

November 1, 2019 • Volume 79 • Number 21

## BREAKING INSIGHTS

- 5461** Highlights from Recent Cancer Literature

## REVIEWS

- 5463** Use of Natural Language Processing to Extract Clinical Cancer Phenotypes from Electronic Medical Records

Guergana K. Savova, Ioana Danciu, Folami Alamudun, Timothy Miller, Chen Lin, Danielle S. Bitterman, Georgia Tourassi, and Jeremy L. Warner

- 5471** Targeting Cancer Cell Metastasis by Converting Cancer Cells into Fat

Dana Ishay-Ronen and Gerhard Christofori

## CANCER RESEARCH HIGHLIGHTS

- 5476** Genetics Helps to Find Synergy for Immune Checkpoint and Targeted Combination Therapies

Ludmila Prokunina-Olsson

See related article, p. 5482

- 5479**  $\alpha$ -Particle–Emitter Radiopharmaceutical Therapy: Resistance Is Futile

George Sgouros

See related article, p. 5640

## PRIORITY REPORT

- 5482** HDAC6 Inhibition Synergizes with Anti-PD-L1 Therapy in ARID1A-Inactivated Ovarian Cancer

Takeshi Fukumoto, Nail Fatkhutdinov, Joseph A. Zundell, Evgenii N. Tcyganov, Timothy Nacarelli, Sergey Karakashev, Shuai Wu, Qin Liu, Dmitry I. Gabrilovich, and Rugang Zhang

**Significance:** These findings offer a mechanistic rationale for combining epigenetic modulators and existing immunotherapeutic interventions against a disease that has been so far resistant to checkpoint blockade as a monotherapy.

See related commentary, p. 5476

## GENOME AND EPIGENOME

- 5490** Genetic Variants Implicate Dual Oxidase-2 in Familial and Sporadic Nonmedullary Thyroid Cancer

Darrin V. Bann, Qunyan Jin, Kathryn E. Sheldon, Kenneth R. Houser, Lan Nguyen, Joshua I. Warrick, Maria J. Baker, James R. Broach, Glenn S. Gerhard, and David Goldenberg

**Significance:** This study provides novel insights into the genetic and molecular mechanisms underlying familial and sporadic thyroid cancers.

- 5500** Dynamics of Genomic, Epigenomic, and Transcriptomic Aberrations during Stepwise Hepatocarcinogenesis

Byul A. Jee, Ji-Hye Choi, Hyungjin Rhee, Sarah Yoon, So Mee Kwon, Ji Hae Nahm, Jeong Eun Yoo, Youngsic Jeon, Gi Hong Choi, Hyun Goo Woo, and Young Nyun Park

**Significance:** Multiomics profiling and integrative analyses of stepwise hepatocarcinogenesis reveal novel mechanistic and clinical insights into hepatocarcinogenesis.

## MOLECULAR CELL BIOLOGY

- 5513** Macrophage ABHD5 Suppresses NF $\kappa$ B-Dependent Matrix Metalloproteinase Expression and Cancer Metastasis



Shenglan Shang, Xinran Ji, Lili Zhang, Jun Chen, Chuan Li, Rongchen Shi, Wei Xiang, Xia Kang, Dapeng Zhang, Fan Yang, Rongyang Dai, Peng Chen, Shan Chen, Yongchuan Chen, Yongsheng Li, and Hongming Miao

**Significance:** These findings highlight the mechanism by which reduced expression of the metabolic enzyme ABHD5 in macrophages promotes cancer metastasis.

- 5527** A Biophysical Model Uncovers the Size Distribution of Migrating Cell Clusters across Cancer Types



Federico Bocci, Mohit Kumar Jolly, and José Nelson Onuchic

**Significance:** A biophysical model of cancer cell invasion integrates phenotypic heterogeneity and cell migration to interpret experimental observations of circulating tumor cell clusters and provides new predictions.

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## TUMOR BIOLOGY AND IMMUNOLOGY

**5536** Chromosomal Instability and mTORC1 Activation through PTEN Loss Contribute to Proteotoxic Stress in Ovarian Carcinoma



M. Herman Chui, Sasha A. Doodnauth, Natalie Erdmann, Rodger E. Tiedemann, Fabrice Sircoulomb, Ronny Drapkin, Patricia Shaw, and Robert Rottapel

**Significance:** Chromosome instability and protein synthesis are important factors that determine the efficacy of proteotoxic stress-inducing agents, such as proteasome inhibitors, in the treatment of ovarian cancer.

**5550** Activation of Aryl Hydrocarbon Receptor by Kynurenine Impairs Progression and Metastasis of Neuroblastoma



Pei-Yi Wu, I-Shing Yu, Yueh-Chien Lin, Yu-Tzu Chang, Chien-Chin Chen, Kuan-Hung Lin, Tzu-Hsuan Tseng, Mati Kargren, Yu-Ling Tai, Tang-Long Shen, Yen-Lin Liu, Bo-Jeng Wang, Chi-Hao Chang, Wei-Min Chen, Hsueh-Fen Juan, Shiu-Feng Huang, Ya-Yun Chan, Yung-Feng Liao, Wen-Ming Hsu, and Hsin-yu Lee

**Significance:** These findings show that AHR may function as a tumor suppressor in childhood neuroblastoma, potentially influencing the aetiologic and therapeutic targeting of the disease.

**5563** SNAI1 Promotes the Cholangiocellular Phenotype, but not Epithelial–Mesenchymal Transition, in a Murine Hepatocellular Carcinoma Model

Meng Xu, Jingxiao Wang, Zhong Xu, Rong Li, Pan Wang, Runze Shang, Antonio Cigliano, Silvia Ribback, Antonio Solinas, Giovanni Mario Pes, Katja Evert, Haichuan Wang, Xinhua Song, Shu Zhang, Li Che, Rosa Maria Pascale, Diego Francesco Calvisi, Qingguang Liu, and Xin Chen

**Significance:** These findings report a new function of SNAI1 to promote cholangiocellular transdifferentiation instead of epithelial–mesenchymal transition in hepatocellular carcinoma.

**5575** Kras/ADAM17-Dependent Jag1-ICD Reverse Signaling Sustains Colorectal Cancer Progression and Chemoresistance

Maria Pelullo, Francesca Nardoza, Sabrina Zema, Roberta Quaranta, Carmine Nicoletti, Zein Mersini Besharat, Maria Pia Felli, Bruna Cerbelli, Giulia d'Amati, Rocco Palermo, Carlo Capalbo, Claudio Talora, Lucia Di Marcotullio, Giuseppe Giannini, Saula Checquolo, Isabella Screpanti, and Diana Bellavia

**Significance:** These findings present a novel role of the transcriptionally active Jag1-ICD fragment to confer and mediate some of the activity of oncogenic KRAS.

**5587** An Allosteric PRC2 Inhibitor Targeting EED Suppresses Tumor Progression by Modulating the Immune Response



Hongping Dong, Shaojun Liu, Xuejie Zhang, Sheng Chen, Lijing Kang, Yanni Chen, Shichao Ma, Xianlei Fu, Yanchao Liu, Hailong Zhang, and Bin Zou

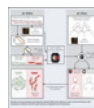
**Significance:** BR-001, a potent inhibitor of the EED subunit of the PRC2 complex, suppresses tumor progression by modulating the tumor microenvironment.

## TRANSLATIONAL SCIENCE

**5597** Drug Sensitivity Prediction Models Reveal a Link between DNA Repair Defects and Poor Prognosis in HNSCC



Paul B.M. Essers, Martijn van der Heijden, Caroline V.M. Verhagen, Emily M. Ploeg, Reinout H. de Roest, C. René Leemans, Ruud H. Brakenhoff, Michiel W.M. van den Brekel, Harry Bartelink, Marcel Verheij, and Conchita Vens



**Significance:** This study uses innovative machine learning-based approaches to derive models that predict the effect of DNA repair defects on treatment outcome in HNSCC.

**5612** Predictive Signatures Inform the Effective Repurposing of Decitabine to Treat KRAS–Dependent Pancreatic Ductal Adenocarcinoma



Carla Mottini, Hideo Tomihara, Diego Carrella, Alessia Lamolinara, Manuela Iezzi, Justin K. Huang, Carla A. Amoreo, Simonetta Buglioni, Isabella Manni, Frederick S. Robinson, Rosalba Minelli, Ya'an Kang, Jason B. Fleming, Michael P. Kim, Christopher A. Bristow, Daniela Trisciuglio, Antonella Iuliano, Donatella Del Bufalo, Diego Di Bernardo, Davide Melisi, Giulio F. Draetta, Gennaro Ciliberto, Alessandro Carugo, and Luca Cardone

**Significance:** Decitabine is a promising drug for cancer cells dependent on RAS signaling.

**5626** Neutrophil Extracellular Traps Drive Mitochondrial Homeostasis in Tumors to Augment Growth

Hamza O. Yazdani, Eva Roy, Alexander J. Comerchi, Dirk J. van der Windt, Hongji Zhang, Hai Huang, Patricia Loughran, Sruti Shiva, David A. Geller, David L. Bartlett, Allan Tsung, Tai Sheng, Richard L. Simmons, and Samer Tohme

**Significance:** Neutrophils through the release of NETs facilitate the growth of stressed cancer cells by altering their bioenergetics, the inhibition of which induces cell death.

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## 5640 Cellular and Genetic Determinants of the Sensitivity of Cancer to $\alpha$ -Particle Irradiation



Brian D. Yard, Priyanka Gopal, Kristina Bannik, Gerhard Siemeister, Urs B. Hagemann, and Mohamed E. Abazeed

**Significance:** *These findings address limitations in the preclinical guidance and prediction of radionuclide tumor sensitivity by identifying intrinsic cellular and genetic determinants of cancer cell survival following exposure to  $\alpha$ -particle irradiation.*

See related commentary, p. 5479

## 5652 Drugging MYCN Oncogenic Signaling through the MYCN-PA2G4 Binding Interface



Jessica Koach, Jessica K. Holien, Hassina Massudi, Daniel R. Carter, Olivia C. Ciampa, Mika Herath, Taylor Lim, Janith A. Seneviratne, Giorgio Milazzo, Jayne E. Murray, Joshua A. McCarroll, Bing Liu, Chelsea Mayoh, Bryce Keenan, Brendan W. Stevenson, Michael A. Gorman, Jessica L. Bell, Larissa Doughty, Stefan Hüttelmaier, Andre Oberthuer, Matthias Fischer, Andrew J. Gifford, Tao Liu, Xiaoling Zhang, Shizhen Zhu, W. Clay Gustafson, Michelle Haber, Murray D. Norris, Jamie I. Fletcher, Giovanni Perini, Michael W. Parker, Belamy B. Cheung, and Glenn M. Marshall

**Significance:** *Competitive chemical inhibition of the PA2G4–MYCN protein interface provides a basis for drug design of small molecules targeting MYC and MYCN-binding partners in malignancies driven by MYC family oncoproteins.*

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## CONVERGENCE AND TECHNOLOGIES

### 5668 PEG10 Promoter–Driven Expression of Reporter Genes Enables Molecular Imaging of Lethal Prostate Cancer

Mariya Shapovalova, John K. Lee, Yingming Li, Donald J. Vander Griend, Ilsa M. Coleman, Peter S. Nelson, Scott M. Dehm, and Aaron M. LeBeau

**Significance:** *PEG10 is expressed by prostate cancer with constitutively active AR-splice variants that can be exploited for noninvasive molecular imaging of this aggressive prostate cancer subtype.*

## CORRECTIONS

### 5681 Correction: EGFR Cooperates with EGFRvIII to Recruit Macrophages in Glioblastoma

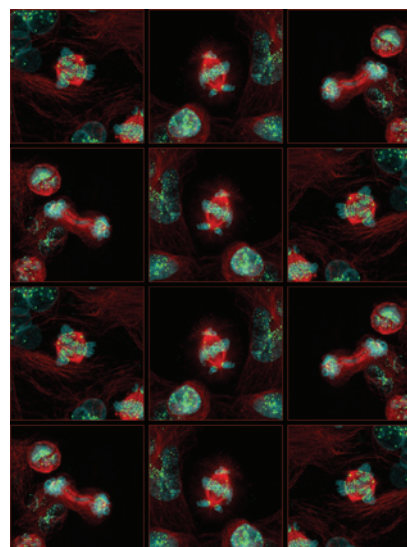
Zhenyi An, Christiane B. Knobbe-Thomsen, Xiaohua Wan, Qi Wen Fan, Guido Reifenberger, and William A. Weiss

### 5682 Correction: Upregulation of PD-L1 via HMGB1-Activated IRF3 and NF- $\kappa$ B Contributes to UV Radiation–Induced Immune Suppression

Wei Wang, Nicole M. Chapman, Bo Zhang, Mingqi Li, Meiyun Fan, R. Nicholas Larabee, M. Raza Zaidi, Lawrence M. Pfeffer, Hongbo Chi, and Zhao-Hui Wu

## ABOUT THE COVER

The fallopian tube precursor lesion for high-grade serous ovarian cancer is characterized by chromosomal instability and a high level of aneuploidy. Treatment of fallopian tube epithelial cells with inhibitors to Mps1 and CENP-E induces chromosomal instability and formation of "atypical mitoses," characterized by multipolar spindles, polar chromosomes, and lagging chromosomes during anaphase. The aneuploid post-mitotic cells incur proteotoxic stress and acquire sensitivity to proteasome inhibition. For details, see the article by Chui and colleagues on page 5536.



# Cancer Research

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

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