# CANCER RESEARCH

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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 Tuberous Sclerosis Complex-Associated Tumorigenesis

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

This study identifies activation of the ATX-LPA/S1P 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 Kado, Stephen Court, Jonathan M. Hoare, Kirill Veselkov, Robert Goldin, Zoltan Takats, 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.
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2790 A Novel Micropeptide Encoded by Y-Linked LINC00278 Links Cigarette Smoking and AR Signaling in Male Esophageal Squamous Cell Carcinoma
Siqi Wu, Liiyuang Zheng, Jieqing Deng, Binbin Guo, Fang Li, Yirong Wang, Rui Wu, Shenghua Zhang, Jiachun Lu, and Yifeng Zhou
Posttranscriptional modification of a micropeptide-encoding IncRNA is negatively impacted by cigarette smoking, disrupting negative regulation of the AR signaling pathway in male ESCC.
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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, Kohfei Fujikura, Kim-Vy Nguyen-Ngoc, Neil M. Neumann, Vincent P. Groot, John F. Timms, Christopher Halloran, William Greenhal, 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.

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, Zhaqiaoan 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 ΔNp63 by TGFβ-Regulated miRNAs Is Essential for Cancer Metastasis
Ngoc H.B. Bui, Marco Napoli, Andrew John Davis, Hussein A. Abbas, Kimal Rajapakshe, Cristian Coarfa, and Elsa R. Flores
This study unveils TGFβ signaling and a network of four miRNAs as upstream regulators of ΔNp63, providing key information for the development of therapeutic strategies to treat cancers that commonly overexpress ΔNp63.

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.
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2861 Fibroblasts from Distinct Pancreatic Pathologies Exhibit Disease-Specific Properties
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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-κB-Dependent Differentiation of Monocytic MDSCs
Chiara Porta, Francesca Maria Consonni, Sara Morlacchi, Sabina Sangaletti, Augusto Bele, 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 Solda, Stefano Duga, Viviana Piccolo, Renato Ostuni, Giosaichino Natoli, Vincenzo Bronte, Fiorella Balzac, Emilia Turco, Emilio Hirsch, Mario P. Colombo, and Antonio Sica
Tumor-derived PGE2-mediated induction of nuclear p50 NF-κB epigenetically reprograms the response of monocytes to IFNγ towards an immunosuppressive phenotype, thus retrieving the anticancer properties of IFNγ.

2889 Allosteric Inhibition of SHP2 Stimulates Antitumor Immunity by Transforming the Immunosuppressive Environment
Elsa Quintana, Christopher J. Schulze, Darienne R. Myers, Tiffany J. Choy, Kasia Mordc, David Wildes, Nataliya Tobvis Shirrin, 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.
The PET-Tracer $^{89}$Zr-Df-IAB22M2C Enables Monitoring of Intratumoral CD8 T-cell Infiltrates in Tumor-Bearing Humanized Mice after T-cell Bispecific Antibody Treatment

Christoph M. Griessinger, Tove Olafsen, Alessandro Mascioni, Ziyue Karen Jiang, Charles Zamilpa, Fang Jia, Michael Torgov, Jason M. Romero, Filippo Marchioni, Peter Brünker, Marina Bacac, Pablo Umana, Dominik Rüttiger, 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 $^{89}$Zr-Df-IAB22M2C for PET imaging is of prime importance to identify patients responding early to cancer immunotherapy.

ERRα 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 Benetello, Yuji Yoshiko, Martine Dutertre-Coquillaud, Philippe Clézardin, Julien C. Marie, and Edith Bonnelye

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

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 IFNα in targeting IRF8-AR axis in CRPC.

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.

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


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.
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.