

BREAKING INSIGHTS

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REVIEW

- 1019** **AKT as a Therapeutic Target for Cancer**
Mengqiu Song, Ann M. Bode, Zigang Dong, and Mee-Hyun Lee

CANCER RESEARCH HIGHLIGHTS

- 1032** **IFN γ , a Double-Edged Sword in Cancer Immunity and Metastasis**
Chengfei Liu and Allen C. Gao
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- 1034** **Is Estrogen the Answer for Osteosarcoma?**
Ryan D. Roberts
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- 1041** **Streamlining Detection of Fusion Genes in Colorectal Cancer: Having "Faith" in Precision Oncology in the (Tissue) "Agnostic" Era**
Nicola Valeri
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CONTROVERSY AND CONSENSUS

- 1044** **Tumor Cell Escape from Therapy-Induced Senescence as a Model of Disease Recurrence after Dormancy**
Tareq Saleh, Liliya Tyutyunyk-Massey, and David A. Gewirtz

PRIORITY REPORT

- 1047** **Colorectal Carcinomas Containing Hypermethylated MLH1 Promoter and Wild-Type BRAF/KRAS Are Enriched for Targetable Kinase Fusions**
Emiliano Cocco, Jamal Benhamida, Sumit Middha, Ahmet Zehir, Kerry Mullaney, Jinru Shia, Rona Yaeger, Liying Zhang, Donna Wong, Liliana Villafania, Khedoudja Nafa, Maurizio Scaltriti, Alexander Drilon, Leonard Saltz, Alison M. Schram, Zsofia K. Stadler, David M. Hyman, Ryma Benayed, Marc Ladanyi, and Jaclyn F. Hechtman

Significance: A high frequency of targetable kinase fusions in BRAF/RAS wild-type, microsatellite instability-high colorectal carcinoma offers rationale for screening to identify colorectal cancer patients with kinase fusions that may respond to kinase inhibitors.

See related commentary, p. 1041

GENOME AND EPIGENOME

- 1054** **Activation of Estrogen Receptor Alpha by Decitabine Inhibits Osteosarcoma Growth and Metastasis**
Maria Angeles Lillo Osuna, Jesus Garcia-Lopez, Ikbale El Ayachi, Iram Fatima, Aysha B. Khalid, Jerusha Kumpati, Alexandria V. Slayden, Tiffany N. Seagroves, Gustavo A. Miranda-Carboni, and Susan A. Krum
Significance: These findings describe the effects of DNA methyltransferase inhibition on ER α and its potential role as a tumor suppressor in osteosarcoma.
See related commentary, p. 1034
See related article by El Ayachi and colleagues; Cancer Res 79(5);982-93

METABOLISM AND CHEMICAL BIOLOGY


- 1069** **Mitochondrial miRNA Determines Chemoresistance by Reprogramming Metabolism and Regulating Mitochondrial Transcription**
 Song Fan, Tian Tian, Weixiong Chen, Xiaobin Lv, Xinyuan Lei, Hanqing Zhang, Sheng Sun, Lei Cai, Guokai Pan, Lile He, Zhanpeng Ou, Xinyu Lin, Xinhui Wang, Matthew Francis Perez, Zhiming Tu, Soldano Ferrone, Bakhos A. Tannous, and Jinsong Li
Significance: These findings uncover a novel mechanism by which mitomiRNA regulates mitochondrial transcription and provide rationale for use of mitomiRNA and mtDNA-encoded genes to predict chemosensitivity and patient clinical prognosis.

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MOLECULAR CELL BIOLOGY

1085 **Drak/STK17A Drives Neoplastic Glial Proliferation through Modulation of MRLC Signaling**

Alexander S. Chen, Joanna Wardwell-Ozgo, Nilang N. Shah, Deidre Wright, Christina L. Appin, Krishanthan Vigneswaran, Daniel J. Brat, Harley I. Kornblum, and Renee D. Read

Significance: These findings reveal new insights into differential regulation of cell proliferation in malignant brain tumors, which will have a broader impact on research regarding mechanisms of oncogene cooperation and dependencies in cancer.

See related commentary, p. 1036

1098 **IFN γ -Induced IFIT5 Promotes Epithelial-to-Mesenchymal Transition in Prostate Cancer via miRNA Processing**

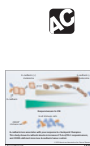
U-Ging Lo, Rey-Chen Pong, Diane Yang, Leah Gandee, Elizabeth Hernandez, Andrew Dang, Chung-Jung Lin, John Santoyo, Shihong Ma, Rajni Sonavane, Jun Huang, Shu-Fen Tseng, Loredana Moro, Arnaldo A. Arbini, Payal Kapur, Ganesh V. Raj, Dalin He, Chih-Ho Lai, Ho Lin, and Jer-Tsong Hsieh

Significance: A unique IFIT5-XRN1 complex involved in the turnover of specific tumor suppressive microRNAs is the underlying mechanism of IFN γ -induced epithelial-to-mesenchymal transition in prostate cancer.

See related commentary, p. 1032

TUMOR BIOLOGY AND IMMUNOLOGY

1113 **Loss of E-Cadherin Inhibits CD103 Antitumor Activity and Reduces Checkpoint Blockade Responsiveness in Melanoma**



Bradley D. Shields, Brian Koss, Erin M. Taylor, Aaron J. Storey, Kirk L. West, Stephanie D. Byrum, Samuel G. Mackintosh, Rick Edmondson, Fade Mahmoud, Sara C. Shalin, and Alan J. Tackett

Significance: These findings identify the mechanism behind checkpoint blockade resistance observed in melanoma that has undergone mesenchymal transition and suggest activation of CD103⁺ immune cells as a therapeutic strategy against other E-cadherin-expressing malignancies.

1124 **Constant Degradation of the Androgen Receptor by MDM2 Conserves Prostate Cancer Stem Cell Integrity**



Premkumar Vummidi Giridhar, Karin Williams, Andrew P. VonHandorf, Paul L. Deford, and Susan Kasper

Significance: These findings provide a novel mechanistic aspect of prostate cancer cell stemness that advances our understanding of the diverse transcriptional activity that bypasses AR in contributing to therapeutic resistance, tumor progression, and metastasis.

1138 **IDO1 and Kynurenine Pathway Metabolites Activate PI3K-Akt Signaling in the Neoplastic Colon Epithelium to Promote Cancer Cell Proliferation and Inhibit Apoptosis**

Kumar S. Bishnupuri, David M. Alvarado, Alexander N. Khouri, Mark Shabsovich, Baosheng Chen, Brian K. Dieckgraefe, and Matthew A. Ciorba

Significance: This study defines a new mechanistic link between IDO1 activity and PI3K/AKT signaling, both of which are important pathways involved in cancer growth and resistance to cancer therapy.

1151 **Natural Killer-Derived Exosomal miR-186 Inhibits Neuroblastoma Growth and Immune Escape Mechanisms**

Paolo Neviani, Petra M. Wise, Mariam Murtadha, Cathy W. Liu, Chun-Hua Wu, Ambrose Y. Jong, Robert C. Seeger, and Muller Fabbri

Significance: These findings highlight the therapeutic potential of NK cell-derived exosomes containing the tumor suppressor miR-186 that inhibits growth, spreading, and TGF β -dependent immune escape mechanisms in neuroblastoma.

1165 **An ARC-Regulated IL1 β /Cox-2/PGE2/ β -Catenin/ARC Circuit Controls Leukemia-Microenvironment Interactions and Confers Drug Resistance in AML**

Bing Z. Carter, Po Yee Mak, Xiangmeng Wang, Wenjing Tao, Vivian Ruvolo, Duncan Mak, Hong Mu, Jared K. Burks, and Michael Andreeff

Significance: The antiapoptotic protein ARC promotes AML aggressiveness by enabling detrimental cross-talk with bone marrow mesenchymal stromal cells.

1178 **GARP Dampens Cancer Immunity by Sustaining Function and Accumulation of Regulatory T Cells in the Colon**

Mohammad Salem, Caroline Wallace, Maria Velegraki, Anqi Li, Ephraim Ansa-Addo, Alessandra Metelli, Hyunwoo Kwon, Brian Riesenberg, Bill Wu, Yongliang Zhang, Silvia Guglietta, Shaoli Sun, Bei Liu, and Zihai Li

Significance: These findings uncover functions of membrane-bound TGF β and GARP that tune the activity of Treg cells, highlighting a potential treatment strategy in autoimmune diseases and cancer.

1191 **BET Inhibitors Potentiate Chemotherapy and Killing of SPOP-Mutant Colon Cancer Cells via Induction of DR5**

Xiao Tan, Jingshan Tong, Yi-Jun Wang, Rochelle Fletcher, Robert E. Schoen, Jian Yu, Liangfang Shen, and Lin Zhang

Significance: These findings reveal how BET inhibition sensitizes chemotherapy and kills a subset of colon cancer cells with specific genetic alterations and may provide a new molecular marker for improving colon cancer therapies.



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TRANSLATIONAL SCIENCE

1204 Early Noninvasive Detection of Response to Targeted Therapy in Non–Small Cell Lung Cancer



Jillian Phallen, Alessandro Leal, Brian D. Woodward, Patrick M. Forde, Jarushka Naidoo, Kristen A. Marrone, Julie R. Brahmer, Jacob Fiksel, Jamie E. Medina, Stephen Cristiano, Doreen N. Palsgrove, Christopher D. Gocke, Daniel C. Bruhm, Parissa Keshavarzian, Vilmos Adleff, Elizabeth Weihe, Valsamo Anagnostou, Robert B. Scharpf, Victor E. Velculescu, and Hatim Husain

Significance: Cell-free tumor load provides a novel approach for evaluating longitudinal changes in ctDNA during systemic treatment with tyrosine kinase inhibitors and serves an unmet clinical need for real-time, noninvasive detection of tumor response to targeted therapies before radiographic assessment.

See related commentary, p. 1038

1214 Dynamics of Tumor and Immune Responses during Immune Checkpoint Blockade in Non–Small Cell Lung Cancer



Valsamo Anagnostou, Patrick M. Forde, James R. White, Noushin Niknafs, Carolyn Hruban, Jarushka Naidoo, Kristen Marrone, I.K. Ashok Sivakumar, Daniel C. Bruhm, Samuel Rosner, Jillian Phallen, Alessandro Leal, Vilmos Adleff, Kellie N. Smith, Tricia R. Cottrell, Lamia Rhymee, Doreen N. Palsgrove, Christine L. Hann, Benjamin Levy, Josephine Feliciano, Christos Georgiades, Franco Verde, Peter Illei, Qing Kay Li, Edward Gabrielson, Malcolm V. Brock, James M. Isbell, Jennifer L. Sauter, Janis Taube, Robert B. Scharpf, Rachel Karchin, Drew M. Pardoll, Jamie E. Chaft, Matthew D. Hellmann, Julie R. Brahmer, and Victor E. Velculescu

Significance: Rapid and sensitive detection of circulating tumor DNA dynamic changes and T-cell expansion can be used to guide immune targeted therapy for patients with lung cancer.

See related commentary, p. 1038

1226 A DNA Repair and Cell-Cycle Gene Expression Signature in Primary and Recurrent Glioblastoma: Prognostic Value and Clinical Implications



Matthieu Gobin, Petr V. Nazarov, Rolf Warta, Marco Timmer, Guido Reifenberger, Joerg Felsberg, Laurent Vallar, Anthony J. Chalmers, Christel C. Herold-Mende, Roland Goldbrunner, Simone P. Niclou, and Eric Van Dyck

Significance: These findings suggest that classification of GBM tumors based on a DNA repair and cell-cycle gene expression signature exposes vulnerabilities to standard-of-care therapies and offers the potential for personalized therapeutic strategies.

1239 Blockade of a Laminin-411–Notch Axis with CRISPR/Cas9 or a Nanobioconjugate Inhibits Glioblastoma Growth through Tumor–Microenvironment Cross-talk



Tao Sun, Rameshwar Patil, Anna Galstyan, Dmytro Klymyshyn, Hui Ding, Alexandra Chesnokova, Webster K. Cavenee, Frank B. Furnari, Vladimir A. Ljubimov, Ekaterina S. Shatalova, Shawn Wagner, Debiao Li, Adam N. Mamelak, Serguei I. Bannykh, Chirag G. Patil, Jeremy D. Rudnick, Jethro Hu, Zachary B. Grodzinski, Arthur Rekechenetskiy, Vida Falahatian, Alexander V. Lyubimov, Yongmei L. Chen, Lai S. Leoh, Tracy R. Daniels-Wells, Manuel L. Penichet, Eggehard Holler, Alexander V. Ljubimov, Keith L. Black, and Julia Y. Ljubimova

Significance: Laminin-411 expression in the glioma microenvironment correlates with Notch and other cancer stem cell markers and can be targeted by a novel, clinically translatable nanobioconjugate to inhibit glioma growth.

POPULATION AND PREVENTION SCIENCE

1252 Epidemiologic and Clinical Analyses of Cervical Cancer Using Data from the Population-Based Osaka Cancer Registry



Asami Yagi, Yutaka Ueda, Mamoru Kakuda, Yusuke Tanaka, Sayaka Ikeda, Shinya Matsuzaki, Eiji Kobayashi, Toshitaka Morishima, Isao Miyashiro, Keisuke Fukui, Yuri Ito, Tomio Nakayama, and Tadashi Kimura

Significance: A large cohort analysis of cervical cancer cases reveals that age-adjusted incidence in Japan has increased since 2000 and that age may negatively correlate with resistance to radiation therapy.

CORRECTION

1260 Correction: Brain-Mimetic 3D Culture Platforms Allow Investigation of Cooperative Effects of Extracellular Matrix Features on Therapeutic Resistance in Glioblastoma

Weikun Xiao, Rongyu Zhang, Alireza Sohrabi, Arshia Ehsanipour, Songping Sun, Jesse Liang, Christopher M. Walthers, Lisa Ta, David A. Nathanson, and Stephanie K. Seidlits

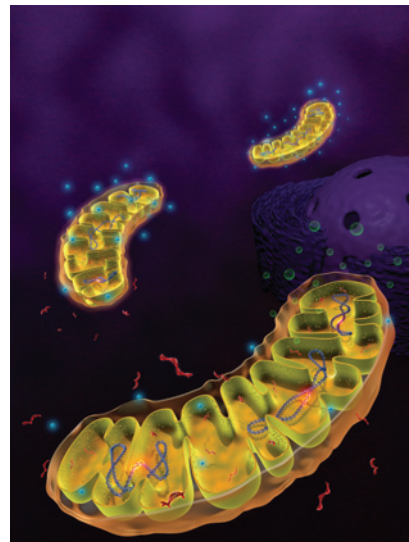
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ABOUT THE COVER

MicroRNAs, detected in mitochondria, have been termed mitomiRs. Among them, mitomiR-2392 was shown to be enriched in tongue squamous cell carcinoma cells and to regulate their chemoresistance by reprogramming cell metabolism. Mechanistically, mitomiR-2392 recognizes and binds target sequences in the H-strand of mtDNA with AGO2 and partially inhibits mtDNA transcription. MitomiR-2392 may be a useful biomarker for clinical risk evaluation and an attractive target to overcome chemoresistance. For details, see article by Fan and colleagues on page 1069.



Cancer Research

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

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