**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

**PRIORITY REPORT**

5228  Targeting a Single Alternative Polyadenylation Site Cooperatively 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.

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 Vegnasubramanian, 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 Transcriptional Alterations at the Embryonic Stage Govern Tumorigenesis and Clinical Outcome in MYCN-Driven Neuroblastoma
Shoma Tsubota, Satoshi Kishida, Tepppei Shimamura, Miki Ohiza, Satoshi Yamashita, Dongliang Cao, Shinichi Kiyonari, Toshikazu Ushijima, and Kenji Kadomatsu
Précis: A novel spheroid culture for tumorigenic cells revealed that the transcriptional 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.
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, 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 Dinkelmann, 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. Steinleider, 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. Molldrem, George E. Peoples, Gheath Alatrash, and Elizabeth A. Mittendorf
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, Rongxin 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
Précis: These findings demonstrate that BET inhibitors can target genes such as LIN9, whose chromatin lacks super-enhancer-associated epigenetic marks.
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
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.