

CANCER RESEARCH

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IN THE SPOTLIGHT

- 1955 Targeted Degradation of Mutant p53 Reverses the Pro-oncogenic Dominant-Negative Effect**
Jovanka Gencel-Augusto and Guillermina Lozano
[See related article, p. 1978](#)
- 1957 PROX1: A Key Regulator of Hepatocyte Identity and Tumorigenesis**
Terence Kin Wah Lee and Stephanie Ma

CANCER BIOLOGY

- 1960 FGFR2 Abrogation Intercepts Pancreatic Ductal Adenocarcinoma Development**
Claudia Tonelli, Astrid Deschênes, Victoria A. Gaeth, Amanda Jensen, Nandan Vithlani, Melissa A. Yao, Zhen Zhao, Youngkyu Park, and David A. Tuveson
FGFR2 inhibition reduces mutant KRAS signaling, which can impair mutant KRAS-expressing pancreatic cancer precursor lesions that are prevalent in the average healthy adult and delay pancreatic ductal adenocarcinoma progression.
- 1978 The Prolonged Half-Life of the p53 Missense Variant R248Q Promotes Accumulation and Heterotetramer Formation with Wild-Type p53 to Exert the Dominant-Negative Effect**
Nancy Klemm, Roman R. Schimmer, Nils K. Konrad, Flavian Thelen, Jonas Fullin, Ebru Topçu, Christian Koch, Milena Treacy, Matthew Joseph Leventhal, Marco M. Bühler, Veronika Lysenko, Alexandre P.A. Theocharides, Kari J. Kurppa, Stefan Balabanov, Tuncay Baubec, Andrei V. Krivtsov, Peter G. Miller, Scott A. Armstrong, Benjamin L. Ebert, Markus G. Manz, Cesar Nombela-Arrieta, and Steffen Boettcher
Heterotetramerization between R248Q mutant and wild-type p53 in conjunction with supraphysiologic p53^{R248Q} accumulation underlies the dominant-negative effect, highlighting the need to develop pharmacologic strategies to decrease the elevated R248Q:WT ratio.
[See related commentary, p. 1955](#)

CANCER IMMUNOLOGY

- 1997 Mutation of SMARCA4 Induces Cancer Cell-Intrinsic Defects in the Enhancer Landscape and Resistance to Immunotherapy**
Yawen Wang, Ismail M. Meraz, Md Quadratullah, Sasikumar Kotagiri, Yanyan Han, Yuanxin Xi, Jing Wang, Kadir C. Akdemir, Jack A. Roth, and Yonathan Lissanu
Epigenetic reprogramming in SMARCA4-mutant cancer cells alters immune infiltration and limits immunotherapy efficacy by downregulating immunostimulatory gene expression, which could potentially be targeted to overcome immunotherapy resistance in SMARCA4-deficient tumors.
- 2014 Blocking the TCA Cycle in Cancer Cells Potentiates CD36⁺ T-cell-Mediated Antitumor Immunity by Suppressing ER Stress-Associated THBS2 Signaling**
Jianqiang Yang, Fanghui Chen, Zhenzhen Fu, Fan Yang, Nabil F. Saba, and Yong Teng
The immunomodulatory role of the TCA cycle in cancer cells provides a therapeutic opportunity to enhance antitumor immunity by targeting tumor cell metabolism.

CANCER METABOLISM AND MOLECULAR MECHANISMS

- 2027 SMYD3 Activates Fatty Acid β -Oxidation to Promote Self-Renewal of Leukemia Stem Cells**
Min Zhou, Zihao Wu, Fen Wei, Chen Duan, Xiaoying Lin, Waiyi Zou, Chang Liu, Jingxuan Pan, and Yanli Jin
The epigenetic modulator SMYD3 promotes leukemogenesis and self-renewal of leukemia stem cells by upregulating FABP5 to stimulate fatty acid β -oxidation, which can be targeted to treat chronic myeloid leukemia.
- 2046 CRTC2 Forms Co-Condensates with YTHDF2 That Enhance Translational Efficiency of m⁶A-Modified mRNAs to Drive Hepatocarcinogenesis and Lenvatinib Resistance**
Meixi Wang, Fangdi Zou, Shengxin Wang, Yichen Yang, Cong Xia, Lu Chen, Ben Liu, Lian Li, Mulin Jun Li, Haixin Li, Weijie Song, Ruifang Niu, Zhiyong Yuan, Jie Yang, Xiangchun Li, Kexin Chen, Zhiqiang Wu, and Zeyun Mi
CRTC2 hijacks the YTHDF2-m⁶A pathway to increase translation of c-Jun and promote hepatocellular carcinoma development and lenvatinib resistance, indicating that CRTC2 is a promising biomarker and therapeutic target.

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THERAPEUTIC DEVELOPMENT AND CHEMICAL BIOLOGY

2067 An Anti-EGFR Antibody-Drug Radioconjugate Labeled with Actinium-225 Elicits Durable Antitumor Responses in KRAS- and BRAF-Mutant Colorectal Cancer

Anjong Florence Tikum, Nikita W. Henning, Jessica Pougoue Ketchemen, Alireza Doroudi, Hanan Babeker, Fabrice Ngoh Njotu, Emmanuel Nwangele, Alissar Monzer, Bridget Gray, Emina Torlakovic, Maruti Uppalapati, and Humphrey Fonge

Radiolabeling with [²²⁵Ac]Ac improves the efficacy of an anti-EGFR antibody-drug conjugate in KRAS- and BRAF^{V600E}-mutant colorectal cancer, providing hope for patients with these mutations who do not qualify for EGFR-targeted therapies.

TRANSLATIONAL CANCER BIOLOGY

2081 Perivascular Niche-Resident Alveolar Macrophages Promote Interstitial Pneumonitis Related to Trastuzumab Deruxtecan Treatment

Qing Wei, Teng Yang, Ziwen Zhang, Fei Wang, Yuxuan Yang, Jiayu Zhu, Xiu Zhu, Yuanzheng Li, Yun Xing, Ye Lu, Xuefei Tian, Mengyang Fan, Yuchao Zhang, Xiru Xue, Meng Li, Chuanfei Yu, Lan Wang, Takaya Shimura, Jianmin Fang, Zhiwei Cao, Jieer Ying, Peng Guo, and Xiangdong Cheng

Preconditioning the perivascular niche can prevent lung inflammation induced by antibody-drug conjugate phagocytosis by alveolar macrophages and subsequent SPP1^{high} macrophage differentiation, providing a clinically viable strategy for mitigating interstitial lung disease.

2100 Targeting the SP/KLF Transcriptional Regulatory Network Synergizes with HDAC Inhibition to Impede Progression of H3K27M Diffuse Intrinsic Pontine Glioma

Yu Kong, Fan Wang, Renwei Jing, Qian Zhao, Xuejiao Lv, Yingying Zhao, Ye Yuan, Xianyou Xia, Yu Sun, Yujie Tong, Han Yan, Qian Li, Ting Li, Lei Cao, Deng Liu, Dawei Huo, Shao-Kai Sun, Francisco Morís, Yujie Tang, and Xudong Wu

The SP/KLF transcriptional regulatory network is activated in H3K27M-mutated diffuse intrinsic pontine glioma and represents a promising therapeutic target in combination with HDAC inhibitors for combating these lethal pediatric brain tumors.

2117 Combining Apatinib and Oxaliplatin Remodels the Immunosuppressive Tumor Microenvironment and Sensitizes Desert-Type Gastric Cancer to Immunotherapy

Guang-Tan Lin, Cheng Yan, Lu-Jie Li, Xiao-Wen Qiu, Yu-Xuan Zhao, Ju-Li Lin, Yu-Jing Chen, Chuan Feng, Shao-Qiong Chen, Jian-Wei Xie, Chao-Hui Zheng, Sachiyo Nomura, Chang-Ming Huang, Ping Li, and Long-Long Cao

Apatinib combined with oxaliplatin reprograms the tumor immune microenvironment in desert-type gastric cancer, enhancing the efficacy of immune checkpoint blockade and paving the way for optimized combination immunotherapeutic strategies.

EDITOR'S NOTES

2134 Editor's Note: Normoxic Stabilization of Hypoxia-Inducible Factor-1 α by Modulation of the Labile Iron Pool in Differentiating U937 Macrophages: Effect of Natural Resistance-Associated Macrophage Protein 1

Helen J. Knowles, David R. Mole, Peter J. Ratcliffe, and Adrian L. Harris

2135 Editor's Note: Effects of Transferrin Receptor Blockade on Cancer Cell Proliferation and Hypoxia-Inducible Factor Function and Their Differential Regulation by Ascorbate

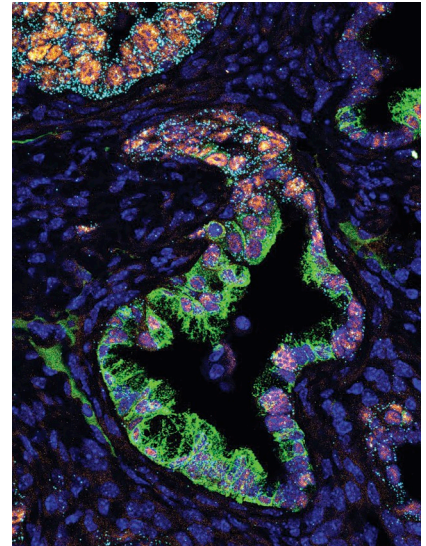
Dylan T. Jones, Ian S. Trowbridge, and Adrian L. Harris

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ABOUT THE COVER

Mutant KRAS drives pancreatic ductal adenocarcinoma (PDAC) initiation and progression. The receptor tyrosine kinase FGFR2 supports mutant KRAS signaling in the early phases of pancreatic tumorigenesis and the inactivation of FGFR2 intercepts disease development. The cover image depicts a murine precancerous lesion expressing FGFR2 (green), acquiring invasive features (p53 accumulation in orange and increased CDKN2A/ARF transcriptional expression in cyan), and progressing to PDAC. For details, see article by Tonelli and colleagues on page 1960.

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