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: HMGAl—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 Raingard, 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 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, Siebyle 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.
NRAS-Mutated Rhabdomyosarcoma Cells Are Vulnerable to Mitochondrial Apoptosis Induced by Coinhibition of MEK and PI3Kα
Nadezda Dolgikh, Manuela Hugle, Meike Vogler, and Simone Fulda

Significance: 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.
TRANSLATIONAL SCIENCE

2065 Small-Molecule Activators of Protein Phosphatase 2A for the Treatment of Castration-Resistant Prostate Cancer
Kimberly McClintch, Rita A. Avelar, David Callejas, Sudeh Izadmehr, Danica Wiredja, Abbey Perl, Jaya Sangodkar, David B. Kastrinsky, Daniela Schlatzer, Maxwell Cooper, Janna Kisela, Agnes Stachnik, Shen Yao, Divya Hoon, Daniel McQuaid, Nilesh Zaware, Yixuan Gong, David I. Brautigan, Stephen R. Plymate, Cynthia C.T. Sprenger, 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.

CONVERGENCE AND TECHNOLOGIES

2115 Modulation of Macropinocytosis-Mediated Internalization Decreases Ocular Toxicity of Antibody–Drug Conjugates
Hui Zhao, John Atkinson, Sara Guleserian, 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 Laethby, 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.

RESOURCE REPORT

2140 CrosstalkNet: A Visualization Tool for Differential Co-expression Networks and Communities
Venkata Manem, George Alexandru Adam, Tina Cnossos, 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.
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.