

BREAKING INSIGHTS

- 4103** Highlights from Recent Cancer Literature

EDITORIAL

- 4105** The Half-Lives of Facts, Paradigm Shifts, and Reproducibility in Cancer Research
Chi Van Dang

REVIEW

- 4107** CRISPR–Cas13 Precision Transcriptome Engineering in Cancer
Javier T. Granados-Riveron and Guillermo Aquino-Jarquin

GENOME AND EPIGENOME

- 4114** The Tumor Suppressor CIC Directly Regulates MAPK Pathway Genes via Histone Deacetylation
Simon Weissmann, Paul A. Cloos, Simone Sidoli, Ole N. Jensen, Steven Pollard, and Kristian Helin
Significance: Inactivation of CIC inhibits its direct repression of MAPK pathway genes, leading to their increased expression and mitogen-independent growth.

- 4126** TET1-Mediated Hypomethylation Activates Oncogenic Signaling in Triple-Negative Breast Cancer
Charly Ryan Good, Shoghag Panjarian, Andrew D. Kelly, Jozef Madzo, Bela Patel, Jaroslav Jelinek, and Jean-Pierre J. Issa
Significance: This study addresses a critical gap in knowledge of how and why methylation is prognostic in breast cancer and shows how this information can be used to stratify patients with TNBC for targeted therapy.

- 4138** Oncogenic Properties of NEAT1 in Prostate Cancer Cells Depend on the CDC5L–AGRN Transcriptional Regulation Circuit
Xin Li, Xianteng Wang, Wanlu Song, Hui Xu, Rongyao Huang, Yuting Wang, Wenwei Zhao, Zhengtao Xiao, and Xuerui Yang
Significance: An integrative methodology uncovers CDC5L–AGRN signaling as critical to the tumor-promoting function of long noncoding RNA NEAT1 in prostate cancer cells.

MOLECULAR CELL BIOLOGY

- 4150** Twist1 Regulates Vimentin through Cul2 Circular RNA to Promote EMT in Hepatocellular Carcinoma



Jing Meng, Shuang Chen, Jing-Xia Han, Baoxin Qian, Xiao-Rui Wang, Wei-Long Zhong, Yuan Qin, Heng Zhang, Wan-Feng Gao, Yue-Yang Lei, Wei Yang, Lan Yang, Chao Zhang, Hui-Juan Liu, Yan-Rong Liu, Hong-Gang Zhou, Tao Sun, and Cheng Yang

Significance: A circRNA-based mechanism drives Twist1-mediated regulation of vimentin during EMT and provides potential therapeutic targets for treatment of HCC.

- 4163** Long Noncoding RNA AB074169 Inhibits Cell Proliferation via Modulation of KHSRP-Mediated CDKN1a Expression in Papillary Thyroid Carcinoma



Qiheng Gou, Linbo Gao, Xinwen Nie, Wenchen Pu, Jingqiang Zhu, Yichao Wang, Xuesha Liu, Shuangyan Tan, Jian-Kang Zhou, Yanqiu Gong, Juan He, Ke Wu, Yuxin Xie, Wanjun Zhao, Lunzhi Dai, Lunxu Liu, Rong Xiang, Yu-Quan Wei, Lin Zhang, and Yong Peng

Significance: These findings identify a tumor-suppressive long noncoding RNA in papillary thyroid carcinoma.

- 4175** miR-590-3p Promotes Ovarian Cancer Growth and Metastasis via a Novel FOXA2–Versican Pathway

Mohamed Salem, Jacob A. O'Brien, Stefanie Bernaudo, Heba Shawer, Gang Ye, Jelena Brkić, Asma Amleh, Barbara C. Vanderhyden, Basel Refky, Burton B. Yang, Sergey N. Krylov, and Chun Peng


Significance: Low FOXA2/high VCAN levels mediate the tumor-promoting effects of miR-590-3p and negatively correlate with ovarian cancer survival.

- 4191** Reciprocal Regulation of DUSP9 and DUSP16 Expression by HIF1 Controls ERK and p38 MAP Kinase Activity and Mediates Chemotherapy-Induced Breast Cancer Stem Cell Enrichment
Haiquan Lu, Linh Tran, Youngrok Park, Ivan Chen, Jie Lan, Yangyiran Xie, and Gregg L. Semenza

Significance: These findings provide a molecular mechanism that may account for the increased relapse rate of women with TNBC who are treated with cytotoxic chemotherapy and suggest that combining chemotherapy with an inhibitor of HIF1 or p38 activity may increase patient survival.


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
- 4203** Hexavalent Chromium–Induced Chromosome Instability Drives Permanent and Heritable Numerical and Structural Changes and a DNA Repair–Deficient Phenotype
Sandra S. Wise, Abou El-Makarim Aboueissa, Julieta Martino, and John Pierce Wise, Sr.
Significance: Chromium, a major public health concern and human lung carcinogen, causes fundamental changes in chromosomes and DNA repair in human lung cells.

- 4215** Syntaphilin Ubiquitination Regulates Mitochondrial Dynamics and Tumor Cell Movements

Jae Ho Seo, Ekta Agarwal, Kelly G. Bryant, M. Cecilia Caino, Eui Tae Kim, Andrew V. Kossenkov, Hsin-Yao Tang, Lucia R. Languino, Dmitry I. Gabrilovich, Andrew R. Cohen, David W. Speicher, and Dario C. Altieri
Significance: These findings reveal a new mechanism of metastasis suppression by establishing the role of SNPH ubiquitination in inhibiting mitochondrial dynamics, chemotaxis, and metastasis.

- 4229** FGFR1-Activated Translation of WNT Pathway Components with Structured 5' UTRs Is Vulnerable to Inhibition of EIF4A-Dependent Translation Initiation
Tuan M. Nguyen, Elena B. Kabotyanski, Yongchao Dou, Lucas C. Reineke, Peng Zhang, Xiang H.-F. Zhang, Anna Malovannaya, Sung Yun Jung, Qianxing Mo, Kevin P. Roarty, Yiwen Chen, Bing Zhang, Joel R. Neilson, Richard E. Lloyd, Charles M. Perou, Matthew J. Ellis, and Jeffrey M. Rosen
Significance: The RNA helicase EIF4A may serve as a therapeutic target for breast cancers that require FGF and WNT signaling.

TUMOR BIOLOGY AND IMMUNOLOGY

- 4241** Macrophages Promote Circulating Tumor Cell–Mediated Local Recurrence following Radiotherapy in Immunosuppressed Patients

Marjan Rafat, Todd A. Aguilera, Marta Vilalta, Laura L. Bronsart, Luis A. Soto, Rie von Eyben, Meghana A. Golla, Yasaman Ahrari, Stavros Melemenidis, Anosheh Afghahi, Melissa J. Jenkins, Allison W. Kurian, Kathleen C. Horst, Amato J. Giaccia, and Edward E. Graves
Significance: This study establishes the importance of macrophages in driving tumor cell recruitment to sites of local radiation therapy and suggests that this mechanism contributes to local recurrence in women with TNBC that are also immunosuppressed.

- 4253** Macrophage-Derived Granulin Drives Resistance to Immune Checkpoint Inhibition in Metastatic Pancreatic Cancer

Valeria Quaranta, Carolyn Rainer, Sebastian R. Nielsen, Meirion L. Raymant, Muhammad S. Ahmed, Dannielle D. Engle, Arthur Taylor, Trish Murray, Fiona Campbell, Daniel H. Palmer, David A. Tuveson, Ainhoa Mielgo, and Michael C. Schmid
Significance: These findings uncover a mechanism by which metastatic PDAC tumors evade the immune response and provide the rationale for targeting granulin in combination with immune checkpoint inhibitors for the treatment of metastatic PDAC.

- 4270** Combined VEGF and PD-L1 Blockade Displays Synergistic Treatment Effects in an Autochthonous Mouse Model of Small Cell Lung Cancer
Lydia Meder, Philipp Schuldt, Martin Thelen, Anna Schmitt, Felix Dietlein, Sebastian Klein, Sven Borchmann, Kerstin Wennhold, Ignacija Vlastic, Sebastian Oberbeck, Richard Riedel, Alexandra Florin, Kristina Golfmann, Hans A. Schlößer, Margarete Odenthal, Reinhard Buettner, Juergen Wolf, Michael Hallek, Marco Herling, Michael von Bergwelt-Baildon, H. Christian Reinhardt, and Roland T. Ullrich
Significance: Combining VEGF and PD-L1 blockade could be of therapeutic benefit to patients with small cell lung cancer.

- 4282** Radiotherapy and CD40 Activation Separately Augment Immunity to Checkpoint Blockade in Cancer
Andrew J. Rech, Hannah Dada, Jonathan J. Kotzin, Jorge Henao-Mejia, Andy J. Minn, Christina Twyman-Saint Victor, and Robert H. Vonderheide
Significance: Radiotherapy and α CD40 disrupt key links between innate and adaptive immunity, ameliorating resistance to immune checkpoint blockade in pancreatic cancer via multiple cellular mechanisms.

- 4292** Helicase-Driven Activation of NF κ B-COX2 Pathway Mediates the Immunosuppressive Component of dsRNA-Driven Inflammation in the Human Tumor Microenvironment
Marie-Nicole Theodoraki, Saigopalakrishna Yerneni, Saumendra N. Sarkar, Brian Orr, Ravikumar Muthuswamy, Jamie Voyten, Francesmary Modugno, Weijian Jiang, Melissa Grimm, Per H. Basse, David L. Bartlett, Robert P. Edwards, and Pawel Kalinski
Significance: This study characterizes two different poly-I:C-induced signaling pathways in their induction of immunostimulatory and suppressive factors and suggests improved ways to reprogram the TME to enhance the antitumor efficacy of immunotherapies.

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4303 Ornithine Decarboxylase in Macrophages Exacerbates Colitis and Promotes Colitis-Associated Colon Carcinogenesis by Impairing M1 Immune Responses

Kshipra Singh, Lori A. Coburn, Mohammad Asim, Daniel P. Barry, Margaret M. Allaman, Chanjuan Shi, M. Kay Washington, Paula B. Luis, Claus Schneider, Alberto G. Delgado, M. Blanca Piazuelo, John L. Cleveland, Alain P. Gobert, and Keith T. Wilson

Significance: Ornithine decarboxylase (ODC) contributes to the pathogenesis of colitis and associated carcinogenesis by impairing M1 macrophage responses needed for antitumoral immunity; targeting ODC in macrophages may represent a new strategy for chemoprevention.

4316 Loss of XIST in Breast Cancer Activates MSN-c-Met and Reprograms Microglia via Exosomal miRNA to Promote Brain Metastasis

Fei Xing, Yin Liu, Shih-Ying Wu, Kerui Wu, Sambad Sharma, Yin-Yuan Mo, Jiamei Feng, Stephanie Sanders, Guangxu Jin, Ravi Singh, Pierre-Alexandre Vidi, Abhishek Tyagi, Michael D. Chan, Jimmy Ruiz, Waldemar Debinski, Boris C. Pasche, Hui-Wen Lo, Linda J. Metheny-Barlow, Ralph B. D'Agostino Jr, and Kounosuke Watabe

Significance: These findings describe mechanisms of how loss of the lncRNA XIST promotes brain metastasis in breast cancer and identify fludarabine as a potential therapeutic agent that specifically eliminates XIST^{low} tumor cells in the brain.

4360 Combined c-Met/Trk Inhibition Overcomes Resistance to CDK4/6 Inhibitors in Glioblastoma

Inan Olmez, Ying Zhang, Laryssa Manigat, Mouadh Benamar, Breanna Brenneman, Ichiro Nakano, Jakub Godlewski, Agnieszka Bronisz, Jeongwu Lee, Tarek Abbas, Roger Abounader, and Benjamin Purow

Significance: CDK4/6 inhibition in glioblastoma activates the c-Met and TrkA-B pathways mediated by NF- κ B and can be reversed by a dual c-Met/Trk inhibitor.

4370 Licofelone Enhances the Efficacy of Paclitaxel in Ovarian Cancer by Reversing Drug Resistance and Tumor Stem-like Properties



Jeff Hirst, Harsh B. Pathak, Stephen Hyter, Ziyang Y. Pessetto, Thuc Ly, Stefan Graw, Devin C. Koestler, Adam J. Krieg, Katherine F. Roby, and Andrew K. Godwin

Significance: This study highlights the use of an in vitro spheroid 3D drug screening model to identify new therapeutic approaches to reverse chemotherapy resistance in ovarian cancer.

4386 Specific Targeting of MTAP-Deleted Tumors with a Combination of 2'-Fluoroadenine and 5'-Methylthioadenosine

Baiqing Tang, Hyung-Ok Lee, Serim S. An, Kathy Q. Cai, and Warren D. Kruger

Significance: Loss of MTAP occurs in about 15% of all human cancers; the MTAP protection strategy presented in this study could be very effective in treating these cancers.

TRANSLATIONAL SCIENCE

4331 BET Inhibition Overcomes Receptor Tyrosine Kinase-Mediated Cetuximab Resistance in HNSCC



Brandon Leonard, Toni M. Brand, Rachel A. O'Keefe, Eliot D. Lee, Yan Zeng, Jacquelyn D. Kemmer, Hua Li, Jennifer R. Grandis, and Neil E. Bhola

Significance: Inhibition of bromodomain protein BRD4 represents a potential therapeutic strategy to circumvent the toxicities and financial burden of targeting the multiple receptor tyrosine kinases that drive cetuximab resistance in HNSCC and NSCLC.

4344 Restraining Network Response to Targeted Cancer Therapies Improves Efficacy and Reduces Cellular Resistance

Tirtha K. Das, Jessica Esernio, and Ross L. Cagan

Significance: These findings with a strong therapeutic potential provide an innovative approach of identifying effective combination treatments for cancer.

CONVERGENCE AND TECHNOLOGIES

4396 Integrative Modeling Identifies Key Determinants of Inhibitor Sensitivity in Breast Cancer Cell Lines



Katarzyna Jastrzebski, Bram Thijssen, Roelof J.C. Kluin, Klaas de Lint, Ian J. Majewski, Roderick L. Beijersbergen, and Lodewyk F.A. Wessels


Significance: By estimating how different oncogenic mutations and drug resistance mechanisms affect the response of cancer cells to kinase inhibitors, we can better understand and ultimately predict response to these anticancer drugs.

4411 Integrative Genome-Wide Analysis of Long Noncoding RNAs in Diverse Immune Cell Types of Melanoma Patients

Lei Wang, Sara J. Felts, Virginia P. Van Keulen, Adam D. Scheid, Matthew S. Block, Svetomir N. Markovic, Larry R. Pease, and Yuji Zhang

Significance: These findings elucidate melanoma-associated changes to the noncoding transcriptional landscape of distinct immune cell classes, thus providing cell type-specific guidance to targeted immunotherapy regimens.

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- 4424**  **TCIApathfinder: An R Client for the Cancer Imaging Archive REST API**
Pamela Russell, Kelly Fountain, Dulcy Wolverton, and Debashis Ghosh

Significance: These findings present a new tool, TCIApathfinder, the first client for The Cancer Imaging Archive (TCIA) for use in the highly popular R computing environment, that will dramatically lower the barrier of access to the valuable tools in TCIA.

POPULATION AND PREVENTION SCIENCE

- 4427** **Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Santé Cohort**
Céline Lavalette, Moufidath Adjibade, Bernard Srour, Laury Sellem, Thibault Fiolet, Serge Hercberg, Paule Latino-Martel, Philippine Fassier, Mélanie Deschasaux, Emmanuelle Kesse-Guyot, and Mathilde Touvier

Significance: This large prospective population-based cohort study suggests that following dietary recommendations such as the ones proposed by the World Cancer Research Fund/American Institute for Cancer Research could significantly contribute to cancer prevention.

- 4436** **Projections in Breast and Lung Cancer Mortality among Women: A Bayesian Analysis of 52 Countries Worldwide**

Juan Carlos Martín-Sánchez, Nuno Lunet, Adrián González-Marrón, Cristina Lidón-Moyano, Nuria Matilla-Santander, Ramon Clèries, Matteo Malvezzi, Eva Negri, Samantha Morais, Ana Rute Costa, Ana Ferro, Luisa Lopes-Conceição, Carlo La Vecchia, and Jose M. Martínez-Sánchez

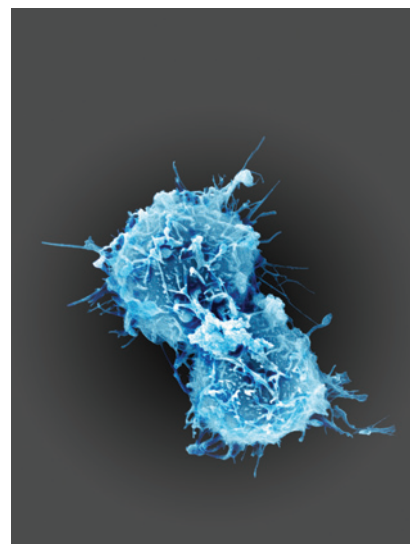
Significance: The mortality for lung and breast cancer is projected to be higher in high-income countries than in middle-income countries, where lung cancer mortality is expected to surpass breast cancer mortality before 2030.

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ABOUT THE COVER

Twist1 regulates Cul2 pre-mRNA to alternatively spliced circRNA. The circRNA absorbs miRNAs targeting vimentin, thereby improving the expression of vimentin and driving epithelial-mesenchymal transition mediated by Twist1 in hepatocellular carcinoma. The image shows the epithelial phenotype of hepatocellular carcinoma cells released from the Twist1 pathway. For details, see article by Meng and colleagues on page 4150.



Cancer Research

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