# CANCER RESEARCH

## TABLE OF CONTENTS

### BREAKING INSIGHTS

4371  
**Highlights from Recent Cancer Literature**

### REVIEWS

4373  
**60 Years Young: The Evolving Role of Allogeneic Hematopoietic Stem Cell Transplantation in Cancer Immunotherapy**  
Nicoletta Cieri, Katie Maurer, and Catherine J. Wu

4385  
**Fatty Acid Synthesis in Prostate Cancer: Vulnerability or Epiphenomenon?**  
Laura A. Sena and Samuel R. Denmeade

### CANCER RESEARCH LANDMARKS

4394  
**The Landmark Discovery That Paved the Way to a Mechanistic Understanding of P53 Gain of Function and Personalized Medicine**  
Marco Napoli, Avani A. Deshpande, and Elsa R. Flores  
See related article by Baker and colleagues, Cancer Res 1990;50:7717–22

### CANCER RESEARCH HIGHLIGHTS

4397  
**LGR4: Not Just for Wnt Anymore?**  
Payton D. Stevens and Bart O. Williams  
See related article, p. 4441

### CONTROVERSY AND CONSENSUS

4399  
**Patient-Derived Xenografts to Study Cancer Metabolism: When Does X Mark the Spot?**  
Christopher S. Nabel and Matthew G. Vander Heiden

### GENOME AND EPIGENOME

4402  
**The Proteomic Landscape of Growth Factor Signaling Networks Associated with FAS Mutations in Head and Neck Cancers**  
Zhengjiu Chen, Chao Zhang, Jianhong Chen, Dongsheng Wang, Jiqi Tu, Carter Van Waes, Nabil F. Saba, Zhuo G. Chen, and Zhong Chen  
Integrative bioinformatics and statistical analyses reveal a panel of genes and proteins associated with FAS mutation in HNSCC, providing important insights into prospective clinical investigations with targeted therapies.

### METABOLISM AND CHEMICAL BIOLOGY

4417  
**Metabolic Enzyme DLST Promotes Tumor Aggression and Reveals a Vulnerability to OXPHOS Inhibition in High-Risk Neuroblastoma**  
Nicole M. Anderson, Xiaodan Qin, Jennifer M. Finan, Andrew Lam, Jacob Athoe, Rindert Missiaen, Nicolas Skuli, Annie Kennedy, Amanda L. Saini, Ting Tao, Shizhen Zhu, Itzhak Nissim, A. Thomas Look, Guoliang Qing, M. Celeste Simon, and Hui Feng  
These findings demonstrate a novel role for DLST in neuroblastoma aggression and identify the OXPHOS inhibitor IACS-010759 as a potential therapeutic strategy for this deadly disease.

4431  
**PPARα Agonist Fenofibrate Enhances Cancer Vaccine Efficacy**  
Arezki Chekaoui and Hildegund C.J. Ertl  
These findings suggest that metabolic manipulations using already approved drugs may offer an easy pathway to increase the efficacy of vaccines against solid tumors.

### MOLECULAR CELL BIOLOGY

4441  
**A Wnt-Independent LGR4–EGFR Signaling Axis in Cancer Metastasis**  
Fei Yue, Weiyou Jiang, Amy T. Ku, Adelaide I.J. Young, Weijie Zhang, Eric P. Souto, Yankun Gao, Zihan Yu, Yi Wang, Chad J. Creighton, Chandandeep Nagi, Tao Wang, Susan G. Hilsenbeck, Xin-Hua Feng, Shixia Huang, Cristian Coarfa, Xiang H.-F. Zhang, Qingyun Liu, Xia Lin, and Yi Li  
This work demonstrates a Wnt-independent mechanism by which LGR4 promotes cancer metastasis.  
See related commentary, p. 4397
4455 AP-2α-Mediated Activation of E2F and EZH2 Drives Melanoma Metastasis
Jeffrey R. White, Dakota T. Thompson, Kelsey E. Koch, Boris S. Kiriazov, Anna C. Beck, Dana M. van der Heide, Benjamin G. Grimm, Mikhail V. Kulak, and Ronald J. Weigel
AP-2α drives melanoma metastasis by upregulating E2F pathway genes including EZH2 through inhibition of the NuRD repression complex, serving as a biomarker to predict responsiveness to EZH2 inhibitors.

4471 MAP3K7-IKK Inflammatory Signaling Modulates AR Protein Degradation and Prostate Cancer Progression
Zhenlin Huang, Bo Tang, Yinhui Yang, Zhaogang Yang, Lei Shi, Yang Bai, Binyuan Yan, R. Jeffrey Karnes, Jun Zhang, Rafael Jimenez, Liguang Wang, Qiang Wei, Jinjian Yang, Wanhai Xu, Zhankui Jia, and Haojie Huang
This study identifies that MAP3K7-IKK signaling plays a tumor suppressive role in prostate cancer by degrading AR, revealing potential prognostic and therapeutic strategies for MAP3K7-deficient tumors.

4485 Fusobacterium Nucleatum Promotes the Development of Colorectal Cancer by Activating a Cytochrome P450/Epoxyoctadecenoic Acid Axis via TLR4/Keap1/NRF2 Signaling
Cheng Kong, Xuebing Yan, Yefei Zhu, Huiyuan Zhu, Ying Luo, Peipei Liu, Sylvain Ferrandon, Matthew F. Kalady, Renyuan Gao, Jide He, Fang Yin, Xiao Qu, Jiayi Zheng, Yaohui Gao, Fang Wang, Penghui Zhou, Jinyun Liu, Peng Huang, Xiaodong Xia, and Xiaojun Xia
This study uncovers a mechanism by which Fusobacterium nucleatum regulates colorectal cancer metabolism to drive metastasis, suggesting this axis as a potential target for cancer immunotherapy.

4499 Nonsense-Mediated RNA Decay Is a Unique Vulnerability of Cancer Cells Harboring SF3B1 or U2AF1 Mutations
Abigael Cheruiyot, Shan Li, Sridhar Nonavinkeeratt Srivatsan, Tanvir Ahmed, Yuhao Chen, Delphine S. Lemacon, Ying Li, Zheng Yang, Brian A. Wadugu, Wayne A. Warner, Shondra M. Pruett-Miller, Esther A. Obeng, Daniel C. Link, Dalin He, Fei Xiao, Xiaowei Wang, Julie M. Bailis, Matthew J. Walter, and Zhongsheng You
This study has developed a novel NMD reporter system and identified a potential therapeutic approach of targeting the NMD pathway to treat cancer with spliceosome gene mutations.

4514 Mevalonate Blockade in Cancer Cells Triggers CLEC9A+ Dendritic Cell-Mediated Antitumor Immunity
Feifei Xu, Zining Wang, Hongxia Zhang, Jiemin Chen, Xiaojuan Wang, Lei Cui, Chunyan Xie, Mengyun Li, Fang Wang, Penghui Zhou, Jinyun Liu, Peng Huang, Xiaodong Xia, and Xiaojun Xia
These findings suggest that mevalonate blockade in cancer cells disrupts Rac1 prenylation to increase recognition and cross-presentation by conventional dendritic cells, suggesting this axis as a potential target for cancer immunotherapy.

4529 E2A Modulates Stemness, Metastasis, and Therapeutic Resistance of Breast Cancer
Celia López-Menéndez, Alberto Vázquez-Naharro, Vanesa Santos, Pierre Dubus, Patricia G. Santamaría, Ángel Martínez-Ramírez, Francisco Portillo, Gema Moreno-Bueno, Marisa M. Faraldo, and Amparo Cano
These findings identify key functions of E2A factors in breast cancer cell stemness, metastasis, and drug resistance, supporting a therapeutic vulnerability to targeting E2A proteins in breast cancer.

4545 o1-Acid Glycoprotein Enhances the Immunosuppressive and Protumor Functions of Tumor-Associated Macrophages
Kotaro Matsuoka, Yukio Fujiwara, Cheng Pan, Shigeyuki Esumi, Yoichi Saito, Jing Bi, Yuka Nakamura, Ayumi Mukunoki, Toru Takeo, Naomi Nakagata, Daisuke Yoshii, Ryo Fukuda, Taisei Nagasaki, Ryusei Tanaka, Hisakazu Komori, Hitoshi Maeda, Hiroshi Watanabe, Koji Tamada, Yoshihiro Komohara, and Toru Maruyama
AGP-mediated suppression of antitumor immunity contributes to tumor progression by inducing PD-L1 expression and IL6 production in TMAs.

4560 Development of a Novel Mouse Model of Spontaneous High-Risk HPV16/E7-Expressing Carcinoma in the Cervicovaginal Tract
Talia R. Henkle, Brandon Lam, Yu Jui Kung, John Lin, Ssu-Hsueh Tseng, Louise Ferrall, Deyin Xing, Chien-Fu Hung, and T.-C. Wu
This study describes the development of a clinically relevant mouse model of cervicovaginal carcinoma that progresses from high-grade lesions and recapitulates key features of human HPV+ cervical cancer.
Quantitative In Vivo Analyses Reveal a Complex Pharmacogenomic Landscape in Lung Adenocarcinoma

Chuan Li, Wen-Yang Lin, Hira Rizvi, Hongchen Cai, Christopher D. McFarland, Zoe N. Rogers, Maryam Yousefi, Ian P. Winters, Charles M. Rudin, Dmitri A. Petrov, and Monte M. Winslow

An experimental and analytical framework to generate in vivo pharmacogenomic maps that relate tumor genotypes to therapeutic responses reveals a surprisingly complex map of genotype-specific resistance and sensitivity.

Treatment with HIV-Protease Inhibitor Nelfinavir Identifies Membrane Lipid Composition and Fluidity as a Therapeutic Target in Advanced Multiple Myeloma

Lenka Besse, Andrej Besse, Sara C. Stolze, Amin Sobh, Esther A. Zaal, Alwin J. van der Ham, Mario Ruiz, Santosh Phuyal, Lorina Büchler, Marc Sathianathan, Bogdan I. Florea, Jan Borén, Marcus Stahlman, Julia Huber, Arnold Bolomsky, Heinz Ludwig, J. Thomas Hannich, Alex Loguinov, Bart Everts, Celia R. Berkers, Marc Pilon, Hesso Farhan, Christopher D. Vulpe, Herman S. Overkleeft, and Christoph Driessen

Nelfinavir induces lipid bilayer stress in cellular organelles that disrupts mitochondrial respiration and transmembrane protein transport, resulting in broad anticancer activity via metabolic rewiring and activation of the unfolded protein response.

Interventional Optical Imaging Permits Instant Visualization of Pathological Zones of Ablated Tumor Periphery and Residual Tumor Detection

Xuefeng Kan, Guanhui Zhou, Feng Zhang, Hongxiu Ji, Hui Zheng, Jeffrey Forris Beecham Chick, Karim Valji, Chuansheng Zheng, and Xiaoeming Yang

Interventional optical imaging can instantly visualize pathologic zones of ablated tumor peripheries to detect residual tumors, which could revolutionize current image-guided interventional oncologic ablation techniques.

Cell Line–Specific Network Models of ER⁺ Breast Cancer Identify Potential PI3Kα Inhibitor Resistance Mechanisms and Drug Combinations

Jorge Gómez Tejeda Zañudo, Pingping Mao, Clara Alcon, Kailey Kowalski, Gabriela N. Johnson, Guotai Xu, Jose Baselga, Maurizio Scaltriti, Anthony Letai, Joan Montero, Réka Albert, and Nikhil Wagle

Network-based mathematical models of oncogenic signaling and experimental validation of its predictions can identify resistance mechanisms for targeted therapies, as this study demonstrates for PI3Kα-specific inhibitors in breast cancer.

Genetic Risk for Overall Cancer and the Benefit of Adherence to a Healthy Lifestyle

Meng Zhu, Tianpei Wang, Yanqian Huang, Xiaoyu Zhao, Yuqing Ding, Mengyi Zhu, Mengmeng Ji, Cheng Wang, Juncheng Dai, Rong Yin, Lin Xu, Hongxia Ma, Qingyi Wei, Guangfu Jin, Zhabin Hu, and Hongbing Shen

A new indicator of cancer polygenic risk score measures genetic risk for overall cancer, which could identify individuals with high cancer risk to facilitate decision-making about lifestyle modifications for personalized prevention.

β-HPV positivity may be a useful biomarker for identifying individuals who could benefit from increased screening or novel cutaneous squamous cell carcinoma prevention strategies.
ABOUT THE COVER

LGR4/5/6 proteins play critical roles in development and cancer. The biological functions of these proteins have been primarily attributed to their roles in potentiating Wnt signaling. The mosaic photo illustrates widespread lung metastases in mice xenografted with green fluorescence–labeled human breast cancer cells expressing LGR4 mutants that cannot potentiate Wnt signaling, revealing that LGR4 promotes metastasis even when disengaged from Wnt signaling. For details, see article by Yue and colleagues on page 4441.

doi: 10.1158/0008-5472.CAN-81-17-CVR