

CANCER RESEARCH

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- 2816** **A Nonconserved Histidine Residue on KRAS Drives Paralog Selectivity of the KRAS^{G12D} Inhibitor MRTX1133**
Miles A. Keats, John J.W. Han, Yeon-Hwa Lee, Chih-Shia Lee, and Ji Luo
The nonconserved H95 residue on KRAS is required for the selectivity of the KRAS^{G12D} inhibitor MRTX1133 and can be exploited for the development of pan-KRAS inhibitors.

CANCER BIOLOGY

- 2824** **CD36 Drives Metastasis and Relapse in Acute Myeloid Leukemia**
Thomas Farge, Jean Nakhle, Damien Lagarde, Guillaume Cognet, Nathaniel Polley, Rémy Castellano, Marie-Laure Nicolau, Claudie Bosc, Marie Sabatier, Ambrine Sahal, Estelle Saland, Yannick Jeanson, Nathan Guiraud, Emeline Boet, Camille Bergoglio, Mathilde Gotanègre, Pierre-Luc Mouchel, Lucille Stuan, Clément Larrue, Marie Sallese, Véronique De Mas, Cedric Moro, Cédric Dray, Yves Collette, Isabelle Raymond-Letron, Isabelle Ader, Christian Récher, Jean-Emmanuel Sarry, Florence Cabon, François Vergez, and Audrey Carrière
CD36 promotes blast migration and extramedullary disease in acute myeloid leukemia and represents a critical target that can be exploited for clinical prognosis and patient treatment.

2839 **Breast Cancer Mutations HER2^{V777L} and PIK3CA^{H1047R} Activate the p21-CDK4/6-Cyclin D1 Axis to Drive Tumorigenesis and Drug Resistance**

Xiaoqing Cheng, Yirui Sun, Maureen Highkin, Nagalaxmi Vemalapally, Xiaohua Jin, Brandon Zhou, Julie L. Prior, Ashley R. Tipton, Shunqiang Li, Anton Iliuk, Samuel Achilefu, Ian S. Hagemann, John R. Edwards, and Ron Bose

In HER2-mutated breast cancer, PIK3CA mutation activates p21-CDK4/6-cyclin D1 signaling to drive resistance to HER2-targeted therapies, which can be overcome using CDK4/6 inhibitors.

CANCER IMMUNOLOGY

- 2858** **Activation of the cGAS/STING Axis in Genome-Damaged Hematopoietic Cells Does Not Impact Blood Cell Formation or Leukemogenesis**
Nicole Dressel, Loreen Natusch, Clara M. Munz, Santiago Costas Ramon, Mina N.F. Morcos, Anja Löff, Björn Hiller, Christa Haase, Livia Schulze, Patrick Müller, Mathias Lesche, Andreas Dahl, Hella Luksch, Angela Rösen-Wolff, Axel Roers, Rayk Behrendt, and Alexander Gerbaulet

Loss of cGAS/STING signaling does not impact DNA damage-driven leukemogenesis or alter steady-state, perturbed or malignant hematopoiesis, indicating that the cGAS/STING axis is not a crucial antioncogenic mechanism in the hematopoietic system.

See related commentary, p. 2807

2873 **Preexisting Immunity Drives the Response to Neoadjuvant Chemotherapy in Esophageal Adenocarcinoma**

Giuseppina Arbore, Luca Albarello, Gabriele Bucci, Marco Punta, Andrea Cossu, Lorella Fanti, Aurora Maurizio, Francesco Di Mauro, Vito Bilello, Gianluigi Arrigoni, Silvia Bonfiglio, Donatella Biancolini, Francesco Puccetti, Ugo Elmore, Luca Vago, Stefano Cascinu, Giovanni Tonn, Riccardo Rosati, Giulia Casorati, and Paolo Dellabona

Multidimensional profiling of pretreatment esophageal adenocarcinoma shows patient response to nCT is correlated with active preexisting immunity and indicates molecular pathways of resistance that may be targeted to improve clinical outcomes.

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CANCER METABOLISM AND MOLECULAR MECHANISMS

2889 Targeting CaMKK2 Inhibits Actin Cytoskeletal Assembly to Suppress Cancer Metastasis

Debarati Mukherjee, Rebecca A. Previs, Corinne Haines, Muthana Al Abo, Patrick K. Juras, Kyle C. Strickland, Binita Chakraborty, Sandeep Artham, Regina S. Whitaker, Katherine Hebert, Jake Fontenot, Steven R. Patierno, Jennifer A. Freedman, Frank H. Lau, Matthew E. Burow, Ching-Yi Chang, and Donald P. McDonnell

CaMKK2 regulates actin cytoskeletal dynamics to promote tumor invasiveness and can be inhibited to suppress metastasis of breast and ovarian cancer, indicating CaMKK2 inhibition as a therapeutic strategy to arrest disease progression.

2908 SENP1 Decreases RNF168 Phase Separation to Promote DNA Damage Repair and Drug Resistance in Colon Cancer

Min Wei, Xiping Huang, Liming Liao, Yonglu Tian, and Xiaofeng Zheng

Sentrin/SUMO-specific protease 1 decreases RNF168 SUMOylation and liquid-liquid phase separation to promote DNA damage repair, safeguarding genomic integrity and driving chemotherapy resistance.

THERAPEUTIC DEVELOPMENT AND CHEMICAL BIOLOGY

2924 Nanoparticle-Based Combination Therapy Enhances Fulvestrant Efficacy and Overcomes Tumor Resistance in ER-Positive Breast Cancer

Bozhao Li, Feilong Qi, Fei Zhu, Zefang Lu, Meiqi Wang, Tianjiao Chu, Suying Wu, Jingyan Wei, Zhenchuan Song, Saraswati Sukumar, Cheng Zhang, Jiangfei Xu, Suping Li, and Guangjun Nie

A smart nanomedicine encapsulating fulvestrant to improve its half-life, bioavailability, and tumor-targeting and coloaded with CDK4/6 inhibitor abemaciclib to block resistance is a safe and effective therapy for ER-positive breast cancer.

TRANSLATIONAL CANCER BIOLOGY

2938 Supraphysiological Androgens Promote the Tumor Suppressive Activity of the Androgen Receptor through cMYC Repression and Recruitment of the DREAM Complex

Michael D. Nyquist, Ilsa M. Coleman, Jared M. Lucas, Dapei Li, Brian Hanratty, Hannah Meade, Elahe A. Mostaghel, Stephen R. Plymate, Eva Corey, Michael C. Haffner, and Peter S. Nelson

Determining the molecular pathways by which supraphysiological androgens promote growth arrest and treatment responses in prostate cancer provides opportunities for biomarker-selected clinical trials and the development of strategies to augment responses.

CANCER LANDSCAPES

2952 Mesenchymal-like Tumor Cells and Myofibroblastic Cancer-Associated Fibroblasts Are Associated with Progression and Immunotherapy Response of Clear Cell Renal Cell Carcinoma

Guillaume Davidson, Alexandra Helleux, Yann A. Vano, Véronique Lindner, Antonin Fattori, Marie Cerciat, Reza T. Elaidi, Virginie Verkarre, Cheng-Ming Sun, Christine Chevreau, Mostefa Bennamoun, Hervé Lang, Thibault Tricard, Wolf H. Fridman, Catherine Sautes-Fridman, Xiaoping Su, Damien Plassard, Celine Keime, Christelle Thibault-Carpentier, Philippe Barthelemy, Stéphane M. Oudard, Irwin Davidson, and Gabriel G. Malouf

Single-cell and spatial transcriptomics reveal the proximity of mesenchymal tumor cells to myofibroblastic cancer-associated fibroblasts and their association with disease outcome and immune checkpoint inhibitor response in clear cell renal cell carcinoma.

COMPUTATIONAL CANCER BIOLOGY AND TECHNOLOGY

2970 Whole Slide Imaging-Based Prediction of TP53 Mutations Identifies an Aggressive Disease Phenotype in Prostate Cancer

Marija Pizurica, Maarten Larmuseau, Kim Van der Eecken, Louise de Schaetzen van Brien, Francisco Carrillo-Perez, Simon Isphording, Nicolaas Lumen, Jo Van Dorpe, Piet Ost, Sofie Verbeke, Olivier Gevaert, and Kathleen Marchal

Deep learning models predicting TP53 mutations from whole slide images of prostate cancer capture histologic phenotypes associated with stromal composition, lymph node metastasis, and biochemical recurrence, indicating their potential as *in silico* prognostic biomarkers.

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ABOUT THE COVER

Studies have suggested that only around 30% of esophageal adenocarcinoma patients show a pathologic complete response to neoadjuvant chemotherapy. Multidimensional profiling of esophageal adenocarcinoma prior to neoadjuvant chemotherapy treatment was used to identify mechanisms and biomarkers of response. Patient response to neoadjuvant chemotherapy correlated with active preexisting immunity. The cover image shows spatial proteomics profiling of a formalin-fixed and paraffin-embedded esophageal adenocarcinoma biopsy to evaluate tumor epithelial cells (PanCK, green), macrophages (CD68, yellow), and T cells (CD3, red); nuclei were stained with DAPI (blue). For details, see article by Arbore and colleagues on page 2873.

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