

BREAKING INSIGHTS

- 585** Highlights from Recent Cancer Literature

REVIEWS

- 587** Evidence for the ISG15-Specific Deubiquitinase USP18 as an Antineoplastic Target
Lisa Maria Mustachio, Yun Lu, Masanori Kawakami, Jason Roszik, Sarah J. Freemantle, Xi Liu, and Ethan Dmitrovsky
- 593** Oncogenic Ras Isoforms Signaling Specificity at the Membrane
Ruth Nussinov, Chung-Jung Tsai, and Hyunbum Jang
- 603** T-type Ca²⁺ Channels: T for Targetable
Marta C. Sallán, Anna Visa, Soni Shaikh, Mireia Nàger, Judit Herrerros, and Carles Cantí

PRIORITY REPORT

- 610** T-Cell Densities in Brain Metastases Are Associated with Patient Survival Times and Diffusion Tensor MRI Changes
Rasheed Zakaria, Angela Platt-Higgins, Nitika Rathi, Mark Radon, Sumit Das, Kumar Das, Maneesh Bhojak, Andrew Brodbelt, Emmanuel Chavredakis, Michael D. Jenkinson, and Philip S. Rudland
- Significance:* These findings show that white matter tract integrity is degraded in areas where T-cell infiltration is highest, providing a noninvasive method to identify immunologically active microenvironments in secondary brain tumors.

GENOME AND EPIGENOME

- 617** Mutational Mechanisms That Activate Wnt Signaling and Predict Outcomes in Colorectal Cancer Patients
William Hankey, Michael A. McIlhatton, Kenechi Ebede, Brian Kennedy, Baris Hancioglu, Jie Zhang, Guy N. Brock, Kun Huang, and Joanna Groden
- Significance:* These findings suggest that colon adenomas driven by APC mutations are distinct from those driven by WNT gain-of-function mutations, with implications for identifying at-risk patients with advanced disease based on gene expression patterns.

- 631** Genomic and Epigenomic Signatures in Ovarian Cancer Associated with Resensitization to Platinum Drugs

Fang Fang, Horacio Cardenas, Hao Huang, Guanglong Jiang, Susan M. Perkins, Chi Zhang, Harold N. Keer, Yunlong Liu, Kenneth P. Nephew, and Daniela Matei

Significance: Epigenomic targeting may improve therapeutic outcomes in platinum-resistant and recurrent ovarian cancer in part by effects on DNA repair and antitumor immune responses.

MOLECULAR CELL BIOLOGY

- 645** SIRT6 Is a Target of Regulation by UBE3A That Contributes to Liver Tumorigenesis in an ANXA2-Dependent Manner

Saishruti Kohli, Abhishek Bhardwaj, Richa Kumari, and Sanjeev Das

Significance: These findings provide mechanistic insights into regulation of the tumor suppressive sirtuin SIRT6 and its implications for the development of hepatocellular carcinoma.

TUMOR BIOLOGY AND IMMUNOLOGY

- 659** Radiotherapy-Activated Cancer-Associated Fibroblasts Promote Tumor Progression through Paracrine IGF1R Activation

Joke Tommelein, Elly De Vlieghere, Laurine Verset, Elodie Melsens, Justine Leenders, Benedicte Descamps, Annelies Debucquoy, Christian Vanhove, Patrick Pauwels, Christian P. Gespach, Anne Vral, Astrid De Boeck, Karin Haustermans, Pascal de Tullio, Wim Ceelen, Pieter Demetter, Tom Boterberg, Marc Bracke, and Olivier De Wever

Significance: These findings reveal that paracrine IGF1/IGF1R signaling promotes colorectal cancer progression, establishing a preclinical rationale to target this activation loop.

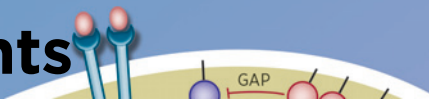
- 671** Tamoxifen Resistance in Breast Cancer Is Regulated by the EZH2-ER α -GREB1 Transcriptional Axis



Yanming Wu, Zhao Zhang, Mauro E. Cenciari, Cecilia J. Proietti, Matias Amasino, Tao Hong, Mei Yang, Yiji Liao, Huai-Chin Chiang, Virginia G. Kalkamani, Rinath Jeselsohn, Ratna K. Vadlamudi, Tim Hui-Ming Huang, Rong Li, Carmine De Angelis, Xiaoyong Fu, Patricia V. Elizalde, Rachel Schiff, Myles Brown, and Kexin Xu

Significance: This study suggests a new strategy to overcome endocrine resistance in metastatic breast cancer by targeting a particular epigenetic program defined within.

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685 Deletion of Neuropilin 1 from Microglia or Bone Marrow–Derived Macrophages Slows Glioma Progression

Jeremy Tetsuo Miyachi, Michael D. Caponegro, Danling Chen, Matthew K. Choi, Melvin Li, and Stella E. Tsirka

Significance: This study highlights the proangiogenic receptor neuropilin 1 in macrophages and microglial cells in gliomas as a pivotal modifier of tumor neovascularization and immunosuppression, strengthening emerging evidence of the functional coordination of these two fundamental traits of cancer.

695 Tumor-Associated Fatigue in Cancer Patients Develops Independently of IL1 Signaling

Aaron J. Grossberg, Elisabeth G. Vichaya, Diana L. Christian, Jessica M. Molkentine, Daniel W. Vermeer, Phillip S. Gross, Paola D. Vermeer, John H. Lee, and Robert Dantzer

Significance: These findings challenge the current understanding of fatigue in cancer patients, the most common and debilitating sequela associated with malignancy.

TRANSLATIONAL SCIENCE

706 Small-Molecule Inhibition of PD-1 Transcription Is an Effective Alternative to Antibody Blockade in Cancer Therapy



Alison Taylor, David Rothstein, and Christopher E. Rudd

Significance: These findings show how GSK-3 inhibitors that downregulate PD-1 expression can enhance CD8⁺ T-cell function in cancer therapy to a similar degree as PD-1 blocking antibodies, offering a next-generation approach in the design of immunotherapeutic approaches for cancer management.

718 Oncolytic Virotherapy Blockade by Microglia and Macrophages Requires STAT1/3

Zahid M. Delwar, Yvonne Kuo, Yan H. Wen, Paul S. Rennie, and William Jia

Significance: These findings suggest a strategy to enhance the therapeutic efficacy of oncolytic virotherapy in glioblastoma.

731 VEGFR2–Mediated Reprogramming of Mitochondrial Metabolism Regulates the Sensitivity of Acute Myeloid Leukemia to Chemotherapy

Sandrina Nóbrega-Pereira, Francisco Caíado, Tânia Carvalho, Inês Matias, Gonçalo Graça, Luís G. Gonçalves, Bruno Silva-Santos, Haakan Norell, and Sérgio Dias

Significance: These findings reveal a mitochondrial metabolic vulnerability that might be exploited to kill chemotherapy-resistant acute myeloid leukemia cells.

742 Synthetic Lethality of PARP Inhibitors in Combination with MYC Blockade Is Independent of BRCA Status in Triple-Negative Breast Cancer

Jason P.W. Carey, Cansu Karakas, Tuyen Bui, Xian Chen, Smruthi Vijayaraghavan, Yang Zhao, Jing Wang, Keith Mikule, Jennifer K. Litton, Kelly K. Hunt, and Khandan Keyomarsi

Significance: Dual targeting of MYC-regulated homologous recombination and PARP-mediated DNA repair yields potent synthetic lethality in triple-negative breast tumors and other aggressive tumors characterized by MYC overexpression.

758 Improved Tumor Penetration and Single-Cell Targeting of Antibody–Drug Conjugates Increases Anticancer Efficacy and Host Survival

Cornelius Cilliers, Bruna Menezes, Ian Nessler, Jennifer Linderman, and Greg M. Thurber

Significance: This study shows how lowering the drug-to-antibody ratio during treatment can improve the intratumoral distribution of a antibody-drug conjugate, with implications for improving the efficacy of this class of cancer drugs.

769 Transcription Factor Activities Enhance Markers of Drug Sensitivity in Cancer



Luz Garcia-Alonso, Francesco Iorio, Angela Matchan, Nuno Fonseca, Patricia Jaaks, Gareth Peat, Miguel Pignatelli, Fiammetta Falcone, Cyril H. Benes, Ian Dunham, Graham Bignell, Simon S. McDade, Mathew J. Garnett, and Julio Saez-Rodriguez

Significance: Systematic analysis of transcriptional dysregulation in cancer cell lines and patient tumor specimens offers a publicly searchable foundation to discover new opportunities to refine personalized cancer therapies.

781 CDKN2A/p16 Deletion in Head and Neck Cancer Cells Is Associated with CDK2 Activation, Replication Stress, and Vulnerability to CHK1 Inhibition



Mayur A. Gadhikar, Jiexin Zhang, Li Shen, Xiayu Rao, Jing Wang, Mei Zhao, Nene N. Kalu, Faye M. Johnson, Lauren A. Byers, John Heymach, Walter N. Hittelman, Durga Udayakumar, Raj K. Pandita, Tej K. Pandita, Curtis R. Pickering, Abena B. Redwood, Helen Piwnicka-Worms, Katharina Schlacher, Mitchell J. Frederick, and Jeffrey N. Myers

Significance: These results suggest a biomarker-driven strategy for selecting HNSCC patients who may benefit the most from therapy with CHK inhibitors.

798 Aptamer-Conjugated Extracellular Nanovesicles for Targeted Drug Delivery

Yuan Wan, Lixue Wang, Chuandong Zhu, Qin Zheng, Guoxiang Wang, Jinlong Tong, Yuan Fang, Yiqiu Xia, Gong Cheng, Xia He, and Si-Yang Zheng

Significance: A new and rapid method for production of drug-targeting nanovesicles has implications for cancer treatment by chimeric antigen receptor T cells and other therapies.

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809 IDO Immune Status after Chemoradiation May Predict Survival in Lung Cancer Patients

Weili Wang, Lei Huang, Jian-Yue Jin, Shruti Jolly, Yong Zang, Huanmei Wu, Li Yan, Wenhui Pi, Lang Li, Andrew L. Mellor, and Feng-Ming (Spring) Kong

Significance: Radiotherapy appears to influence systemic IDO activity and to exert a significant impact on metastatic risk and overall survival, with possible implications for defining a biomarker to optimize radiation dose in patients to improve outcomes.

817 Peripheral Neuropathy Induced by Microtubule-Targeted Chemotherapies: Insights into Acute Injury and Long-term Recovery

Krystyna M. Wozniak, James J. Vornov, Ying Wu, Ying Liu, Valentina A. Carozzi, Virginia Rodriguez-Menendez, Elisa Ballarini, Paola Alberti, Eleonora Pozzi, Sara Semperboni, Brett M. Cook, Bruce A. Littlefield, Kenichi Nomoto, Krista Condon, Sean Eckley, Christopher DesJardins, Leslie Wilson, Mary A. Jordan, Stuart C. Feinstein, Guido Cavaletti, Michael Polydefkis, and Barbara S. Slusher

Significance: This detailed preclinical study of the long-term effects of widely used antitubulin cancer drugs on the peripheral nervous system may help guide clinical evaluations to improve personalized care in limiting neurotoxicity in cancer survivors.

CONVERGENCE AND TECHNOLOGIES

830 Modeling the Subclonal Evolution of Cancer Cell Populations

Diego Chowell, James Napier, Rohan Gupta, Karen S. Anderson, Carlo C. Maley, and Melissa A. Wilson Sayres

Significance: The model presented in this paper addresses tumor heterogeneity by framing expectations for the number of resistant subclones in a tumor, with implications for future studies of the evolution of therapeutic resistance.

CORRECTIONS

840 Correction: Extracellular Matrix Receptor Expression in Subtypes of Lung Adenocarcinoma Potentiates Outgrowth of Micrometastases

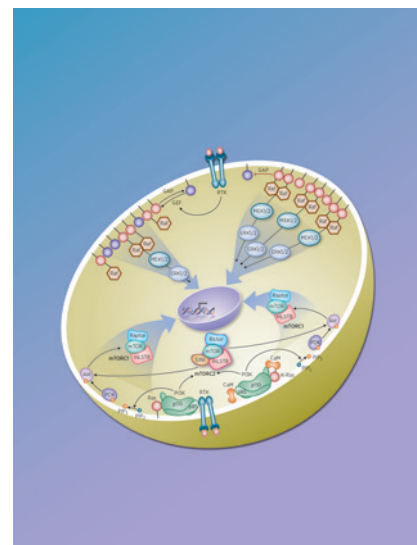
841 Correction: Morphoproteomic Characterization of Lung Squamous Cell Carcinoma Fragmentation, a Histological Marker of Increased Tumor Invasiveness

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ABOUT THE COVER

Membrane-anchored wild-type and mutant Ras form dimers (or nanoclusters). Dimerization (or nanoclustering) is required for Raf's dimerization, activation, and Raf/MEK/ERK (MAPK) signaling (top part of the figure). By contrast, Ras dimerization (nanoclustering) is not required for PI3K α activation, because PI3K α essentially acts as a single unit (bottom part of the figure). Wild-type Ras activation of PI3K α is helped by the phosphorylated C-terminal motif of RTK, which releases the autoinhibition of the p110 subunit by the p85 subunit. In the absence of RTK signaling, phosphorylated calmodulin helps oncogenic KRas. Because only KRas binds calmodulin, only KRas can fully activate PI3K α /Akt signaling. Full activation of both MAPK and PI3K α /Akt proliferative pathways by oncogenic KRas4B, but not by HRas or NRas, may help explain why the KRas4B isoform is especially highly populated in certain cancers. For details, see article by Nussinov and colleagues on page 593.



Cancer Research

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

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