# CANCER RESEARCH

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**A Transcriptionally Distinct Subpopulation of Healthy Acinar Cells Exhibit Features of Pancreatic Progenitors and PDAC**  
Vishaka Gopalan, Arashdeep Singh, Farid Rashidi Mehrabadi, Li Wang, Eytan Ruppin, H. Efsun Arda, and Sridhar Hannenhalli  
These findings show “edge” epithelial cell states with oncogenic transcriptional activity in human organs without oncogenic mutations. In the pancreas, the fraction of acinar cells increases with age.

3971  
**Gene Fusions Create Partner and Collateral Dependencies Essential to Cancer Cell Survival**  
Riaz Gillani, Bo Kyung A. Seong, Jett Crowdis, Jake R. Conway, Neekesh V. Dharia, Saif Alimohamed, Brian J. Haas, Kyuho Han, Ji hye Park, Felix Dietlein, Meng Xiao He, Alma Imamovic, Clément Ma, Michael C. Bassik, Jesse S. Boehm, Francisca Vazquez, Alexander Gusev, David Liu, Katherine A. Janeway, James M. McFarland, Kimberly Stegmaier, and Eliezer M. Van Allen

This study provides insights into how fusions contribute to fitness in different cancer contexts beyond partner-gene activation events, identifying partner and collateral dependencies that may have direct implications for clinical care.

3985  
**The Ratio of Toxic-to-Nontoxic miRNAs Predicts Platinum Sensitivity in Ovarian Cancer**  
Monal Patel, Yinu Wang, Elizabeth T. Bartom, Rohin Dhir, Kenneth P. Nephew, Daniela Matei, Andrea E. Murmann, Ernst Lengyel, and Marcus E. Peter  
These findings demonstrate that the balance of miRNAs that carry toxic and nontoxic 6mer seeds contributes to platinum resistance in ovarian cancer.

### METABOLISM AND CHEMICAL BIOLOGY

4001  
**Hypoxia-Driven Oncometabolite L-2HG Maintains Stemness-Differentiation Balance and Facilitates Immune Evasion in Pancreatic Cancer**  
This study shows that promiscuous LDH activity produces L-2HG in pancreatic tumor and stromal cells, modulating tumor stemness and immune cell function and infiltration in the tumor microenvironment.
4014 Gut Microbiota–Derived Short-Chain Fatty Acids Promote Prostate Cancer Growth via IGF1 Signaling

These results suggest that intestinal bacteria, acting through short-chain fatty acids, regulate systemic and local prostate IGF1 in the host, which can promote proliferation of prostate cancer cells.

4027 Alteration of MDM2 by the Small Molecule YF438 Exerts Antitumor Effects in Triple-Negative Breast Cancer
Peipei Shan, Feifei Yang, Hongzhao Qi, Yunjie Hu, Sujie Zhu, Zhenqing Sun, Zhe Zhang, Caixiao Wang, Chuanxiao Wang, Caixia Hou, Jie Yu, Lirong Wang, Zhihui Zhou, Peifeng Li, Hua Zhang, and Kun Wang

This study uncovers the essential role of MDM2 in TNBC progression and suggests that targeting the HDAC1–MDM2–MDMX axis with a hydroxamate-based HDACi could be a promising therapeutic strategy for TNBC.

4041 Valosin-Containing Protein Stabilizes Mutant p53 to Promote Pancreatic Cancer Growth
Jieqiong Wang, Yajie Chen, Canhwa Huang, Qian Hao, Shelyu X. Zeng, Sara Omari, Yu Zhang, Xiang Zhou, and Hua Lu

These findings identify valosin-containing protein (VCP) as a novel regulator of p53-R273H stability and suggest VCP as a potential target for development of pancreatic cancer therapy.

4054 Targeting Glucose Metabolism Sensitizes Pancreatic Cancer to MEK Inhibition
Liang Yan, Bo Tu, Jun Yao, Jing Gong, Alessandro Carugo, Christopher A. Bristow, Quyuan Wang, Cihui Zhu, Bingbing Dai, Ya’an Kang, Leng Han, Ningning Feng, Yanying Jin, Jason Fleming, Timothy P. Heffernan, Wantong Yao, and Haoqiang Ying

This study demonstrates the critical role of glucose metabolism in resistance to MAPK inhibition in KRAS-driven pancreatic cancer, uncovering a potential therapeutic approach for treating this aggressive disease.

4066 Stress-Mediated Reprogramming of Prostate Cancer One-Carbon Cycle Drives Disease Progression

These findings demonstrate that the mitochondrial, but not cytoplasmic, one-carbon cycle has a key role in prostate cancer cell growth and survival and may serve as a biomarker and/or therapeutic target.

4079 NEIL3 Prevents Senescence in Hepatocellular Carcinoma by Repairing Oxidative Lesions at Telomeres during Mitosis
Zhenjun Zhao, Helge Gad, Carlos Benitez-Buelga, Kumar Sanjiv, Hua Xiangwei, He Kang, Mingxuan Feng, Zhicong Zhao, Ulrika Warpmans Berglund, Qieng Xia, and Thomas Helladay

This study describes compartmentalization of base excision repair during mitosis that is dependent on NEIL3, APE1, and POLB to repair oxidative damage accumulating at telomeres in hepatocellular carcinoma.
Intravital Imaging Identifies the VEGF-TXA2 Axis as a Critical Promoter of PGE2 Secretion from Tumor Cells and Immune Evasion
Yoshinobu Konishi, Hiroshi Ichise, Tetsuya Watabe, Choji Oki, Shinya Tsukiji, Yoko Hamazaki, Yasuhito Murakawa, Akifumi Takaori-Kondo, Kentaro Terai, and Michiyuki Matsuda
This study identifies the VEGF-TXA2 axis as a potentially targetable regulator of PGE2 secretion, which provides novel strategies for prevention and treatment of multiple types of malignancies.

Lymphatic PD-L1 Expression Restricts Tumor-Specific CD8⁺ T-cell Responses
Nikola Cousin, Stefan Cap, Manuel Dihr, Carlotta Tacconi, Michael Detmar, and Lothar C. Dieterich
A new lymphatic-specific PD-L1 knockout mouse model reveals that lymphatic endothelial PD-L1 expression reduces tumor immunity, inducing apoptosis in tumor-specific CD8⁺ central memory cells in tumor-draining lymph nodes.

About the Cover
Circulating tumor cells (CTC) and macrophages interact and form pairs. The interactions increase metastatic potential of CTCs. Atomic force microscopy (AFM) imaging created the pseudo-3D reliefs of CTCs (yellow-orange-red) and macrophages (blue-navy-green), isolated from the blood of prostate cancer patients. Nanomechanical analysis by AFM helped to assess mechanical fitness of CTCs, indicating their capacity to survive and initiate metastasis. For details, see article by Osmulski and colleagues on page 4110.
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