

## BREAKING INSIGHTS

- 1887** Highlights from Recent Cancer Literature

## EDITORIAL

- 1889** *Cancer Research: Embracing the Complexity of Cancer and Emergence of Truth*  
Chi Van Dang


## REVIEW

- 1890** Lessons from the Crypt: HMGA1—Amping up Wnt for Stem Cells and Tumor Progression  
Linda Resar, Lionel Chia, and Lingling Xian

## POINT-COUNTERPOINT REVIEWS

- 1898** The Plausibility of Obesity Paradox in Cancer  
Yikyung Park, Lindsay L. Peterson, and Graham A. Colditz  
*See Counterpoint by Caan, et al., p. 1906 and Reply by Cespedes Feliciano, et al., p. 1904*

- 1904** The Plausibility of the Obesity Paradox in Cancer—Response  
Elizabeth M. Cespedes Feliciano, Candyce H. Kroenke, and Bette J. Caan  
*See Point by Park et al., p. 1898*

- 1906**  The Importance of Body Composition in Explaining the Overweight Paradox in Cancer  
Bette J. Caan, Elizabeth M. Cespedes Feliciano, and Candyce H. Kroenke  
*See Point and Reply by Park, et al., p. 1898 and p. 1913*

- 1913** Evidence for an Overweight Paradox in Cancer: Insights from Body Composition  
Yikyung Park, Lindsay L. Peterson, and Graham A. Colditz  
*See Counterpoint by Caan, et al., p. 1906*

## GENOME AND EPIGENOME

- 1914** Germline Mutations in the Mitochondrial 2-Oxoglutarate/Malate Carrier *SLC25A11* Gene Confer a Predisposition to Metastatic Paragangliomas  
Alexandre Buffet, Aurélie Morin, Luis-Jaime Castro-Vega, Florence Habarou, Charlotte Lussey-Lepoutre, Eric Letouzé, Hervé Lefebvre, Isabelle Guilhem, Magalie Haissaguerre, Isabelle Raingeard, Mathilde Padilla-Girola, Thi Tran, Lucien Tchara, Jérôme Bertherat, Laurence Amar, Chris Ottolenghi, Nelly Burnichon, Anne-Paule Gimenez-Roqueplo, and Judith Favier

*Significance: A gene encoding a mitochondrial carrier is implicated in a hereditary cancer predisposition syndrome, expanding the role of mitochondrial dysfunction in paraganglioma.*

## METABOLISM AND CHEMICAL BIOLOGY

- 1923** LPA Induces Metabolic Reprogramming in Ovarian Cancer via a Pseudo-hypoxic Response  
Ji Hee Ha, Rangasudhagar Radhakrishnan, Muralidharan Jayaraman, Mingda Yan, Jeremy D. Ward, Kar-Ming Fung, Katherine Moxley, Anil K. Sood, Ciro Isidoro, Priyabrata Mukherjee, Yong Sang Song, and Danny N. Dhanasekaran  
*Significance: These findings establish LPA as a potential therapeutic target in ovarian cancer, revealing its role in the activation of HIF $\alpha$ -mediated metabolic reprogramming in this disease.*

## MOLECULAR CELL BIOLOGY

- 1935** Tumorigenic and Antiproliferative Properties of the TALE-Transcription Factors MEIS2D and MEIS2A in Neuroblastoma  
Anja Groß, Catrine Schulz, Jasmine Kolb, Jan Koster, Sibylle Wehner, Sebastian Czaplinski, Abdulghani Khilan, Hermann Rohrer, Patrick N. Harter, Thomas Klingebiel, Julian D. Langer, Dirk Geerts, and Dorothea Schulte  
*Significance: This study illuminates the basis for spontaneous regressions that can occur in a common pediatric tumor, with implications for the development of new treatment strategies.*

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**1948** S-Nitrosylation of cIAP1 Switches Cancer Cell Fate from TNF $\alpha$ /TNFR1-Mediated Cell Survival to Cell Death

Sabrina Romagny, Sarra Bouaouiche, Géraldine Lucchi, Patrick Ducoroy, Jean B. Bertoldo, Hernan Terenzi, Ali Bettaieb, and Stéphanie Plenchette

*Significance:* Combination of an NO donor with chemotherapeutic drug-induced TNF $\alpha$  represents a potentially valuable anticancer strategy.

**1958** RNF6 Promotes Colorectal Cancer by Activating the Wnt/ $\beta$ -Catenin Pathway via Ubiquitination of TLE3



Lei Liu, Yanquan Zhang, Chi Chun Wong, Jingwan Zhang, Yujuan Dong, Xiangchun Li, Wei Kang, Francis K.L. Chan, Joseph J.Y. Sung, and Jun Yu

*Significance:* RNF6-mediated ubiquitination and degradation of TLE3 activates the Wnt/ $\beta$ -catenin pathway in colorectal carcinogenesis.

## TUMOR BIOLOGY AND IMMUNOLOGY

**1972** ME1 Regulates NADPH Homeostasis to Promote Gastric Cancer Growth and Metastasis



Yun-Xin Lu, Huai-Qiang Ju, Ze-Xian Liu, Dong-Liang Chen, Yun Wang, Qi Zhao, Qi-Nian Wu, Zhao-lei Zeng, Hai-Bo Qiu, Pei-Shan Hu, Zhi-Qiang Wang, Dong-Sheng Zhang, Feng Wang, and Rui-Hua Xu

*Significance:* These findings reveal the role of malic enzyme in growth and metastasis in vitro and in vivo.

**1986** Silencing the Snail-Dependent RNA Splice Regulator ESRP1 Drives Malignant Transformation of Human Pulmonary Epithelial Cells

Tonya C. Walser, Zhe Jing, Linh M. Tran, Ying Q. Lin, Natalie Yakobian, Gerald Wang, Kostyantyn Krysan, Li X. Zhu, Sherven Sharma, Mi-Heon Lee, John A. Belperio, Aik T. Ooi, Brigitte N. Gomperts, Jerry W. Shay, Jill E. Larsen, John D. Minna, Long-sheng Hong, Michael C. Fishbein, and Steven M. Dubinett

*Significance:* This study defines a Snail-ESRP1 cancer axis that is crucial for human lung carcinogenesis, with implications for new intervention strategies and translational opportunities.

**2000** NRAS-Mutated Rhabdomyosarcoma Cells Are Vulnerable to Mitochondrial Apoptosis Induced by Coinhibition of MEK and PI3K $\alpha$

Nadezda Dolgikh, Manuela Hugle, Meike Vogler, and Simone Fulda

*Significance:* These findings offer a mechanistic rationale for combining MEK- and PI3K $\alpha$ -specific inhibitors in the clinical treatment of RAS-mutated forms of often untreatable rhabdomyosarcomas.

**2014** ER $\alpha$ -Mediated Nuclear Sequestration of RSK2 Is Required for ER<sup>+</sup> Breast Cancer Tumorigenesis

Katarzyna A. Ludwik, Oliver G. McDonald, David R. Brenin, and Deborah A. Lannigan

*Significance:* Nuclear accumulation of active RSK drives a protumorigenic transcriptional program and renders ER<sup>+</sup> breast cancer susceptible to endocrine-based therapies.

**2026** CXCL12 $\gamma$  Promotes Metastatic Castration-Resistant Prostate Cancer by Inducing Cancer Stem Cell and Neuroendocrine Phenotypes

Younghun Jung, Frank C. Cackowski, Kenji Yumoto, Ann M. Decker, Jingcheng Wang, Jin Koo Kim, Eunsohl Lee, Yugang Wang, Jae-Seung Chung, Amy M. Gursky, Paul H. Krebsbach, Kenneth J. Pienta, Todd M. Morgan, and Russell S. Taichman

*Significance:* Expression of CXCL12 $\gamma$  induces the expression of a cancer stem cell and neuroendocrine phenotypes, resulting in the development of aggressive m-CRPC.

**2040** HER2 Overexpression Triggers an IL1 $\alpha$  Proinflammatory Circuit to Drive Tumorigenesis and Promote Chemotherapy Resistance

Shou Liu, Ji Shin Lee, Chunfa Jie, Min Ho Park, Yoichiro Iwakura, Yogin Patel, Mithil Soni, David Reisman, and Hexin Chen

*Significance:* IL1 $\alpha$  signaling driven by HER2 promotes chronic inflammation needed to support cancer stem-like cell maintenance in HER2-positive breast cancers.

**2052** Targeting Brain-Adaptive Cancer Stem Cells Prohibits Brain Metastatic Colonization of Triple-Negative Breast Cancer

Ding Ren, Xiaoping Zhu, Ren Kong, Zhen Zhao, Jianting Sheng, Jiang Wang, Xiaoyun Xu, Jiyong Liu, Kemi Cui, Xiang H.-F. Zhang, Hong Zhao, and Stephen T.C. Wong

*Significance:* These findings identify a compound to block adaptive signaling between cancer stem cells and brain astrocytes.

## TRANSLATIONAL SCIENCE

### 2065 Small-Molecule Activators of Protein Phosphatase 2A for the Treatment of Castration-Resistant Prostate Cancer

Kimberly McClinch, Rita A. Avelar, David Callejas, Sudeh Izadmehr, Danica Wiredja, Abbey Perl, Jaya Sangodkar, David B. Kastrinsky, Daniela Schlatzer, Maxwell Cooper, Janna Kiselar, Agnes Stachnik, Shen Yao, Divya Hoon, Daniel McQuaid, Nilesh Zaware, Yixuan Gong, David L. Brautigam, Stephen R. Plymate, Cynthia C.T. Sprenger, William K. Oh, Alice C. Levine, Alexander Kirschenbaum, John P. Sfakianos, Rosalie Sears, Analisa DiFeo, Yiannis Ioannou, Michael Ohlmeyer, Goutham Narla, and Matthew D. Galsky

*Significance: A novel class of small-molecule activators of the tumor suppressor PP2A, a serine/threonine phosphatase that inhibits many oncogenic signaling pathways, is shown to deregulate the phosphoproteome and to destabilize the androgen receptor in advanced prostate cancer.*

### 2081 Age-Dependent Cellular and Behavioral Deficits Induced by Molecularly Targeted Drugs Are Reversible



Joseph Scafidi, Jonathan Ritter, Brooke M. Talbot, Jorge Edwards, Li-Jin Chew, and Vittorio Gallo

*Significance: Targeted therapeutics elicit age-dependent long-term consequences on the developing brain, which can be ameliorated with environmental enrichment.*

### 2096 Discovery of Potent and Selective MRCK Inhibitors with Therapeutic Effect on Skin Cancer



Mathieu Unbekandt, Simone Belshaw, Justin Bower, Maeve Clarke, Jacqueline Cordes, Diane Crighton, Daniel R. Croft, Martin J. Drysdale, Mathew J. Garnett, Kathryn Gill, Christopher Gray, David A. Greenhalgh, James A.M. Hall, Jennifer Konczal, Sergio Lilla, Duncan McArthur, Patricia McConnell, Laura McDonald, Lynn McGarry, Heather McKinnon, Carol McMenemy, Mokdad Mezna, Nicolas A. Morrice, June Munro, Gregory Naylor, Nicola Rath, Alexander W. Schüttelkopf, Mairi Sime, and Michael F. Olson

*Significance: The development of selective small-molecule inhibitors of the Cdc42-binding MRCK kinases reveal their essential roles in cancer cell viability, migration, and invasive character.*

### 2115 Modulation of Macropinocytosis-Mediated Internalization Decreases Ocular Toxicity of Antibody-Drug Conjugates

Hui Zhao, John Atkinson, Sara Gulesserian, Zhilan Zeng, Jenny Nater, Jimmy Ou, Peng Yang, Karen Morrison, Jeffrey Coleman, Faisal Malik, Pia Challita-Eid, Sher Karki, Hector Aviña, René Hubert, Linnette Capó, Josh Snyder, Sung-Ju Moon, Roland Luethy, Brian A. Mendelsohn, David R. Stover, and Fernando Doñate

*Significance: These findings reveal a mechanism for nonreceptor-mediated toxicities of antibody drug conjugates and potential solutions to alleviate these toxicities.*

## CONVERGENCE AND TECHNOLOGIES

### 2127 Spatial Heterogeneity and Evolutionary Dynamics Modulate Time to Recurrence in Continuous and Adaptive Cancer Therapies

Jill A. Gallaher, Pedro M. Enriquez-Navas, Kimberly A. Luddy, Robert A. Gatenby, and Alexander R.A. Anderson

*Significance: By using drug dose modulation or treatment vacations, adaptive therapy strategies control the emergence of tumor drug resistance by spatially suppressing less fit resistant populations in favor of treatment sensitive ones.*

## RESOURCE REPORT

### 2140 CrosstalkNet: A Visualization Tool for Differential Co-expression Networks and Communities

Venkata Manem, George Alexandru Adam, Tina Grusso, Mathieu Gigoux, Nicholas Bertos, Morag Park, and Benjamin Haibe-Kains

*Significance: This web application enables researchers to mine complex networks and to decipher novel biological processes in tumor epithelial-stroma cross-talk as well as in other studies of intercompartmental interactions.*

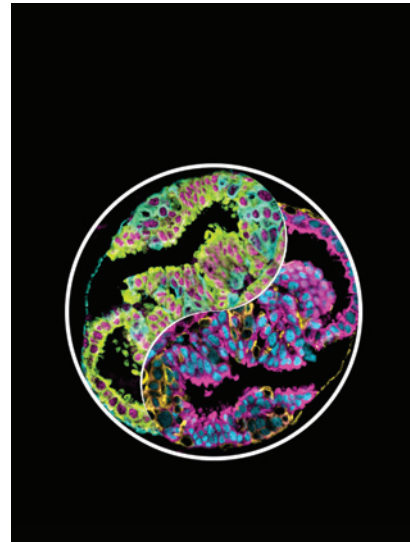
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## ABOUT THE COVER

Nuclear active RSK2 (magenta, left) correlates with ER $\alpha$  (blue, right) in sixty percent of ER $^{+}$  patients as visualized in this serial section from an ER $^{+}$  tumor. In each section the cells were also stained for cytokeratin 8 (lime, left; magenta, right) and cytokeratin 14 (cyan, left; yellow, right). In the left image, cells that are positive for both K8 and K14 are teal and on the right, these dual-positive cells are orange. Sequestration of RSK2 by ER $\alpha$  in the nucleus drives a pro-neoplastic transcriptional program critical to the ER $^{+}$  lineage in the mammary gland, neoplasia, and differing patient responses to antiestrogen therapies. For details, see article by Ludwik and colleagues on page 2014.



# Cancer Research

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

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