

## CANCER RESEARCH

## TABLE OF CONTENTS

## BREAKING INSIGHTS

**2703** Highlights from Recent Cancer Literature

## REVIEW

**2705** The Matrix Revolution: Matricellular Proteins and Restructuring of the Cancer Microenvironment

**A C** Casimiro Gerarduzzi, Ursula Hartmann, Andrew Leask, and Elliot Drobetsky

## CANCER RESEARCH HIGHLIGHTS

**2718** When the Smoke Clears m<sup>6</sup>A from a Y Chromosome-Linked lncRNA, Men Get an Increased Risk of Cancer

A. Rouf Banday, Brenen W. Papenberg, and Ludmila Prokunina-Olsson

See related article, p. 2790

**2720** Not Black or White but Shades of Gray: Homologous Recombination Deficiency as a Continuous Variable Modulated by RNF168

Lin Wang and Gerburg M. Wulf

See related article, p. 2848

## GENOME AND EPIGENOME

**2722** Lineage-Specific Epigenomic and Genomic Activation of Oncogene HNF4A Promotes Gastrointestinal Adenocarcinomas

**A C** Jian Pan, Tiago C. Silva, Nicole Gull, Qian Yang, Jasmine T. Plummer, Stephanie Chen, Kenji Daigo, Takao Hamakubo, Sigal Gery, Ling-Wen Ding, Yan-Yi Jiang, Shaoyan Hu, Li-Yan Xu, En-Min Li, Yanbing Ding, Samuel J. Klempner, Simon A. Gayther, Benjamin P. Berman, H. Phillip Koeffler, and De-Chen Lin

These findings show that GIAC-specific master regulatory transcription factors control HNF4A via three distal enhancers to promote GIAC cell proliferation and survival.

**2737** The EZH2-PHACTR2-AS1-Ribosome Axis induces Genomic Instability and Promotes Growth and Metastasis in Breast Cancer

Wenhui Chu, Xi Zhang, Lihua Qi, Yenan Fu, Peng Wang, Wei Zhao, Juan Du, Jing Zhang, Jun Zhan, Yunling Wang, Wei-Guo Zhu, Yu Yu, and Hongquan Zhang

These findings reveal that EZH2 mediates ribosomal DNA stability via silencing of PHACTR2-AS1, representing a potential therapeutic target to control breast cancer growth and metastasis.

## METABOLISM AND CHEMICAL BIOLOGY

**2751** Therapeutic Targeting of the Secreted Lysophospholipase D Autotaxin Suppresses Tuberosclerosis Complex-Associated Tumorigenesis

You Feng, William J. Mischler, Ashish C. Gurung, Taylor R. Kavanagh, Grigoriy Androsof, Peter M. Sadow, Zachary T. Herbert, and Carmen Priolo

This study identifies activation of the ATX-LPA/SIP pathway as a novel mode of metabolic dysregulation upon TSC2 loss, highlighting critical roles for ATX in TSC2-deficient cell fitness and in TSC tumorigenesis.

**2764** De Novo Lipogenesis Alters the Phospholipidome of Esophageal Adenocarcinoma

Nima Abbassi-Ghadi, Stefan S. Antonowicz, James S. McKenzie, Sacheen Kumar, Juzheng Huang, Emrys A. Jones, Nicole Strittmatter, Gemma Petts, Hiromi Kudo, Stephen Court, Jonathan M. Hoare, Kirill Veselkov, Robert Goldin, Zoltán Takáts, and George B. Hanna

These results call for accelerated diagnosis studies using DESI-MSI in the upper gastrointestinal endoscopy suite, as well as functional studies to determine how polyunsaturated phosphatidylglycerols contribute to esophageal carcinogenesis.

## MOLECULAR CELL BIOLOGY

**2775** A Premalignant Cell-Based Model for Functionalization and Classification of PTEN Variants

Jesse T. Chao, Rocio Hollman, Warren M. Meyers, Fabian Meili, Kenneth A. Matreyek, Pamela Dean, Douglas M. Fowler, Kurt Haas, Calvin D. Roskelley, and Christopher J.R. Loewen

Combined three-dimensional tumor spheroid modeling and machine learning classifies PTEN missense variants, over 70% of which are currently listed as variants of uncertain significance.

# TABLE OF CONTENTS

- 2790** **A Novel Micropeptide Encoded by Y-Linked LINC00278 Links Cigarette Smoking and AR Signaling in Male Esophageal Squamous Cell Carcinoma**  
Siqi Wu, Liyuan Zhang, Jieqiong Deng, Binbin Guo, Fang Li, Yirong Wang, Rui Wu, Shenghua Zhang, Jiachun Lu, and Yifeng Zhou  
Posttranscriptional modification of a micropeptide-encoding lncRNA is negatively impacted by cigarette smoking, disrupting negative regulation of the AR signaling pathway in male ESCC.  
**See related commentary, p. 2718**
- 2804** **Pattern of Invasion in Human Pancreatic Cancer Organoids Is Associated with Loss of SMAD4 and Clinical Outcome**  
Wenjie Huang, Bernat Navarro-Serer, Yea Ji Jeong, Peter Chianchiano, Limin Xia, Claudio Luchini, Nicola Veronese, Cameron Dowiak, Tammy Ng, Maria A. Trujillo, Bo Huang, Michael J. Pflüger, Anne M. Macgregor-Das, Gemma Lionheart, Danielle Jones, Kohei Fujikura, Kim-Vy Nguyen-Ngoc, Neil M. Neumann, Vincent P. Groot, Alina Hasanain, A. Floortje van Oosten, Sandra E. Fischer, Steven Gallinger, Aatur D. Singhi, Amer H. Zureikat, Randall E. Brand, Matthias M. Gaida, Stefan Heinrich, Richard A. Burkhardt, Jin He, Christopher L. Wolfgang, Michael G. Goggins, Elizabeth D. Thompson, Nicholas J. Roberts, Andrew J. Ewald, and Laura D. Wood  
Organoid models of PDAC highlight the importance of SMAD4 loss in invasion, demonstrating that invasion programs in *SMAD4*-mutant and *SMAD4* wild-type tumors are different in both morphology and molecular mechanism
- 2818** **Prostaglandin E1 Inhibits *GLI2* Amplification-Associated Activation of the Hedgehog Pathway and Drug Refractory Tumor Growth**  
Fujia Wu, Chenze Zhang, Chen Zhao, Hao Wu, Zhaoqian Teng, Tao Jiang, and Yu Wang  
These findings show that PGE1 exhibits pan-inhibition against multiple drug refractory activities for Hedgehog-targeted therapies and elicits significant antitumor effects in xenograft models of drug refractory human medulloblastoma mimicking *GLI2* amplification.
- 2833** **Spatiotemporal Regulation of  $\Delta$ Np63 by TGF $\beta$ -Regulated miRNAs Is Essential for Cancer Metastasis**  
**A C** Ngoc H.B. Bui, Marco Napoli, Andrew John Davis, Hussein A. Abbas, Kimal Rajapakshe, Cristian Coarfa, and Elsa R. Flores  
This study unveils TGF $\beta$  signaling and a network of four miRNAs as upstream regulators of  $\Delta$ Np63, providing key information for the development of therapeutic strategies to treat cancers that commonly overexpress  $\Delta$ Np63.
- 2848** **RNF168-Mediated Ubiquitin Signaling Inhibits the Viability of *BRCA1*-Null Cancers**  
John J. Krais, Yifan Wang, Andrea J. Bernhardt, Emma Clausen, Jessica A. Miller, Kathy Q. Cai, Clare L. Scott, and Neil Johnson  
This study explores the concept that homologous recombination DNA repair is not an all-or-nothing concept, but a spectrum, and that where a tumor stands on this spectrum may have therapeutic relevance.  
**See related commentary, p. 2720**
- 2861** **Fibroblasts from Distinct Pancreatic Pathologies Exhibit Disease-Specific Properties**  
Lawrence N. Barrera, Anthony Evans, Brian Lane, Sarah Brumskill, Frances E. Oldfield, Fiona Campbell, Timothy Andrews, Zipeng Lu, Pedro A. Perez-Mancera, Triantafillos Liloglou, Milton Ashworth, Mehdi Jalali, Rebecca Dawson, Quentin Nunes, Phoebe A. Phillips, John F. Timms, Christopher Halloran, William Greenhalf, John P. Neoptolemos, and Eithne Costello  
Primary fibroblasts derived from various types of pancreatic diseases possess and retain distinct molecular and functional characteristics in culture, providing a series of cellular models for treatment development and disease-specific research.
- ## TUMOR BIOLOGY AND IMMUNOLOGY
- 2874** **Tumor-Derived Prostaglandin E2 Promotes p50 NF- $\kappa$ B-Dependent Differentiation of Monocytic MDSCs**  
Chiara Porta, Francesca Maria Consonni, Sara Morlacchi, Sabina Sangaletti, Augusto Bleve, Maria Grazia Totaro, Paola Larghi, Monica Rimoldi, Claudio Tripodo, Laura Strauss, Stefania Banfi, Mariangela Storto, Tiziana Pressiani, Lorenza Rimassa, Silvia Tartari, Alessandro Ippolito, Andrea Doni, Giulia Soldà, Stefano Duga, Viviana Piccolo, Renato Ostuni, Gioacchino Natoli, Vincenzo Bronte, Fiorella Balzac, Emilia Turco, Emilio Hirsch, Mario P. Colombo, and Antonio Sica  
Tumor-derived PGE2-mediated induction of nuclear p50 NF- $\kappa$ B epigenetically reprograms the response of monocytic cells to IFN $\gamma$  towards an immunosuppressive phenotype, thus retrieving the anticancer properties of IFN $\gamma$ .
- 2889** **Allosteric Inhibition of SHP2 Stimulates Antitumor Immunity by Transforming the Immunosuppressive Environment**  
**A C** Elsa Quintana, Christopher J. Schulze, Darienne R. Myers, Tiffany J. Choy, Kasia Mordec, David Wildes, Nataliya Tobvis Shifrin, Amira Belwafa, Elena S. Koltun, Adrian L. Gill, Mallika Singh, Stephen Kelsey, Mark A. Goldsmith, Robert Nichols, and Jacqueline A.M. Smith  
Inhibition of SHP2 causes direct and selective depletion of protumorigenic M2 macrophages and promotes antitumor immunity, highlighting an investigational therapeutic approach for some RAS pathway-driven cancers.

# TABLE OF CONTENTS

- 2903**    **The PET-Tracer <sup>89</sup>Zr-Df-IAB22M2C Enables Monitoring of Intratumoral CD8 T-cell Infiltrates in Tumor-Bearing Humanized Mice after T-cell Bispecific Antibody Treatment**

**AC**

Christoph M. Griessinger, Tove Olafsen, Alessandro Mascioni, Ziyue Karen Jiang, Charles Zamilpa, Fang Jia, Michael Torgov, Jason M. Romero, Filippo Marchioni, Daulet Satpayev, Chenyu Lee, Green Zhang, Tapan K. Nayak, Mudita Pincha, Maria Amann, Preethi L.B. Mohan, Marine Richard, Valeria G. Nicolini, Johannes Sam, Christina Claus, Claudia Ferrara, Peter Brünker, Marina Bacac, Pablo Umana, Dominik Rüttinger, Ian A. Wilson, Jean Gudas, Christian Klein, and Jean J.L. Tessier

Monitoring the pharmacodynamic activity of cancer immunotherapy with novel molecular imaging tools such as <sup>89</sup>Zr-Df-IAB22M2C for PET imaging is of prime importance to identify patients responding early to cancer immunotherapy.

- 2914**    **ERR $\alpha$  Expression in Bone Metastases Leads to an Exacerbated Antitumor Immune Response**

Mathilde Bouchet, Alexandra Lainé, Cyril Boyault, Mathilde Proponnet-Guerault, Emmanuelle Meugnier, Lamia Bouazza, Casina W.S. Kan, Sandra Geraci, Soumaya El-Moghrabi, Hector Hernandez-Vargas, Claire Benetollo, Yuji Yoshiko, Martine Duterque-Coquillaud, Philippe Clézardin, Julien C. Marie, and Edith Bonnelye

This study places ERR $\alpha$  at the interplay between the immune response and bone metastases of breast cancer, highlighting a potential target for intervention in advanced disease.

## TRANSLATIONAL SCIENCE

- 2927**    **Loss of a Negative Feedback Loop between IRF8 and AR Promotes Prostate Cancer Growth and Enzalutamide Resistance**

Hongxi Wu, Linjun You, Yan Li, Zhili Zhao, Guangjiang Shi, Zhen Chen, Zhuo Wang, Xianjing Li, Shijia Du, Wanli Ye, Xiaofang Gao, Jingjing Duan, Yan Cheng, Weiyan Tao, Jinsong Bian, Jin-Rong Zhou, Qingyi Zhu, and Yong Yang

These findings identify IRF8-mediated AR degradation as a mechanism of resistance to AR-targeted therapy, highlighting the therapeutic potential of IFN $\alpha$  in targeting IRF8-AR axis in CRPC.

- 2940**    **Cancer Exacerbates Chemotherapy-Induced Sensory Neuropathy**

Stephen N. Housley, Paul Nardelli, Dario I. Carrasco, Travis M. Rotterman, Emily Pfahl, Lilya V. Matyunina, John F. McDonald, and Timothy C. Cope

These findings highlight the need to account for pathobiological interactions between cancer and chemotherapy as a major contributor to neuropathy and will have significant and immediate impact on future investigations in this field.

## RESOURCE REPORT

- 2956**    **A Custom Genotyping Array Reveals Population-Level Heterogeneity for the Genetic Risks of Prostate Cancer and Other Cancers in Africa**

Maxine Harlemon, Olabode Ajayi, Paidamoyo Kachambwa, Michelle S. Kim, Corinne N. Simonti, Melanie H. Quiver, Desiree C. Petersen, Anuradha Mittal, Pedro W. Fernandez, Ann W. Hsing, Shakuntala Baichoo, Ilir Agalliu, Mohamed Jalloh, Serigne M. Gueye, Nana Yaa F. Snyder, Ben Adusei, James E. Mensah, Afua O.D. Abrahams, Akindele O. Adebisi, Akin T. Orunmuyi, Oseremen I. Aisuodionoe-Shadrach, Maxwell M. Nwegbu, Maureen Joffe, Wenlong C. Chen, Hayley Irusen, Alfred I. Neugut, Yuri Quintana, Moleboheng Seutloali, Mayowa B. Fadipe, Christopher Warren, Marcos H. Woehrmann, Peng Zhang, Chrissie M. Ongaco, Michelle Mawhinney, Jo McBride, Caroline V. Andrews, Marcia Adams, Elizabeth Pugh, Timothy R. Rebbeck, Lindsay N. Petersen, and Joseph Lachance

This study presents an Africa-specific genotyping array, which enables investigators to identify novel disease associations and to fine-map genetic loci that are associated with prostate and other cancers.

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# TABLE OF CONTENTS

## ABOUT THE COVER

Most germline and somatic cancer variants cannot be annotated due to lack of supporting evidence and are designed as variants of uncertain significance (VUS), confounding diagnosis and treatment. Chao and colleagues developed a cancer variomics approach for annotating variants of the tumor suppressor gene PTEN. They functionally assessed PTEN variants using a clinically relevant 3D tumor cell spheroid assay and reclassified variants with a machine learning model. This integrated approach reassigned many PTEN VUS into actionable classifications, which should allow clinicians to better consolidate data, improving diagnosis and treatment. For details, see article by Chao and colleagues on page 2775.

