

## BREAKING INSIGHTS

- 3099** Highlights from Recent Cancer Literature


## REVIEW

- 3101** Targeting Rac and Cdc42 GTPases in Cancer  
 María del Mar Maldonado and  
 Suranganie Dharmawardhane

## GENOME AND EPIGENOME

- 3112** Mutation Profiling of Key Cancer Genes in Primary Breast Cancers and Their Distant Metastases  
 Willemijne A.M.E. Schrijver, Pier Selenica, Ju Youn Lee, Charlotte K.Y. Ng, Kathleen A. Burke, Salvatore Piscuoglio, Samuel H. Berman, Jorge S. Reis-Filho, Britta Weigelt, Paul J. van Diest, and Cathy B. Moelans

*Significance:* Somatic genetic alterations in ER-negative breast cancer metastases may be distinct from those of their primary tumors, suggesting that for treatment-decision making, genetic analyses of DNA obtained from the metastatic lesion rather than from the primary tumor should be considered.

- 3122** Network Modeling of microRNA-mRNA Interactions in Neuroblastoma Tumorigenesis Identifies miR-204 as a Direct Inhibitor of MYCN  
 Chi Yan Ooi, Daniel R. Carter, Bing Liu, Chelsea Mayoh, Anneleen Beckers, Amit Lalwani, Zsuzsanna Nagy, Sara De Brouwer, Bieke Decaestecker, Tzong-Tyng Hung, Murray D. Norris, Michelle Haber, Tao Liu, Kathleen De Preter, Frank Speleman, Belamy B. Cheung, and Glenn M. Marshall

*Significance:* Network modeling of miRNA-mRNA regulatory interactions in a mouse model of neuroblastoma identifies miR-204 as a tumor suppressor and negative regulator of MYCN.

- 3135** SETD2 Haploinsufficiency for Microtubule Methylation Is an Early Driver of Genomic Instability in Renal Cell Carcinoma  
 Yun-Chen Chiang, In-Young Park, Esteban A. Terzo, Durga Nand Tripathi, Frank M. Mason, Catherine C. Fahey, Menuka Karki, Charles B. Shuster, Bo-Hwa Sohn, Pratim Chowdhury, Reid T. Powell, Ryoma Ohi, Yihsuan S. Tsai, Aguirre A. de Cubas, Abid Khan, Ian J. Davis, Brian D. Strahl, Joel S. Parker, Ruhee Dere, Cheryl L. Walker, and W. Kimryn Rathmell

*Significance:* Loss of a single allele of a chromatin modifier plays a role in promoting oncogenesis, underscoring the growing relevance of tumor suppressor haploinsufficiency in tumorigenesis.

## MOLECULAR CELL BIOLOGY

- 3147** Inhibition of the Wnt/ $\beta$ -Catenin Pathway Overcomes Resistance to Enzalutamide in Castration-Resistant Prostate Cancer  
 Zhuangzhuang Zhang, Lijun Cheng, Jie Li, Elia Farah, Nadia M. Atallah, Pete E. Pascuzzi, Sanjay Gupta, and Xiaoqi Liu

*Significance:* Wnt/ $\beta$ -catenin inhibition resensitizes prostate cancer cells to enzalutamide.

- 3163** Deptor Is a Novel Target of Wnt/ $\beta$ -Catenin/c-Myc and Contributes to Colorectal Cancer Cell Growth  
 Qingding Wang, Yuning Zhou, Piotr Rychahou, Jennifer W. Harris, Yekaterina Y. Zaytseva, Jinpeng Liu, Chi Wang, Heidi L. Weiss, Chunming Liu, Eun Y. Lee, and B. Mark Evers

*Significance:* The mTOR inhibitor DEPTOR acts as a tumor promoter and could be a potential therapeutic target in colorectal cancer.

- 3176** Differential Effects of Estrogen Receptor  $\beta$  Isoforms on Glioblastoma Progression  
 Jinyou Liu, Gangadhara R. Sareddy, Mei Zhou, Suryavathi Viswanadhapalli, Xiaonan Li, Zhao Lai, Rajeshwar R. Tekmal, Andrew Brenner, and Ratna K. Vadlamudi

*Significance:* These findings suggest that only ER $\beta$  isoform 1 has tumor suppressor function in GBM and that ER $\beta$  isoform switching contributes to GBM progression.

- 3190** PHE5A Epigenetically Inhibits Apoptosis to Promote Breast Cancer Progression  
 Yi-Zi Zheng, Meng-Zhu Xue, Hong-Jie Shen, Xiao-Guang Li, Ding Ma, Yue Gong, Yi-Rong Liu, Feng Qiao, Hong-Yan Xie, Bi Lian, Wei-Li Sun, Hai-Yun Zhao, Ling Yao, Wen-Jia Zuo, Da-Qiang Li, Peng Wang, Xin Hu, and Zhi-Ming Shao

*Significance:* This study provides an epigenetic mechanistic basis for the aggressive biology of breast cancer and identifies a translatable therapeutic target.

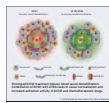
- 3207** Silencing of Long Noncoding RNA MIR22HG Triggers Cell Survival/Death Signaling via Oncogenes YBX1, MET, and p21 in Lung Cancer  
 Wenmei Su, Shumei Feng, Xiuyuan Chen, Xia Yang, Rui Mao, Chunfang Guo, Zhuwen Wang, Dafydd G. Thomas, Jules Lin, Rishindra M. Reddy, Mark B. Orringer, Andrew C. Chang, Zhixiong Yang, David G. Beer, and Guoan Chen

*Significance:* The lncRNA MIR22HG functions as a tumor suppressor, with potential use as a diagnostic/prognostic marker and therapeutic target in lung cancer.

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## TUMOR BIOLOGY AND IMMUNOLOGY

**3220** Blockade of Myeloid-Derived Suppressor Cell Expansion with All-*Trans* Retinoic Acid Increases the Efficacy of Antiangiogenic Therapy



Raimund Bauer, Florian Udonta, Mark Wroblewski, Isabel Ben-Batalla, Ines Miranda Santos, Federico Taverna, Meike Kuhlencord, Victoria Gensch, Sarina Päsler, Stefan Vinckier, Johanna M. Brandner, Klaus Pantel, Carsten Bokemeyer, Thomas Vogl, Johannes Roth, Peter Carmeliet, and Sonja Loges

**Significance:** Increasing the therapeutic efficiency of antiangiogenic drugs by reducing resistance-conferring myeloid-derived suppressor cells might improve breast cancer treatment.

**3233** Sustained Adrenergic Signaling Promotes Intratumoral Innervation through BDNF Induction



Julie K. Allen, Guillermo N. Armaiz-Pena, Archana S. Nagaraja, Nouara C. Sadaoui, Tatiana Ortiz, Robert Dood, Merve Ozcan, Danielle M. Herder, Monika Haemmerle, Kshipra M. Gharpure, Rajesha Rupaimoole, Rebecca A. Previs, Sherry Y. Wu, Sunila Pradeep, Xiaoyun Xu, Hee Dong Han, Behrouz Zand, Heather J. Dalton, Morgan Taylor, Wei Hu, Justin Bottsford-Miller, Myrthala Moreno-Smith, Yu Kang, Lingegowda S. Mangala, Cristian Rodriguez-Aguayo, Vasudha Sehgal, Erika L. Spaeth, Prahlad T. Ram, Stephen T.C. Wong, Frank C. Marini, Gabriel Lopez-Berestein, Steve W. Cole, Susan K. Lutgendorf, Mariella De Biasi, and Anil K. Sood

**Significance:** Sustained adrenergic signaling promotes tumor growth and metastasis through BDNF-mediated intratumoral innervation.

**3243** ERAP1-Dependent Antigen Cross-Presentation Determines Efficacy of Adoptive T-cell Therapy in Mice

Karin Schmidt, Christin Keller, Anja A. Kühl, Ana Textor, Ulrike Seifert, Thomas Blankenstein, Gerald Willimsky, and Peter-Michael Kloetzel

**Significance:** This study demonstrates a role of ERAP1 in the efficacy of adoptive T-cell transfer and has potential to improve personalized T-cell therapy for solid tumors.

**3255** CD163 Is Required for Protumoral Activation of Macrophages in Human and Murine Sarcoma

Daisuke Shiraishi, Yukio Fujiwara, Hasita Horlad, Yoichi Saito, Toyohisa Iriki, Junko Tsuboki, Pan Cheng, Naomi Nakagata, Hiroshi Mizuta, Hirofumi Bekki, Yasuharu Nakashima, Yoshinao Oda, Motohiro Takeya, and Yoshihiro Komohara

**Significance:** Macrophage CD163-mediated induction of IL6 promotes tumor development and progression in murine and human malignant tumors.

**3267** Reactivation of Mutant-EGFR Degradation through Clathrin Inhibition Overcomes Resistance to EGFR Tyrosine Kinase Inhibitors



Ludovic Ménard, Nicolas Floc'h, Matthew J. Martin, and Darren A.E. Cross

**Significance:** These findings extend our mechanistic understanding of NSCLC mutant EGFR trafficking biology, the role that trafficking may play in resistance of mutant EGFR to tyrosine kinase inhibitors, and provide new therapeutic and biological insights to tackle this fundamental issue and improve benefit to patients.

**3280** Intratumoral CpG-B Promotes Antitumoral Neutrophil, cDC, and T-cell Cooperation without Reprogramming Tolerogenic pDC



Marion Humbert, Leslie Guery, Dale Brighthouse, Sylvain Lemeille, and Stephanie Hugues

**Significance:** Intratumoral delivery of CpG-B disrupts the tolerogenic tumor microenvironment and inhibits tumor growth.

**3293** IL22RA1/STAT3 Signaling Promotes Stemness and Tumorigenicity in Pancreatic Cancer

Weizhi He, Jinghua Wu, Juanjuan Shi, Yan-Miao Huo, Wentao Dai, Jing Geng, Ping Lu, Min-Wei Yang, Yuan Fang, Wei Wang, Zhi-Gang Zhang, Aida Habtezion, Yong-Wei Sun, and Jing Xue

**Significance:** IL22RA1/STAT3 signaling enhances stemness and tumorigenicity in pancreatic cancer.

**3306** YAP/TAZ Initiates Gastric Tumorigenesis via Upregulation of MYC

Wonyoung Choi, Jeongsik Kim, Jaeh Park, Da-Hye Lee, Daehee Hwang, Jeong-Hwan Kim, Hassan Ashktorab, Duane Smoot, Seon-Young Kim, Chan Choi, Gou Young Koh, and Dae-Sik Lim

**Significance:** YAP/TAZ activation initiates gastric carcinogenesis with MYC as the key downstream mediator.

## TRANSLATIONAL SCIENCE

**3321** Rho Kinase Inhibition by AT13148 Blocks Pancreatic Ductal Adenocarcinoma Invasion and Tumor Growth



Nicola Rath, June Munro, Marie Francene Cutiongco, Alicja Jagiełło, Nikolaj Gadegaard, Lynn McGarry, Mathieu Unbekandt, Evdokia Michalopoulou, Jurre J. Kamphorst, David Sumpton, Gillian Mackay, Claire Vennin, Marina Pajic, Paul Timpson, and Michael F. Olson

**Significance:** Preclinical evaluation of a small-molecule ROCK inhibitor reveals significant effects on PDAC invasion and tumor growth, further validating ROCK kinases as viable therapeutic targets in pancreatic cancer.

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## 3337 Adoptive Immunotherapy Using PRAME-Specific T Cells in Medulloblastoma



Domenico Orlando, Evelina Miele, Biagio De Angelis, Marika Guercio, Iolanda Boffa, Matilde Sinibaldi, Agnese Po, Ignazio Caruana, Luana Abballe, Andrea Carai, Simona Caruso, Antonio Camera, Annemarie Moseley, Renate S. Hagedoorn, Mirjam H.M. Heemskerk, Felice Giangaspero, Angela Mastronuzzi, Elisabetta Ferretti, Franco Locatelli, and Concetta Quintarelli

*Significance:* These findings identify PRAME as a medulloblastoma tumor-associated antigen that can be targeted using genetically modified T cells.

## 3350 Enhancer Remodeling and MicroRNA Alterations Are Associated with Acquired Resistance to ALK Inhibitors

Mi Ran Yun, Sun Min Lim, Seon-Kyu Kim, Hun Mi Choi, Kyoung-Ho Pyo, Seong Keun Kim, Ji Min Lee, You Won Lee, Jae Woo Choi, Hye Ryun Kim, Min Hee Hong, Keok Haam, Nanhyung Huh, Jong-Hwan Kim, Yong Sung Kim, Hyo Sup Shim, Ross Andrew Soo, Jin-Yuan Shih, James Chih-Hsin Yang, Mirang Kim, and Byoung Chul Cho

*Significance:* Epigenetic deregulation drives acquired resistance to ALK inhibitors in ALK-positive lung cancer.

## 3363 Zika Virus Selectively Kills Aggressive Human Embryonal CNS Tumor Cells *In Vitro* and *In Vivo*



Carolini Kaid, Ernesto Goulart, Luiz C. Caires-Júnior, Bruno H.S. Araujo, Alessandra Soares-Schanoski, Heloisa M.S. Bueno, Kayque A. Telles-Silva, Renato M. Astray, Amanda F. Assoni, Antônio F.R. Júnior, Daniella C. Ventini, Ana L.P. Puglia, Roselane P. Gomes, Mayana Zatz, and Oswaldo K. Okamoto

*Significance:* Brazilian Zika virus strain kills aggressive metastatic forms of human CNS tumors and could be a potential oncolytic agent for cancer therapy.

## CONVERGENCE AND TECHNOLOGIES

### 3375 MVisAGE Identifies Concordant and Discordant Genomic Alterations of Driver Genes in Squamous Tumors



Vonn Walter, Ying Du, Ludmila Danilova, Michele C. Hayward, and D. Neil Hayes

*Significance:* This study presents an important bioinformatics tool that will enable integrated analyses of multiple genomic datatypes.

## POPULATION AND PREVENTION SCIENCE

### 3386 Case Studies of Gastric, Lung, and Oral Cancer Connect Etiologic Agent Prevalence to Cancer Incidence



Andrew F. Brouwer, Marisa C. Eisenberg, and Rafael Meza

*Significance:* Analysis of trends in risk-factor prevalence and cancer incidence can shed light on cancer mechanisms and the way that carcinogen exposure through time shapes the risk of cancer at different ages.

## RETRACTIONS

### 3397 Retraction: Demethylation-Linked Activation of Urokinase Plasminogen Activator Is Involved in Progression of Prostate Cancer

### 3398 Retraction: Small Interfering RNA-Directed Reversal of Urokinase Plasminogen Activator Demethylation Inhibits Prostate Tumor Growth and Metastasis

### 3399 Retraction: The Potential Role of Hypoxia Inducible Factor 1 $\alpha$ in Tumor Progression after Hypoxia and Chemotherapy in Hepatocellular Carcinoma

### 3400 Retraction: Identification of Brain-Derived Neurotrophic Factor as a Novel Functional Protein in Hepatocellular Carcinoma

## CORRECTIONS

### 3401 Correction: AMPK Reverses the Mesenchymal Phenotype of Cancer Cells by Targeting the Akt-MDM2-Foxo3a Signaling Axis

### 3402 Correction: Ubiquitous Release of Exosomal Tumor Suppressor miR-6126 from Ovarian Cancer Cells

### 3403 Correction: TEM8/ANTXR1-Specific CAR T Cells as a Targeted Therapy for Triple-Negative Breast Cancer

### 3404 Correction: miRNA-708 Control of CD44<sup>+</sup> Prostate Cancer-Initiating Cells

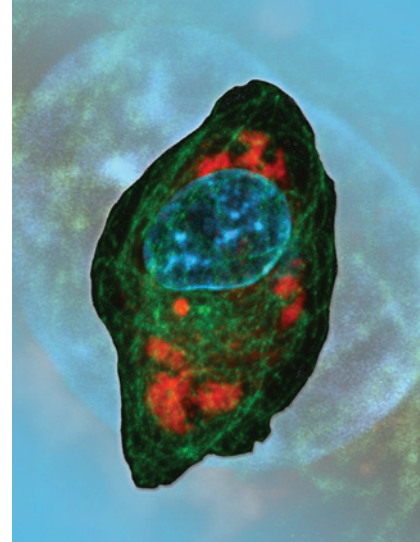
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## ABOUT THE COVER

ZIKV<sup>BR</sup> displays strong and specific oncolytic property against human central nervous system (CNS) embryonal tumors. Tumor cells infected with the virus (red) are readily destroyed and are ineffective in producing new functional viral particles. In tumor-bearing mice, ZIKV<sup>BR</sup> induces significant CNS tumor remission and spinal cord metastasis inhibition. Neural stem-like cancer cells with high Wnt/ $\beta$ -catenin basal activity are more susceptible to the oncolytic effects of ZIKV<sup>BR</sup>. For details, see article by Kaid and colleagues on page 3363.



# Cancer Research

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