# Cancer Research
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### 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  
Yikying Park, Lindsay I. 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, Canduye 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 Canduye 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  
Yikying 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, Aurelie Morin, Luis-Jaime Castro-Vega, Florence Habarou, Charlotte Lussey-Lepoutre, Eric Letouzé, Hervé Lefebvre, Isabelle Guilhem, Magalie Haissaguerre, Isabelle Raingard, Mathilde Padilla-Girola, Thi Tran, Lucien Tchara, Jérôme Bertherat, Laurence Amer, 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 Pseudohypoxic 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 HIFα-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 Czapinski, 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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<td>1948</td>
<td>S-Nitrosylation of cIAP1 Switches Cancer Cell Fate from TNFα/TNFRI-Mediated Cell Survival to Cell Death</td>
<td>Sabrina Romagny, Sarra Bouaouiche, Gérardine Lucchi, Patrick Ducoroy, Jean B. Bertoldo, Hernan Terenzini, Ali Betariah, and Stéphanie Plenchette</td>
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<td>1958</td>
<td>RNF6 Promotes Colorectal Cancer by Activating the Wnt/β-Catenin Pathway via Ubiquitination of TLE3</td>
<td>Lei Liu, Yanquang Zhang, Chi Chun Wong, Jingwan Zhang, Yujuan Dong, Xianghun Li, Wei Kang, Francis K.L. Chan, Joseph J.Y. Sung, and Jun Yu</td>
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<td>1972</td>
<td>ME1 Regulates NADPH Homeostasis to Promote Gastric Cancer Growth and Metastasis</td>
<td>Yun-Xin Lu, Hua-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</td>
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<td>2000</td>
<td>NRAS-Mutated Rhabdomyosarcoma Cells Are Vulnerable to Mitochondrial Apoptosis Induced by Coinhibition of MEK and PI3Kα</td>
<td>Nadezda Dolgikh, Manuela Hugle, Meike Vogler, and Simone Fulda</td>
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<td>2014</td>
<td>ERα-Mediated Nuclear Sequestration of RSK2 Is Required for ERα+ Breast Cancer Tumorigenesis</td>
<td>Katarzyna A. Ludwik, Oliver G. McDonald, David R. Brenin, and Deborah A. Lannigan</td>
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<td>2020</td>
<td>HER2 Overexpression Triggers an IL1α Proinflammatory Circuit to Drive Tumorigenesis and Promote Chemotherapy Resistance</td>
<td>Shou Liu, Ji Shin Lee, Chunfa Jie, Min Ho Park, Yoichiro Iwakura, Yogin Patel, Mithil Soni, David Reisman, and Hexin Chen</td>
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<td>2026</td>
<td>Targeting Brain-Adaptive Cancer Stem Cells Prohibits Brain Metastatic Colonization of Triple-Negative Breast Cancer</td>
<td>Ding Ren, Xiaoping Zhu, Ren Kong, Zhen Zhao, Jianing Sheng, Jiang Wang, Xiaoayun Xu, Jiyong Liu, Remi Cui, Xiang H.-F. Zhang, Hong Zhao, and Stephen T.C. Wong</td>
</tr>
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Significance:

- Combination of an NO donor with chemotherapeutic drug-induced TNFα represents a potentially valuable anticancer strategy.
- RNF6-mediated ubiquitination and degradation of TLE3 activates the Wnt/β-catenin pathway in colorectal carcinogenesis.
- These findings reveal the role of malic enzyme in growth and metastasis in vitro and in vivo.
- This study defines a Snail-ESRP1 cancer axis that is crucial for human lung carcinogenesis, with implications for new intervention strategies and translational opportunities.
- These findings offer a mechanistic rationale for combining MEK- and PI3Kα-specific inhibitors in the clinical treatment of RAS-mutated forms of often untreatable rhabdomyosarcomas.

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TRANSLATIONAL SCIENCE

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, 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.

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.

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 McCurry, Heather McKinnon, Carol McMenemy, Mokdad Mezna, Nicolas A. Morrice, June Muntor, 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.

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 Capo, Josh Snyder, Sung-Ju Moon, Roland Luebhy, 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

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 dosmodulation 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

CrosstalkNet: A Visualization Tool for Differential Co-expression Networks and Communities
Venkata Manem, George Alexandre Adam, Tina Gruosso, Mathieu Gigoux, Nicholos 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 ERα (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 ERα 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.