélie Ernst
These findings identify chromothripsis as a major driving event in human breast cancer.

METABOLISM AND CHEMICAL BIOLOGY

- 4932** KRAS Controls Pancreatic Cancer Cell Lipid Metabolism and Invasive Potential through the Lipase HSL
Cody N. Rozeveld, Katherine M. Johnson, Lizhi Zhang, and Gina L. Razidlo
KRAS-dependent regulation of HSL biases cells towards lipid storage for subsequent utilization during invasion of pancreatic cancer cells, representing a potential target for therapeutic intervention.
See related commentary, p. 4886

MOLECULAR CELL BIOLOGY

- 4946** Specific Mechanisms of Chromosomal Instability Indicate Therapeutic Sensitivities in High-Grade Serous Ovarian Carcinoma
Naoka Tamura, Nadeem Shaikh, Daniel Muliaditan, Tanya N. Soliman, Jennifer R. McGuinness, Eleni Maniati, Daniela Moralli, Mary-Anne Durin, Catherine M. Green, Frances R. Balkwill, Jun Wang, Kit Curtius, and Sarah E. McClelland
These findings characterize multiple deregulated mechanisms of genome stability that lead to CIN in ovarian cancer and demonstrate the benefit of integrating analysis of said mechanisms into predictions of therapy response.

TABLE OF CONTENTS

4960 **Noncanonical IL6 Signaling-Mediated Activation of YAP Regulates Cell Migration and Invasion in Ovarian Clear Cell Cancer**

Walid J. Azar, Elizabeth L. Christie, Chris Mitchell, David S. Liu, George Au-Yeung, and David D.L. Bowtell
This study defines the requirements for and mechanisms of noncanonical signaling by IL6 in human ovarian clear cell adenocarcinoma cell lines and identifies combinatory therapeutic approaches to be explored clinically.

4972 **A Circle RNA Regulatory Axis Promotes Lung Squamous Metastasis via CDR1-Mediated Regulation of Golgi Trafficking**

Emily B. Harrison, Alessandro Porrello, Brittany M. Bowman, Adam R. Belanger, Gabriella Yacovone, Salma H. Azam, Ian A. Windham, Subrata K. Ghosh, Menglin Wang, Nicholas Mckenzie, Trent A. Waugh, Amanda E.D. Van Swearingen, Stephanie M. Cohen, Devon G. Allen, Tyler J. Goodwin, Teresa Mascenik, James E. Bear, Sarah Cohen, Scott H. Randell, Pierre P. Massion, Michael B. Major, Leaf Huang, and Chad V. Pecot
This study shows that circRNA, CDR1as, promotes lung squamous migration, metastasis, and Golgi trafficking through its complimentary transcript, CDR1.

TUMOR BIOLOGY AND IMMUNOLOGY

4986 **Futibatinib Is a Novel Irreversible FGFR 1-4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors**

A C Hiroshi Sootome, Hidenori Fujita, Kenjiro Ito, Hiroaki Ochiwa, Yayoi Fujioka, Kimihiro Ito, Akihiro Miura, Takeshi Sagara, Satoru Ito, Hirokazu Ohsawa, Sachie Otsuki, Kaoru Funabashi, Masakazu Yashiro, Kenichi Matsuo, Kazuhiko Yonekura, and Hiroshi Hirai
Preclinical characterization of futibatinib, an irreversible FGFR1-4 inhibitor, demonstrates selective and potent antitumor activity against FGFR-deregulated cancer cell lines and xenograft models, supporting clinical evaluation in patients with FGFR-driven tumors.

4998 **Hypoxia Alters the Response to Anti-EGFR Therapy by Regulating EGFR Expression and Downstream Signaling in a DNA Methylation-Specific and HIF-Dependent Manner**

Mahelet Mamo, I. Chae Ye, Josh W. DiGiacomo, Je Yeon Park, Bradley Downs, and Daniele M. Gilkes
Hypoxia sensitizes breast cancer cells to EGFR inhibitors in an HIF1 α - and a methylation-specific manner, suggesting patients with hypoxic tumors may benefit from EGFR inhibitors already available to the clinic.

5011 **β -Galactosylceramidase Promotes Melanoma Growth via Modulation of Ceramide Metabolism**

Mirella Belleri, Giuseppe Paganini, Daniela Coltrini, Roberto Ronca, Daniela Zizioli, Michela Corsini, Andrea Barbieri, Elisabetta Grillo, Stefano Calza, Roberto Bresciani, Eugenio Maiorano, Mauro G. Mastropasqua, Tiziana Annese, Arianna Giacomini, Domenico Ribatti, Josefina Casas, Thierry Levade, Gemma Fabrias, and Marco Presta
Data from zebrafish embryos, murine and human cell melanoma lines, and patient-derived tumor specimens indicate that β -galactosylceramidase plays an oncogenic role in melanoma and may serve as a therapeutic target.

5024 **Local Targeting of NAD⁺ Salvage Pathway Alters the Immune Tumor Microenvironment and Enhances Checkpoint Immunotherapy in Glioblastoma**

Ming Li, Ameya R. Kirtane, Juri Kiyokawa, Hiroaki Nagashima, Aaron Lopes, Zain A. Tirmizi, Christine K. Lee, Giovanni Traverso, Daniel P. Cahill, and Hiroaki Wakimoto
Microparticle-mediated local inhibition of NAMPT modulates the tumor immune microenvironment and acts cooperatively with anti-PD-1 checkpoint blockade, offering a combination immunotherapy strategy for the treatment of GBM.

5035 **EpCAM Signaling Promotes Tumor Progression and Protein Stability of PD-L1 through the EGFR Pathway**

Hao-Nien Chen, Kang-Hao Liang, Jun-Kai Lai, Chun-Hsin Lan, Mei-Ying Liao, Shao-Hsi Hung, Yi-Ting Chuang, Kai-Chi Chen, William Wei-Fu Tsuei, and Han-Chung Wu
This study shows that treatment with an EpCAM neutralizing antibody promotes apoptosis while decreasing PD-L1 protein to enhance cytotoxic activity of CD8⁺ T cells.

5051 **FGFR1 Is Critical for RBL2 Loss-Driven Tumor Development and Requires PLCG1 Activation for Continued Growth of Small Cell Lung Cancer**

Kee-Beom Kim, Youngchul Kim, Christopher J. Rivard, Dong-Wook Kim, and Kwon-Sik Park
This study identifies RBL2 and PLCG1 as critical components of amplified FGFR1 signaling in SCLC, thus representing potential targets for biomarker analysis and therapeutic development in this disease.

TRANSLATIONAL SCIENCE

5063 **CD122-Selective IL2 Complexes Reduce Immunosuppression, Promote Treg Fragility, and Sensitize Tumor Response to PD-L1 Blockade**

Justin M. Drerup, Yilun Deng, Sri Lakshmi Pandeswara, Álvaro S. Padrón, Ryan M. Reyes, Xinyue Zhang, Jenny Mendez, Aijie Liu, Curtis A. Clark, Wanjiao Chen, José R. Conejo-García, Vincent Hurez, Harshita Gupta, and Tyler J. Curiel
These findings present CD122-targeted IL2 complexes as an advancement in cancer immunotherapy, as they reduce Treg immunosuppression, improve anticancer immunity, and boost PD-L1 immune checkpoint blockade efficacy in distinct tumors and anatomic locations.

TABLE OF CONTENTS

- 5076 A Functional Genomic Screen Identifies the Deubiquitinase USP11 as a Novel Transcriptional Regulator of ER α in Breast Cancer**
 Lisa Dwane, Aisling E. O'Connor, Sudipto Das, Bruce Moran, Laoighse Mulrane, Adan Pinto-Fernandez, Elspeth Ward, Anna M. Blümel, Brenton L. Cavanagh, Brian Mooney, Annette M. Dirac, Karin Jirstrom, Benedikt M. Kessler, Triona Ni Chonghaile, René Bernards, William M. Gallagher, and Darran P. O'Connor
 A newly identified role for USP11 in ER α transcriptional activity represents a novel mechanism of ER α regulation and a pathway to be exploited for the management of ER-positive breast cancer.
- 5089 Generalized Additive Mixed Modeling of Longitudinal Tumor Growth Reduces Bias and Improves Decision Making in Translational Oncology**
AC William F. Forrest, Bruno Alick, Oleg Mayba, Magdalena Osinska, Michal Jakubczak, Pawel Piatkowski, Lech Choniawko, Alice Starr, and Stephen E. Gould
 This work generalizes the statistical linear mixed modeling paradigm for summarizing longitudinally measured preclinical tumor volume studies to encompass studies with nonlinear and nonmonotonic group response patterns in a statistically rigorous manner.
- 5098 Glutamate Is a Noninvasive Metabolic Biomarker of IDH1-Mutant Glioma Response to Temozolomide Treatment**
 Elavarasan Subramani, Marina Radoul, Chloe Najac, Georgios Batsios, Abigail R. Molloy, Donghyun Hong, Anne Marie Gillespie, Romelyn Delos Santos, Pavithra Viswanath, Joseph F. Costello, Russell O. Pieper, and Sabrina M. Ronen
 These findings show that glutamate can be used as a noninvasive, imageable metabolic marker for early assessment of tumor response to temozolomide, with the potential to improve treatment strategies for mutant IDH1 patients.

CONVERGENCE AND TECHNOLOGIES

- 5109 Integrating Mathematical Modeling with High-Throughput Imaging Explains How Polyploid Populations Behave in Nutrient-Sparse Environments**
 Gregory J. Kimmel, Mark Dane, Laura M. Heiser, Philipp M. Altrock, and Noemi Andor
 This study identifies the double-edged sword of high ploidy as a prerequisite to personalize combination therapies with cytotoxic drugs and inhibitors of signal transduction pathways such as MTOR-Is.
- 5121 Modeling Resistance and Recurrence Patterns of Combined Targeted-Chemoradiotherapy Predicts Benefit of Shorter Induction Period**
 David M. McClatchy, Henning Willers, Aaron N. Hata, Zofia Piotrowska, Lecia V. Sequist, Harald Paganetti, and Clemens Grassberger
 A biomathematical framework based on fundamental principles of evolution and radiobiology for *in silico* clinical trial design allows clinicians to optimize administration of TKIs before chemoradiotherapy in oncogene-driven NSCLC.

POPULATION AND PREVENTION SCIENCE

- 5134 Postdiagnostic Fruit and Vegetable Consumption and Breast Cancer Survival: Prospective Analyses in the Nurses' Health Studies**
 Maryam S. Farvid, Michelle D. Holmes, Wendy Y. Chen, Bernard A. Rosner, Rulla M. Tamimi, Walter C. Willett, and A. Heather Eliassen
 A large-scale study shows that high fruit and vegetable consumption may be associated with better overall survival among breast cancer patients, while high fruit juice consumption may be associated with poorer prognosis.

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TABLE OF CONTENTS

ABOUT THE COVER

Stored lipid droplets promote pancreatic tumor cell migration. The image shows BxPC-3 pancreatic tumor cells migrating in a wound healing assay following loading with oleic acid. Lipid droplets (yellow, BODIPY-FL-C12), actin (red, phalloidin), and nuclei (blue). For details, see article by Rozeveld and colleagues on page 4932.

