

## CANCER RESEARCH

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Dmitry I. Gabrilovich  
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## CANCER RESEARCH HIGHLIGHTS

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Guus A.M.S. van Dongen  
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## GENOME AND EPIGENOME

- 3958** **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 Ruppim, 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, Neelesh V. Dharia, Saif Alimohamed, Brian J. Haas, Kyuho Han, Jihye Park, Felix Dietlein, Meng Xiao He, Alma Imamovic, Clement 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**

Vineet K. Gupta, Nikita S. Sharma, Brittany Durden, Vanessa T. Garrido, Kousik Kesh, Dujon Edwards, Dezhen Wang, Ciara Myer, Beatriz Mateo-Victoriano, Sai Sundeep Kollala, Yuguang Ban, Zhen Gao, Sanjoy K. Bhattacharya, Ashok Saluja, Pankaj K. Singh, and Sulagna Banerjee

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.

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- 4014 Gut Microbiota-Derived Short-Chain Fatty Acids Promote Prostate Cancer Growth via IGF1 Signaling**  
Makoto Matsushita, Kazutoshi Fujita, Takuji Hayashi, Hisako Kayama, Daisuke Motooka, Hiroaki Hase, Kentaro Jingushi, Gaku Yamamichi, Satoru Yumiba, Eisuke Tomiyama, Yoko Koh, Yujiro Hayashi, Kosuke Nakano, Cong Wang, Yu Ishizuya, Taigo Kato, Koji Hatano, Atsunari Kawashima, Takeshi Ujike, Motohide Uemura, Ryoichi Imamura, Maria D.C. Rodriguez Pena, Jennifer B. Gordetsky, George J. Netto, Kazutake Tsujikawa, Shota Nakamura, Kiyoshi Takeda, and Norio Nonomura  
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.
- 4066 Stress-Mediated Reprogramming of Prostate Cancer One-Carbon Cycle Drives Disease Progression**  
Nora Pällmann, Ke Deng, Marte Livgård, Martina Tesikova, Yixin Jin, Nicolai Sebastian Frengen, Nermin Kahraman, Hamada M. Mokhlis, Bulent Ozpolat, Wanja Kildal, Havard Emil Danielsen, Ladan Fazli, Paul S. Rennie, Partha P. Banerjee, Aykut Üren, Yang Jin, Omer F. Kuzu, and Fahri Saatcioglu  
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 Warpman Berglund, Qiang Xia, and Thomas Helleday  
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.
- ## MOLECULAR CELL BIOLOGY
- 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, Chuanxiao Wang, Caixia Hou, Jie Yu, Lirong Wang, Zhixia 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, Canhua Huang, Qian Hao, Shelya 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, Qiuyun Wang, Cihui Zhu, Bingbing Dai, Ya'an Kang, Leng Han, Ningping Feng, Yanqing 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.
- ## TUMOR BIOLOGY AND IMMUNOLOGY
- 4094 ENO1 Promotes Lung Cancer Metastasis via HGFR and WNT Signaling-Driven Epithelial-to-Mesenchymal Transition**  
Hsin-Jung Li, Feng-Yi Ke, Chia-Ching Lin, Mei-Yi Lu, Yi-Huei Kuo, Yi-Ping Wang, Kang-Hao Liang, Shin-Chang Lin, Ya-Hsuan Chang, Hsuan-Yu Chen, Pan-Chyr Yang, and Han-Chung Wu  
This study shows that ENO1 promotes lung cancer metastasis via HGFR and WNT signaling and introduces a novel anti-ENO1 antibody for potential therapeutic use in lung cancer.
- 4110 Contacts with Macrophages Promote an Aggressive Nanomechanical Phenotype of Circulating Tumor Cells in Prostate Cancer**  
Pawel A. Osmulski, Alessandra Cunsolo, Meizhen Chen, Yusheng Qian, Chun-Lin Lin, Chia-Nung Hung, Devalingam Mahalingam, Nameer B. Kirma, Chun-Liang Chen, Josephine A. Taverna, Michael A. Liss, Ian M. Thompson, Tim H.-M. Huang, and Maria E. Gaczynska  
The interaction between macrophages and circulating tumor cells increases the capacity of tumor cells to initiate metastasis and may constitute a new set of blood-based targets for pharmacological intervention.

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**4124 Intravital Imaging Identifies the VEGF-TXA<sub>2</sub> Axis as a Critical Promoter of PGE<sub>2</sub> Secretion from Tumor Cells and Immune Evasion**

Yoshinobu Konishi, Hiroshi Ichise, Tetsuya Watabe, Choji Oki, Shinya Tsukiji, Yoko Hamazaki, Yasuhiro Murakawa, Akifumi Takaori-Kondo, Kenta Terai, and Michiyuki Matsuda

This study identifies the VEGF-TXA<sub>2</sub> axis as a potentially targetable regulator of PGE<sub>2</sub> secretion, which provides novel strategies for prevention and treatment of multiple types of malignancies.

**4133 Lymphatic PD-L1 Expression Restricts Tumor-Specific CD8<sup>+</sup> T-cell Responses**

Nikola Cousin, Stefan Cap, Manuel Dühr, 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<sup>+</sup> central memory cells in tumor-draining lymph nodes.

## TRANSLATIONAL SCIENCE

**4145 Transient Competitive Inhibition Bypasses the Binding Site Barrier to Improve Tumor Penetration of Trastuzumab and Enhance T-DM1 Efficacy**

Brandon M. Bordeau, Yujie Yang, and Joseph P. Balthasar

This study describes the development of a transient competitive inhibition strategy that enhances the tumor penetration and efficacy of anticancer antibodies.

See related commentary, p. 3956

## POPULATION AND PREVENTION SCIENCE

**4155 Diabetes Risk Reduction Diet and Survival after Breast Cancer Diagnosis**

Tengteng Wang, Maryam S. Farvid, Jae H. Kang, Michelle D. Holmes, Bernard A. Rosner, Rulla M. Tamimi, Walter C. Willett, and A. Heather Eliassen

This study suggests that greater adherence to the diabetes risk reduction diet after diagnosis associates with improved survival outcomes among a large number of breast cancer survivors.

## 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.

