CANCER RESEARCH
TABLE OF CONTENTS

EDITORIAL

2347 ***Cancer Research* in the Age of Big Data**
Christine A. Iacobuzio-Donahue

IN THE SPOTLIGHT

2348 **Leveraging Whole-Exome Sequencing and Mutational Signatures to Detect Homologous Recombination Deficiency in Cancer**
Joonoh Lim and Young Seok Ju

See related article, p. 2504

2351 **Cells Keep Diverse Company in Diseased Tissues**
Kieran R. Campbell and Aleksandrina Goeva

CANCER RESEARCH LANDMARKS

2353 **Paving a Path to Clinical Impact with Radiomics: Enabling Reproducibility and Reach**
Mohamad El-Jammal and Caroline Chung

See related article by Nioche and colleagues, Cancer Res 2018;78:4786-89

REVIEWS

2356 **Artificial Intelligence–Driven Cancer Diagnostics: Enhancing Radiology and Pathology through Reproducibility, Explainability, and Multimodality**
Pegah Khosravi, Thomas J. Fuchs, and David Joon Ho

2368 **Illuminating the Noncoding Genome in Cancer Using Artificial Intelligence**
Maria del Mar Alvarez-Torres, Xi Fu, and Raul Rabadan

2376 **Leveraging Artificial Intelligence for Neoantigen Prediction**
Jing Zeng, Zhengjun Lin, Xianghong Zhang, Tao Zheng, Haodong Xu, and Tang Liu

CANCER BIOLOGY

2388 **Dissecting FAP$^+$ Cell Diversity in Pancreatic Cancer Uncovers an Interferon-Response Subtype of Cancer-Associated Fibroblasts with Tumor-Restraining Properties**
Joshua Cumming, Parniyan Maneshi, Mitesh Dongre, Tala Alsaed, Mohammad Javad Dehghan-Nayeri, Agnes Ling, Kristian Pietras, Cedric Patthey, and Daniel Öhlund

Characterization of FAP$^+$ mesenchymal cell heterogeneity in pancreatic cancer identifies a tumor-suppressive interferon-response cancer-associated fibroblast subtype that can be induced by stimulating type I interferon signaling using STING agonists.

2412 **Targeting LTBP2 Derived from Cancer-Associated Fibroblasts Sensitizes Esophageal Squamous Cell Carcinoma to Chemotherapy**
Jiarong Zhan, Mengqing Li, Lei Li, Ting-Ting Zeng, Jun Liu, Qingyun Chen, Chen Jiang, Xin Wang, Dan Xie, Xin-Yuan Guan, and Ying-Hui Zhu

CAF-secreted LTBP2 binds integrin α6β4 and activates Src signaling to drive metastasis and chemoresistance in esophageal cancer, highlighting LTBP2 as a key regulator of CAF-mediated tumor progression that can be therapeutically targeted.

2429 **Chronic Stress Stimulates Protumor Macrophage Polarization to Propel Lung Cancer Progression**
Cuilan Liu, Hengwei Du, Guoxing Yu, Jingjing Qi, Hongliang Dong, Ruiqi Hu, Fei Wang, Bingjie Cui, Weiwei Chen, Qian Zhang, Chen Li, Ran Gao, Clemens A. Schmitt, Jiong Deng, Yong Yu, and Jing Du

Chronic stress facilitates lung cancer immune evasion by inducing M2-like macrophage polarization, supporting the potential of combination therapies targeting both tumor cells and the immune microenvironment for treating stress-related cancers.

TABLE OF CONTENTS

CANCER IMMUNOLOGY

2448 **Ammonia Suppresses the Antitumor Activity of Natural Killer Cells and T Cells by Decreasing Mature Perforin**
Joanna Domagala, Tomasz M. Grzywa, Iwona Baranowska, Magdalena Justyniarska, Ryan Tannir, Agnieszka Graczyk-Jarzynka, Aleksandra Kusowska, Maria Lecka, Marcin Poreba, Klaudyna Fidyt, Katsiaryna Marhelava, Zofia Pilch, Lea K. Picard, Tomasz Wegierski, Kamil Jastrzebski, Marta Krawczyk, Marta Klopotowska, Monika Granica, Doris Urlaub, Szymon Hajduk, Alexandra Neeser, Spencer Moros, Pawel Kozlowski, Malgorzata Bobrowicz, Marta Miaczynska, Leyuan Ma, Carsten Watzl, and Magdalena Winiarska
Ammonia is elevated in the tumor microenvironment and functions as an immunoinhibitory metabolite in cancer by reducing perforin levels, inhibiting NK and T-cell–mediated immunity and limiting the efficacy of immunotherapies.

2468 **Mannose Enhances Immunotherapy Efficacy in Ovarian Cancer by Modulating Gut Microbial Metabolites**
Chen Zhang, Yiying Wang, Mengdi He, Chenyang Wang, Kankan Cao, Yujing Zhong, Xueling Wang, Moran Yang, Guodong Zhang, Jiaqi Lu, Huan Yi, Haiou Liu, and Congjian Xu
Alterations to the gut microbiome induced by mannose engender an immune stimulatory tumor microenvironment responsive to immunotherapy, suggesting that mannose may be an effective and safe adjuvant therapy for stimulating immunotherapy sensitivity.

TRANSLATIONAL CANCER BIOLOGY

2485 **SCD1 Inhibition Blocks the AKT–NRF2–SLC7A11 Pathway to Induce Lipid Metabolism Remodeling and Ferroptosis Priming in Lung Adenocarcinoma**
Utsav Sen, Charles Coleman, Nishant Gandhi, Vrinda Jethalia, Deniz Demircioglu, Andrew Elliott, Ari M. Vanderwalde, Omar Hayatt, Elisa de Stanchina, Balazs Halmos, Patrick C. Ma, Mirela Berisa, Dan Hasson, and Triparna Sen
SCD1 and SLC7A11 are prognostic biomarkers and therapeutic targets for *KRAS/STK11/KEAP1* co-mutant lung adenocarcinoma, which will refocus mechanistic studies and lead to treatment strategies for lung cancer.

COMPUTATIONAL CANCER BIOLOGY AND TECHNOLOGY

2504 **HRProfiler Detects Homologous Recombination Deficiency in Breast and Ovarian Cancers Using Whole-Genome and Whole-Exome Sequencing Data**
Ammal Abbasi, Christopher D. Steele, Erik N. Bergstrom, Azhar Khandekar, Akanksha Farswan, Rana R. McKay, Nischalan Pillay, and Ludmil B. Alexandrov
HRProfiler is a machine learning approach that reliably identifies homologous recombination deficiency in whole-exome–sequenced breast and ovarian cancers, outperforming other tools and providing clinically useful insights.

See related commentary, p. 2348

2514 **Combining Spatial Transcriptomics, Pseudotime, and Machine Learning Enables Discovery of Biomarkers for Prostate Cancer**
Martin Smelik, Daniel Diaz-Roncero Gonzalez, Xiaojing An, Rakesh Heer, Lars Henningsohn, Xinxiu Li, Hui Wang, Yelin Zhao, and Mikael Benson
Integrating spatial transcriptomics, pseudotime, and machine learning analyses is effective for identifying prostate cancer biomarkers that are reliable in different settings and measurable with routine methods, providing potential early diagnosis strategies.

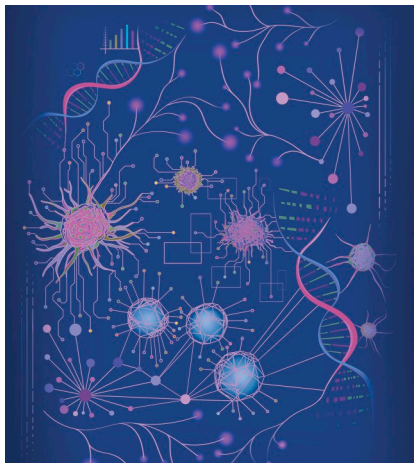
2527 **Multitask Deep Learning Based on Longitudinal CT Images Facilitates Prediction of Lymph Node Metastasis and Survival in Chemotherapy-Treated Gastric Cancer**
Bingjiang Qiu, Yunlin Zheng, Shunli Liu, Ruirui Song, Lei Wu, Cheng Lu, Xianqi Yang, Wei Wang, Zaiyi Liu, and Yanfen Cui
CTSMamba is a multitask deep learning model trained on longitudinal CT images of neoadjuvant chemotherapy-treated locally advanced gastric cancer that accurately predicts lymph node metastasis and overall survival to inform clinical decision-making.

CONVERGENCE SCIENCE

2537 **Eco-Evolutionary Guided Pathomic Analysis Detects Biomarkers to Predict Ductal Carcinoma *In Situ* Upstaging**
Yujie Xiao, Manal Elmasry, Ji Dong K. Bai, Andrew Chen, Yuzhu Chen, Brooke Jackson, Joseph O. Johnson, Prateek Prasanna, Chao Chen, and Mehdi Damaghi
Evolutionary dynamics of the various niches composing the tumor ecosystem can be harnessed for predicting cancer progression, demonstrating how eco-evolutionary–designed approaches can guide biomarkers discovery studies in the era of digital pathology.

TABLE OF CONTENTS

ABOUT THE COVER



The exponential pace at which multiomics data is being generated has coincided with a rapid rise of data science, which enables exciting research providing in-depth insights into cancer biology. As the foundational journal of the AACR, *Cancer Research* aims to be a home for data science studies, with the goal of fostering cross-disciplinary collaborations that will stimulate new ideas to advance the understanding and treatment of cancer. This issue of the journal is launching the special series: Driving Cancer Discoveries with Computational Research, Data Science, and Machine Learning/AI, which contains cutting-edge research and reviews on the frontier of computational and data-driven approaches in cancer research to spur innovative biological discoveries and clinical solutions. Artwork by Bianca Dunn. For details, see the editorial by the Editor-in-Chief, Dr. Christine A. Iacobuzio-Donahue, MD, PhD, on page 2347.

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