

BREAKING ADVANCES

- 5213** Highlights from Recent Cancer Literature

REVIEW

- 5215** Roles for Innate Immunity in Combination Immunotherapies
 Kelly D. Moynihan and Darrell J. Irvine

MEETING REPORT

- 5222** New Advances and Challenges of Targeting Cancer Stem Cells
 Nurmaa K. Dashzeveg, Rokana Taftaf, Erika K. Ramos, Luke Torre-Healy, Anastasia Chumakova, Daniel J. Silver, Tyler J. Alban, Maksim Sinyuk, Praveena S. Thiagarajan, Awad M. Jarrar, Soumya M. Turaga, Caner Saygin, Erin Mulkearns-Hubert, Masahiro Hitomi, Jeremy N. Rich, Stanton L. Gerson, Justin D. Lathia, and Huiping Liu

PRIORITY REPORT

- 5228** Targeting a Single Alternative Polyadenylation Site Coordinately Blocks Expression of Androgen Receptor mRNA Splice Variants in Prostate Cancer
 Jamie L. Van Etten, Michael Nyquist, Yingming Li, Rendong Yang, Yeung Ho, Rachel Johnson, Olivia Ondigi, Daniel F. Voytas, Christine Henzler, and Scott M. Dehm
Précis: These results support the development of new therapies targeting the polyadenylation signal in intron 3 of the androgen receptor gene as a strategy to prevent expression of a broad array of receptor variants that drive advanced prostate cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5236** Loss of *Igf2* Gene Imprinting in Murine Prostate Promotes Widespread Neoplastic Growth
 Nathan A. Damaschke, Bing Yang, Sachin Bhusari, Mele Avilla, Weixiong Zhong, Michael L. Blute Jr, Wei Huang, and David F. Jarrard
Précis: Loss of gene imprinting of the insulin-like growth factor *IGF2*, a common epigenetic alteration in histologically normal human prostate tissues, is shown to be sufficient to encourage neoplastic growth in a mouse model of prostate cancer.

- 5248** A Novel Functional Splice Variant of *AKT3* Defined by Analysis of Alternative Splice Expression in HPV-Positive Oropharyngeal Cancers
 Theresa Guo, Akihiro Sakai, Bahman Afsari, Michael Considine, Ludmila Danilova, Alexander V. Favorov, Srinivasan Yegnasubramanian, Dylan Z. Kelley, Emily Flam, Patrick K. Ha, Zubair Khan, Sarah J. Wheelan, J. Silvio Gutkind, Elana J. Fertig, Daria A. Gaykalova, and Joseph Califano

Précis: This study describes the discovery and characterization of a novel splice isoform of the kinase *AKT3* that drives oncogenesis in HPV-related oral cancers of increasing incidence.

- 5259** PRC2-Mediated Transcriptomic Alterations at the Embryonic Stage Govern Tumorigenesis and Clinical Outcome in MYCN-Driven Neuroblastoma
 Shoma Tsubota, Satoshi Kishida, Teppei Shimamura, Miki Ohira, Satoshi Yamashita, Dongliang Cao, Shinichi Kiyonari, Toshikazu Ushijima, and Kenji Kadomatsu
Précis: A novel spheroid culture for tumorigenic cells revealed that the transcriptomic alterations associated with PRC2 deregulation found at embryonic stages have a strong impact on tumorigenesis and clinical outcome in neuroblastoma.

- 5272** Aneuploid Cell Survival Relies upon Sphingolipid Homeostasis
 Yun-Chi Tang, Hui Yuwen, Kaiying Wang, Peter M. Bruno, Kevin Bullock, Amy Deik, Stefano Santaguida, Marianna Trakala, Sarah J. Pfau, Na Zhong, Tao Huang, Lan Wang, Clary B. Clish, Michael T. Hemann, and Angelika Amon
Précis: These findings suggest that sphingolipid metabolism may be an Achilles' heel in aneuploid cells, with immediate implications for development of a small molecule-based approach to broadly prevent or treat cancers.

- 5287** JCAD Promotes Progression of Nonalcoholic Steatohepatitis to Liver Cancer by Inhibiting LATS2 Kinase Activity
 Juan Ye, Tian-Sheng Li, Gang Xu, Yi-Ming Zhao, Ning-Ping Zhang, Jia Fan, and Jian Wu
Précis: These findings identify the Hippo signaling pathway as a candidate for targeted therapeutic intervention in fatty liver-associated development of hepatocarcinoma, which is rising rapidly in Western countries along with increasing rates of obesity.

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- 5301** Nuclear FAK and Runx1 Cooperate to Regulate IGFBP3, Cell-Cycle Progression, and Tumor Growth
Marta Canel, Adam Byron, Andrew H. Sims, Jessy Cartier, Hitesh Patel, Margaret C. Frame, Valerie G. Brunton, Bryan Serrels, and Alan Serrels

Précis: These findings enhance understanding of the basic biology underlying ongoing clinical trials of FAK inhibitors for cancer therapy.

- 5313** HNF1B Loss Exacerbates the Development of Chromophobe Renal Cell Carcinomas
Mianen Sun, Pan Tong, Wen Kong, Baijun Dong, Yiran Huang, In Young Park, Lijun Zhou, Xian-De Liu, Zhiyong Ding, Xuesong Zhang, Shanshan Bai, Peter German, Reid Powell, Quan Wang, Xuefei Tong, Nizar M. Tannir, Surena F. Matin, W. Kimryn Rathmell, Gregory N. Fuller, Ian E. McCutcheon, Cheryl L. Walker, Jing Wang, and Eric Jonasch

Précis: These findings provide new insights into key epigenetic events, which drive an unusual type of kidney tumor, where additional loss of TP53 function promotes poor prognosis.

- 5327** MRE11 Promotes Tumorigenesis by Facilitating Resistance to Oncogene-Induced Replication Stress
Elizabeth Spehalski, Kayla M. Capper, Cheryl J. Smith, Mary J. Morgan, Maria Dinkelman, Jeffrey Buis, JoAnn M. Sekiguchi, and David O. Ferguson

Précis: New insights into how a DNA repair complex can promote tumorigenesis suggest new approaches to selectively improve cancer cell killing.

TUMOR AND STEM CELL BIOLOGY

- 5339** Chromatin-Associated Protein SIN3B Prevents Prostate Cancer Progression by Inducing Senescence
Anthony J. Bainor, Fang-Ming Deng, Yu Wang, Peng Lee, David J. Cantor, Susan K. Logan, and Gregory David

Précis: These results suggest a tumor suppressor function for SIN3B in prostate cancer, with potential implications for the use of SIN3B and its target genes as candidate diagnostic markers to distinguish indolent from aggressive disease.

- 5349** Oncogenic KRAS and p53 Loss Drive Gastric Tumorigenesis in Mice That Can Be Attenuated by E-Cadherin Expression
Jacob E. Till, Changhwan Yoon, Bang-Jin Kim, Kerry Roby, Prince Addai, Evan Jonokuchi, Laura H. Tang, Sam S. Yoon, and Sandra Ryeom

Précis: These findings describe the first autochthonous mouse model of gastric adenocarcinoma that can recapitulate the metastatic processes that occur widely in patients.

- 5360** S100A4 Is a Biomarker and Regulator of Glioma Stem Cells That Is Critical for Mesenchymal Transition in Glioblastoma
Kin-Hoe Chow, Hee Jung Park, Joshy George, Keiko Yamamoto, Andrew D. Gallup, Joel H. Graber, Yuanxin Chen, Wen Jiang, Dennis A. Steindler, Eric G. Neilson, Betty Y.S. Kim, and Kyuson Yun

Précis: These findings demonstrate the role of S100A4 in glioblastoma as a regulator of the stemness and mesenchymal transition.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 5374**  Trastuzumab Increases HER2 Uptake and Cross-Presentation by Dendritic Cells
Victor A. Gall, Anne V. Philips, Na Qiao, Karen Clise-Dwyer, Alexander A. Perakis, Mao Zhang, Guy T. Clifton, Pariya Sukhumalchandra, Qing Ma, Sangeetha M. Reddy, Dihua Yu, Jeffrey J. Mollidrem, George E. Peoples, Gheath Alatrash, and Elizabeth A. Mittenfior

Précis: These findings describe a potential mechanism by which patients treated with trastuzumab, followed by vaccination with a CD8 T-cell-eliciting vaccine, may experience a robust antitumor immune response.

- 5384** Combination Therapy with Bispecific Antibodies and PD-1 Blockade Enhances the Antitumor Potency of T Cells
Chien-Hsing Chang, Yang Wang, Rongxiu Li, Diane L. Rossi, Donglin Liu, Edmund A. Rossi, Thomas M. Cardillo, and David M. Goldenberg

Précis: Bispecific antibodies that can bind a T cell along with a tumor cell antigen and redirect the T cell to the tumor can leverage the therapeutic benefits of PD1 blockade, an important present goal in immuno-oncological treatment of solid tumors.

- 5395** Mitotic Vulnerability in Triple-Negative Breast Cancer Associated with LIN9 Is Targetable with BET Inhibitors
Jennifer M. Sahni, Sylvia S. Gayle, Bryan M. Webb, Kristen L. Weber-Bonk, Darcie D. Seachrist, Salendra Singh, Steven T. Sizemore, Nicole A. Restrepo, Gurkan Bebek, Peter C. Scacheri, Vinay Varadan, Matthew K. Summers, and Ruth A. Keri

Précis: These findings demonstrate that BET inhibitors can target genes such as LIN9, whose chromatin lacks super-enhancer-associated epigenetic marks.

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INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5409** Integrating Models to Quantify Environment-Mediated Drug Resistance
Noemi Picco, Erik Sahai, Philip K. Maini, and Alexander R.A. Anderson
Précis: Quantification of the environmental contribution to drug resistance reveals that tumor heterogeneity altering treatment dynamics can be exploited for therapeutic gain.

CLINICAL STUDIES

- 5419** Genomic Alterations in Circulating Tumor DNA from Diverse Cancer Patients Identified by Next-Generation Sequencing
Maria Schwaederle, Ranajoy Chattopadhyay, Shumei Kato, Paul T. Fanta, Kimberly C. Banks, In Sil Choi, David E. Piccioni, Sadakatsu Ikeda, AmirAli Talasaz, Richard B. Lanman, Lyudmila Bazhenova, and Razelle Kurzrock
Précis: This milestone study showcases the power of genomic profiling of tumors by next-generation sequencing of circulating tumor DNA, as illustrated in the first large and diverse cohort of cancer patients, including for difficult-to-biopsy tumors.

PREVENTION AND EPIDEMIOLOGY

- 5428** Identification of Novel Breast Cancer Risk Loci
Claire Hian Tzer Chan, Prabhakaran Munusamy, Sau Yeen Loke, Geok Ling Koh, Edward Sern Yuen Wong, Hai Yang Law, Chui Sheun Yoon, Min-Han Tan, Yoon Sim Yap, Peter Ang, and Ann Siew Gek Lee
Précis: Three new risk loci are discovered and validated via a unique approach that could be utilized to uncover risk loci for other cancers.

CORRECTION

- 5438** Evolution of Cancer Stem-like Cells in Endocrine-Resistant Metastatic Breast Cancers Is Mediated by Stromal Microvesicles

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ABOUT THE COVER

JCAD and LATS2 were stained immunohistochemically with specific primary antibodies and secondary antibodies labeled with Alexa-488 (green for JCAD) or Alexa-594 (red for LATS2). The nucleus was visualized by DAPI staining in blue. JCAD is overlaid with LATS2 in the proximity of the nucleus and appears in yellow. For details, see article by Ye and colleagues on page 5287.

