

CANCER RESEARCH

TABLE OF CONTENTS

BREAKING INSIGHTS

2803 Highlights from Recent Cancer Literature

OBITUARY

2805 **George F. Vande Woude: In Memoriam (1935–2021)**
Peter A. Jones

REVIEW

2807 **Roles of the BAP1 Tumor Suppressor in Cell Metabolism**
Anna Han, Timothy J. Purwin, and Andrew E. Aplin

CANCER RESEARCH HIGHLIGHTS

2815 **Loss of Gas7 is a Key Metastatic Switch in Neuroblastoma**
Marie J. Menard
See related article, p. 2995

2817 **To Go or Not to Go?—Targeting Tregs Traveling in Tumors**
Sanjukta Chakraborty and Roberta Zappasodi
See related articles, p. 2970 and p. 2983

CONTROVERSY AND CONSENSUS

2820 **Oncometabolites in Cancer: Current Understanding and Challenges**
Yang Liu and Chunzhang Yang

PRIORITY REPORTS

2824 **Dietary Fructose Promotes Prostate Cancer Growth**
Daniela V. Carreño, Néstor B. Corro, Javier F. Cerda-Infante, Carolina E. Echeverría, Catalina A. Asencio-Barría, Verónica A. Torres-Estay, Gonzalo A. Mayorga-Weber, Pablo A. Rojas, Loreto P. Véliz, Pedro A. Cisternas, Viviana P. Montecinos, Ignacio F. San Francisco, Manuel A. Varas-Godoy, Paula C. Sotomayor, Maite A. Castro, Francisco J. Nualart, Nivaldo C. Inestrosa, and Alejandro S. Godoy
This study identifies increased expression of fructose transporters in prostate cancer and demonstrates a role for fructose as a key metabolic substrate supporting prostate cancer cells, revealing potential therapeutic targets and biomarkers.

GENOME AND EPIGENOME

2833 **Androgen Receptor Regulates CD44 Expression in Bladder Cancer**
Joseph L. Sottnik, Lauren Vanderlinden, Molishree Joshi, Ana Chauca-Diaz, Charles Owens, Donna E. Hansel, Colin Sempeck, Debashis Ghosh, and Dan Theodorescu
This study describes novel AREs that suppress CD44 and an expected inverse correlation of AR-CD44 expression observed in human bladder tumors.

2847 ***N*⁶-Methyladenosine Regulates mRNA Stability and Translation Efficiency of KRT7 to Promote Breast Cancer Lung Metastasis**
Feng Chen, Zhuojia Chen, Tao Guan, Yan Zhou, Lichen Ge, Haisheng Zhang, Yingmin Wu, Guan-Min Jiang, Weiling He, Jiexin Li, and Hongsheng Wang
This study suggests that *N*⁶-methyladenosine is a key driver and potential therapeutic target in breast cancer metastasis.

TABLE OF CONTENTS

METABOLISM AND CHEMICAL BIOLOGY

- 2861 DNA Damage Response Protein CHK2 Regulates Metabolism in Liver Cancer**
Matteo Lulli, Laura Del Coco, Tommaso Mello, Caecilia Sukowati, Stefania Madiari, Laura Gragnani, Paolo Forte, Francesco Paolo Fanizzi, Antonio Mazzocca, Krista Rombouts, Andrea Galli, and Vinicio Carloni
This study uncovers a link between a central effector of DNA damage response, CHK2, and cellular metabolism, revealing potential therapeutic strategies for targeting hepatocellular carcinoma.
- 2874 E2F1 and E2F2-Mediated Repression of CPT2 Establishes a Lipid-Rich Tumor-Promoting Environment**
Francisco González-Romero, Daniela Mestre, Igor Aurrekoetxea, Colm J. O'Rourke, Jesper B. Andersen, Ashwin Woodhoo, Miguel Tamayo-Caro, Marta Varela-Rey, Marta Palomo-Irigoyen, Beatriz Gómez-Santos, Diego Sáenz de Urturi, Maitane Núñez-García, Juan L. García-Rodríguez, Larraitz Fernández-Ares, Xabier Buqué, Ainhoa Iglesias-Ara, Irantzu Bernales, Virginia Gutierrez De Juan, Teresa C. Delgado, Naroa Goikoetxea-Usandizaga, Richard Lee, Sanjay Bhanot, Igotz Delgado, Maria J. Perugorria, Gaizka Errazti, Lorena Mosteiro, Sonia Gaztambide, Idoia Martínez de la Piscina, Paula Iruzubieta, Javier Crespo, Jesus M. Banales, Maria L. Martínez-Chantar, Luis Castaño, Ana M. Zubiaga, and Patricia Aspichueta
These findings identify E2F1 and E2F2 transcription factors as metabolic drivers of hepatocellular carcinoma, where deletion of just one is sufficient to prevent disease.

MOLECULAR CELL BIOLOGY

- 2888 PBRM1 Deficiency Confers Synthetic Lethality to DNA Repair Inhibitors in Cancer**
Roman M. Chabanon, Daphné Morel, Thomas Eychenne, Léo Colmet-Daage, Ilirjana Bajrami, Nicolas Dorvault, Marlène Garrido, Cornelia Meisenberg, Andrew Lamb, Carine Ngo, Suzanna R. Hopkins, Theodoros I. Roumeliotis, Samuel Jouny, Clémence Hénon, Asuka Kawai-Kawachi, Clémence Astier, Asha Konde, Elaine Del Nery, Christophe Massard, Stephen J. Pettitt, Raphaël Margueron, Jyoti S. Choudhary, Geneviève Almouzni, Jean-Charles Soria, Eric Deutsch, Jessica A. Downs, Christopher J. Lord, and Sophie Postel-Vinay
This study demonstrates that PARP and ATR inhibitors are synthetic lethal with the loss of PBRM1, a PBAF-specific subunit, thus providing the rationale for assessing these inhibitors in patients with PBRM1-defective cancer.

- 2903 Combined Inhibition of p38MAPK and PIKfyve Synergistically Disrupts Autophagy to Selectively Target Cancer Cells**
Constandina E. O'Connell and Alex Vassilev
This study demonstrates that PIKfyve and p38MAPK cooperate to regulate lysosome homeostasis and their combined inhibition synergistically blocks autophagy to reduce cancer cell viability *in vitro* and *in vivo*.

- 2918 LncRNA SAMMSON Mediates Adaptive Resistance to RAF Inhibition in BRAF-Mutant Melanoma Cells**
Shujun Han, Yuwei Yan, Yibo Ren, Yiming Hu, Yan Wang, Lei Chen, Zhe Zhi, Yan Zheng, Yongping Shao, and Jiankang Liu
This study highlights the role of a SAMMSON/CARF/p53 signaling axis in modulating the adaptive resistance of mutant BRAF melanoma to RAF inhibitors.

- 2930 A Fusion Transcription Factor-Driven Cancer Progresses to a Fusion-Independent Relapse via Constitutive Activation of a Downstream Transcriptional Target**
A C
Salah Boudjadi, Puspa Raj Pandey, Bishwanath Chatterjee, Thanh Hung Nguyen, Wenyue Sun, and Frederic G. Barr
In a model of cancer initiated by a fusion transcription factor, constitutive activation of a downstream transcriptional target leads to fusion oncoprotein-independent recurrences, thereby highlighting a novel progression mechanism and therapeutic target.

- 2943 STIM1 Mediates Calcium-Dependent Epigenetic Reprogramming in Pancreatic Cancer**
Ana P. Kutschat, Fedaa H. Hamdan, Xin Wang, Alexander Q. Wixom, Zeynab Najafova, Christine S. Gibhardt, Waltraut Kopp, Jochen Gaedcke, Philipp Ströbel, Volker Ellenrieder, Ivan Bogeski, Elisabeth Hessmann, and Steven A. Johnsen
Gemcitabine-resistant and some naïve tumors coamplify *RRM1* and *STIM1*, which elicit gemcitabine resistance and induce a calcium signaling shift, promoting ER stress resistance and activation of NFAT signaling.

- 2956 Nuclear Receptor Coactivator NCOA3 Regulates UV Radiation-Induced DNA Damage and Melanoma Susceptibility**
David de Semir, Vladimir Bezrookove, Mehdi Nosrati, Altaf A. Dar, James R. Miller III, Stanley P. Leong, Kevin B. Kim, Wilson Liao, Liliana Soroceanu, Sean McAllister, Robert J. Debs, Dirk Schadendorf, Sancy A. Leachman, James E. Cleaver, and Mohammed Kashani-Sabet
This study explores NCOA3 as a regulator of the DDR and a therapeutic target in melanoma, where activation of NCOA3 contributes to melanoma development following exposure to ultraviolet light.

TABLE OF CONTENTS

TUMOR BIOLOGY AND IMMUNOLOGY

2970 **GPR15 Facilitates Recruitment of Regulatory T Cells to Promote Colorectal Cancer**

Alexandra Adamczyk, Eva Pastille, Jan Kehrmann, Vivian P. Vu, Robert Geffers, Marie-Hélène Wasmer, Stefan Kasper, Martin Schuler, Christian M. Lange, Beat Muggli, Tilman T. Rau, Diana Klein, Wiebke Hansen, Philippe Krebs, Jan Buer, and Astrid M. Westendorf

The G protein-coupled receptor 15, an unconventional chemokine receptor, directs Tregs into the colon, thereby modifying the tumor microenvironment and promoting intestinal tumorigenesis.

See related commentary, p. 2817

2983 **Fc-Optimized Anti-CCR8 Antibody Depletes Regulatory T Cells in Human Tumor Models**

Joseph R. Campbell, Bryan R. McDonald, Paul B. Mesko, Nathan O. Siemers, Priti B. Singh, Mark Selby, Tim W. Sproul, Alan J. Korman, Logan M. Vlach, Jeff Houser, Sharmila Sambanthamoorthy, Kai Lu, Sandra V. Hatcher, Jack Lohre, Renu Jain, and Ruth Y. Lan

These findings show that selective depletion of regulatory T cells with an anti-CCR8 antibody can improve antitumor immune responses as a monotherapy or in combination with other immunotherapies.

See related commentary, p. 2817

2995 **GAS7 Deficiency Promotes Metastasis in MYCN-Driven Neuroblastoma**

Zhiwei Dong, Kok Siong Yeo, Gonzalo Lopez, Cheng Zhang, Erin N. Dankert Eggum, Jo Lynne Rokita, Choong Yong Ung, Taylor M. Levee, Zuag Paj Her, Cassie J. Howe, Xiaonan Hou, Janine H. van Ree, Shuai Li, Shuning He, Ting Tao, Karen Fritchie, Jorge Torres-Mora, Julia S. Lehman, Alexander Meves, Gina L. Razidlo, Komal S. Rathi, S. John Weroha, A. Thomas Look, Jan M. van Deursen, Hu Li, Jennifer J. Westendorf, John M. Maris, and Shizhen Zhu

Heterozygous deletion or *MYCN*-mediated repression of *GAS7* in neuroblastoma releases an important brake on tumor cell dispersion and migration to distant sites, providing a novel mechanism underlying tumor metastasis in *MYCN*-driven neuroblastoma.

See related commentary, p. 2815

3008 **Epigenetic and Posttranscriptional Modulation of SOS1 Can Promote Breast Cancer Metastasis through Obesity-Activated c-Met Signaling in African-American Women**

Fei Xing, Dan Zhao, Shih-Ying Wu, Abhishek Tyagi, Kerui Wu, Sambad Sharma, Yin Liu, Ravindra Deshpande, Yuezhu Wang, Jacob Cleary, Lance D. Miller, Amar G. Chittiboyina, Chinni Yalamanchili, Yin-Yuan Mo, and Kounosuke Watabe

These findings elucidate the signaling network of *SOS1*-mediated metastasis in African-American patients, from the epigenetic upregulation of *SOS1* to the identification of taxifolin as a potential therapeutic strategy against *SOS1*-driven tumor progression.

3022 **Mesothelin-Specific CAR T Cells Target Ovarian Cancer**

A C

Esther Schoutrop, Ibrahim El-Serafi, Thomas Poirer, Ying Zhao, Okan Gultekin, Rui He, Lidia Moyano-Galceran, Joseph W. Carlson, Kaisa Lehti, Moustapha Hassan, Isabelle Magalhaes, and Jonas Mattsson

These findings demonstrate that *MSLN*-directed CAR T cells can provide antitumor immunity against ovarian cancer.

3036 **A TNFR2-hnRNPK Axis Promotes Primary Liver Cancer Development via Activation of YAP Signaling in Hepatic Progenitor Cells**

Yan Meng, Qiudong Zhao, Liwei An, Shi Jiao, Rong Li, Yan Sang, Jianping Liao, Pingping Nie, Fuping Wen, Junyi Ju, Zhaocai Zhou, and Lixin Wei

This work defines how *hnRNPK* links *TNF α* signaling and Hippo pathway transcription coactivator *YAP* in hepatic progenitor cells during primary liver tumorigenesis.

TRANSLATIONAL SCIENCE

3051 **Alterations in the Global Proteome and Phosphoproteome in Third Generation EGFR TKI Resistance Reveal Drug Targets to Circumvent Resistance**

Xu Zhang, Tapan K. Maity, Karen E. Ross, Yue Qi, Constance M. Cultraro, Meriam Bahta, Stephanie Pitts, Meghana Keswani, Shaojian Gao, Khoa Dang P. Nguyen, Julie Cowart, Fatos Kirkali, Cathy Wu, and Udayan Guha

Global quantitative proteomics reveals changes in the proteome and phosphoproteome in lung cancer cells resistant to third generation EGFR TKIs, identifying the *PI3K/MTOR* inhibitor dactolisib as a potential approach to overcome resistance.

3067 **SLFN11 Inactivation Induces Proteotoxic Stress and Sensitizes Cancer Cells to Ubiquitin Activating Enzyme Inhibitor TAK-243**

Yasuhisa Murai, Ukhyun Jo, Junko Murai, Lisa M. Jenkins, Shar-Yin N. Huang, Sirisha Chakka, Lu Chen, Ken Cheng, Shinsaku Fukuda, Naoko Takebe, and Yves Pommier

This study uncovers that *SLFN11* deficiency induces proteotoxic stress and sensitizes cancer cells to TAK-243, suggesting that profiling *SLFN11* status can serve as a therapeutic biomarker for cancer therapy.

TABLE OF CONTENTS

3079 Inhibition of MDM2 Promotes Antitumor Responses in p53 Wild-Type Cancer Cells through Their Interaction with the Immune and Stromal Microenvironment

Hui Qin Wang, Iain J. Mulford, Fiona Sharp, Jinsheng Liang, Sema Kurtulus, Gina Trabucco, David S. Quinn, Tyler A. Longmire, Nidhi Patel, Roshani Patil, Matthew D. Shirley, Yan Chen, Hao Wang, David A. Ruddy, Claire Fabre, Juliet A. Williams, Peter S. Hammerman, Jennifer Mataraza, Barbara Platzer, and Ensar Halilovic
This study provides a mechanistic rationale for combining checkpoint blockade immunotherapy with MDM2 inhibitors in patients with wild-type p53 tumors.

3092 Rapid Depletion of Intratumoral Regulatory T Cells Induces Synchronized CD8 T- and NK-cell Activation and IFN γ -Dependent Tumor Vessel Regression

Yutaka Kurebayashi, Colleen P. Olkowski, Kelly C. Lane, Olga V. Vasalatiy, Biying C. Xu, Ryuhei Okada, Aki Furusawa, Peter L. Choyke, Hisataka Kobayashi, and Noriko Sato
Intratumoral Treg depletion induces synchronized intratumoral CD8 T- and NK-cell activation, IFN γ -dependent tumor vessel regression, and ischemic tumor necrosis/apoptosis, indicating the roles of intratumoral Tregs to support the tumor vasculature.

3105 Inhibition of the FACT Complex Targets Aberrant Hedgehog Signaling and Overcomes Resistance to Smoothed Antagonists

Jialin Mo, Fang Liu, Xi Sun, Hongting Huang, Kezhe Tan, Xiaojing Zhao, Rui Li, Wenyan Jiang, Yi Sui, Xiaosong Chen, Kunwei Shen, Liye Zhang, Jie Ma, Kewen Zhao, and Yujie Tang
This study identifies FACT inhibition as an anti-hedgehog therapeutic strategy for overcoming resistance to Smoothed inhibitors and provides preclinical support for initiating clinical trials of FACT-targeted drug CBL0137 against hedgehog-driven cancers.

3121 CRISPR-Mediated Kinome Editing Prioritizes a Synergistic Combination Therapy for *FGFR1*-Amplified Lung Cancer

Zhang Yang, Shun-Qing Liang, Haitang Yang, Duo Xu, Rémy Bruggmann, Yanyun Gao, Haibin Deng, Sabina Berezowska, Sean R.R. Hall, Thomas M. Marti, Gregor J. Kocher, Qinghua Zhou, Ralph A. Schmid, and Ren-Wang Peng
The identification of PLK1 as a potent synthetic lethal target for FGFR-targeted therapy provides an innovative rationale for the treatment of lung and other *FGFR1*-amplified cancers.

POPULATION AND PREVENTION SCIENCE

3134 Smoking Modifies Pancreatic Cancer Risk Loci on 2q21.3

Evelina Mocchi, Prosenjit Kundu, William Wheeler, Alan A. Arslan, Laura E. Beane-Freeman, Paige M. Bracci, Paul Brennan, Federico Canzian, Mengmeng Du, Steven Gallinger, Graham G. Giles, Phyllis J. Goodman, Charles Kooperberg, Loic Le Marchand, Rachel E. Neale, Xiao-Ou Shu, Kala Visvanathan, Emily White, Wei Zheng, Demetrius Albanes, Gabriella Andreotti, Ana Babic, William R. Bamlet, Sonja I. Berndt, Amanda L. Blackford, Bas Bueno-de-Mesquita, Julie E. Buring, Daniele Campa, Stephen J. Chanock, Erica J. Childs, Eric J. Duell, Charles S. Fuchs, J. Michael Gaziano, Edward L. Giovannucci, Michael G. Goggins, Patricia Hartge, Manal M. Hassan, Elizabeth A. Holly, Robert N. Hoover, Rayjean J. Hung, Robert C. Kurtz, I-Min Lee, Núria Malats, Roger L. Milne, Kimmie Ng, Ann L. Oberg, Salvatore Panico, Ulrike Peters, Miquel Porta, Kari G. Rabe, Elio Riboli, Nathaniel Rothman, Ghislaine Scelo, Howard D. Sesso, Debra T. Silverman, Victoria L. Stevens, Oliver Strobel, Ian M. Thompson Jr, Anne Tjonneland, Antonia Trichopoulou, Stephen K. Van Den Eeden, Jean Wactawski-Wende, Nicolas Wentzensen, Lynne R. Wilkens, Herbert Yu, Fangcheng Yuan, Anne Zeleniuch-Jacquotte, Laufey T. Amundadottir, Donghui Li, Eric J. Jacobs, Gloria M. Petersen, Brian M. Wolpin, Harvey A. Risch, Peter Kraft, Nilanjan Chatterjee, Alison P. Klein, and Rachael Stolzenberg-Solomon
This large genome-wide interaction study identifies a susceptibility locus on 2q21.3 that significantly modified PDAC risk by smoking status, providing insight into smoking-associated PDAC, with implications for prevention.

CORRECTIONS

3144 Correction: Mitochondrial DNA Repair through OGG1 Activity Attenuates Breast Cancer Progression and Metastasis

Larysa V. Yuzefovych, Andrea G. Kahn, Michele A. Schuler, Lars Eide, Ritu Arora, Glenn L. Wilson, Ming Tan, and Lyudmila I. Rachek

3145 Correction: Epigenetic Regulation of NAMPT by NAMPT-AS Drives Metastatic Progression in Triple-Negative Breast Cancer

Hanwen Zhang, Ning Zhang, Ying Liu, Peng Su, Yiran Liang, Yaming Li, Xiaolong Wang, Tong Chen, Xiaojin Song, Yuting Sang, Yi Duan, Jiashu Zhang, Lijuan Wang, Bing Chen, Wenjing Zhao, Haiyang Guo, Zhaojian Liu, Guohong Hu, and Qifeng Yang

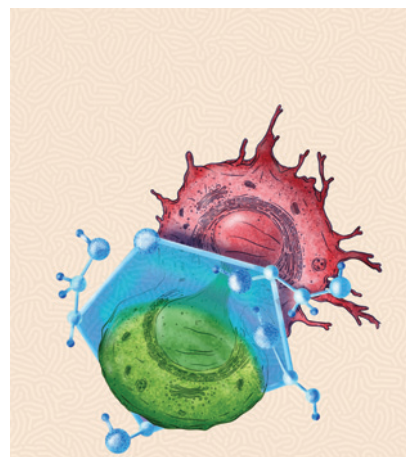
AC icon indicates Author Choice

For more information please visit www.aacrjournals.org

TABLE OF CONTENTS

ABOUT THE COVER

Fructose promotes proliferation and invasiveness of prostate cancer cells *in vitro* and *in vivo*. The cover image depicts fructose (light blue) facilitating the transition of a normal prostate epithelial cell (green) into a malignant prostate cancer cell (red). For details, see article by Carreño and colleagues on page 2824.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

81 (11)

Cancer Res 2021;81:2803-3145.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/81/11>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/81/11>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.