BREAKING ADVANCES

6049  Highlights from Recent Cancer Literature

REVIEWS

6051  Understanding Mitochondrial Polymorphisms in Cancer
Karen M. Bussard and Linda D. Siracusa

6060  Uncoupling the Oncogenic Engine
Axel Schambach, Juliane W. Schott, and Michael A. Morgan

PERSPECTIVE

6065  Connecting Cancer to Its Causes Requires Incorporation of Effects on Tissue Microenvironments
James DeGregori

MOLECULAR AND CELLULAR PATHOBIOLOGY

6069  TET-Mediated Sequestration of miR-26 Drives EZH2 Expression and Gastric Carcinogenesis
Min Deng, Ruixin Zhang, Zhengxi He, Qinwei Qiu, Xihong Lu, Jiang Yin, Hao Liu, Xiaoting Jia, and Zhimin He
Précis: A noncoding function of the TET gene family of DNA demethylases, which facilitates gastric carcinogenesis, may offer a prognostic biomarker and therapeutic target in this disease setting.

6083  Mobilizing Transit-Amplifying Cell-Derived Ectopic Progenitors Prevents Hair Loss from Chemotherapy or Radiation Therapy
Précis: Hair follicles organize a regenerative adaptation to damage caused by chemotherapy or ionizing radiation.

6109  Biallelic Dicer1 Loss Mediated by aP2-Cre Drives Angiosarcoma
Jason A. Hanna, Catherine J. Drummond, Matthew R. Garcia, Jonathan C. Go, David Finkelstein, Jerold E. Rehg, and Mark E. Hatley
Précis: These findings establish an animal model of angiosarcoma that phenocopies the human disease.

6119  Genomic Landscape of Atypical Adenomatous Hyperplasia Reveals Divergent Modes to Lung Adenocarcinoma
Smruthy Sivakumar, F. Anthony San Lucas, Tina L. McDowell, Wenhua Lang, Li Xu, Junya Fujimoto, Jianjun Zhang, P. Andrew Futreal, Junya Fukuda, Yasushi Yatabe, Steven M. Dubinett, Avrum E. Spira, Jerry Fowler, Ernest T. Hawk, Ignacio I. Wistuba, Paul Scheet, and Humam Kadara
Précis: High-throughput sequencing of patient samples underscores driver mutations, genome-wide expression changes, and aberrant immune signaling that offer ideal markers for personalized prevention and early treatment of lung adenocarcinoma.

6131  Proliferating EpCAM-Positive Ductal Cells in the Inflamed Liver Give Rise to Hepatocellular Carcinoma
Tomonori Matsumoto, Atsushi Takai, Yuji Eso, Kazuo Kinoshiha, Toshikazu Mabane, Hiroshi Seno, Tsutomu Chiba, and Hiroyuki Marusawa
Précis: This potentially seminal study provides direct evidence that hepatocellular carcinoma originates from a specific class of putative liver stem-like cells expressing the cell adhesion molecule EpCAM, which proliferates in the inflamed liver.
6144 The Blebbishield Emergency Program Overrides Chromosomal Instability and Phagocytosis Checkpoints in Cancer Stem Cells
Goodwin G. Jinesh and Ashish M. Kamat
Précis: These findings demonstrate how cancer stem cells utilize apoptosis to evade genomic instability and immune phagocytosis checkpoints to ultimately drive cellular transformation.

6157 Retention of Interstitial Genes between TMPRSS2 and ERG Is Associated with Low-Risk Prostate Cancer
Stephen J. Murphy, Farhad Kosari, R. Jeffrey Karnes, Aqsa Nasir, Sarah H. Johnson, Athanasios G. Gaitatzes, James B. Smadbeck, Laureano J. Rangel, George Vasmatis, and John C. Cheville
Précis: Newly characterized TMPRSS2-ERG fusions serve as molecular markers of risk in prostate cancer whose utilization could greatly improve patient management.

6168 miR-130a Deregulates PTEN and Stimulates Tumor Growth
Huijun Wei, Ri Cui, Julian Bahr, Nicola Zanesi, Zhenghua Luo, Wei Meng, Guang Liang, and Carlo M. Croce
Précis: Cell death signaling studies in a H-Ras–dependent model system reveal an oncogenic microRNA with potential utility as a theranostic marker in multiple cancers.

6179 Mechanosignal Transduction in Mesenchymal Stem Cells Induces Proaposin Secretion to Drive the Proliferation of Breast Cancer Cells
Seiichiro Ishihara, David R. Inman, Wan-Ju Li, Suzanne M. Ponik, and Patricia J. Keely
Précis: Noncancerous and multipotent cells found in the tumor microenvironment regulate tumor growth and inhibit metastasis via secretion of proaposin in response to matrix stiffness.

6190 Histone Acetyltransferase KAT6A Upregulates PI3K/AKT Signaling through TRIM24 Binding
Deguan Lv, Feng Jia, Yanli Hou, Youzhou Sang, Angel A. Alvarez, Weiwei Zhang, Wei-Qiang Gao, Bo Hu, Shi-Yuan Cheng, Jianwei Ge, Yanxin Li, and Haizhong Feng
Précis: These findings identify a specific chromatin acetylation event in the PI3K genetic locus as a critical event in the development of deadly gliomas.

6202 Mitochondrial Genomic Backgrounds Affect Nuclear DNA Methylation and Gene Expression
Carolyn J. Vivian, Amanda E. Brinker, Stefan Graw, Devin C. Koestler, Christophe Legendre, Gerald C. Gooden, Bodour Salhia, and Danny R. Welch
Précis: These striking results suggest that mitochondrial DNA polymorphisms can selectively alter DNA methylation and gene expression patterns in the nuclear genome.

6215 FGF19 Protects Hepatocellular Carcinoma Cells against Endoplasmic Reticulum Stress via Activation of FGFR4–GSK3β–Nrf2 Signaling
Yong Teng, Huakan Zhao, Lixia Gao, Wenfa Zhang, Austin Y. Shull, and Chloie Shay
Précis: These findings show how a member of the fibroblast growth factor provides a cytoprotective role against endoplasmic reticulum stress in liver cancer, with potential implications for therapeutic management of this disease.

6226 Skp2-Mediated Stabilization of MTH1 Promotes Survival of Melanoma Cells upon Oxidative Stress
Jia Yu Wang, Guang Zhi Liu, James S. Wilmott, Ting La, Yu Chen Feng, Hamed Yari, Xu GuanYan, Rick F. Thorne, Richard A. Scolyer, Xu Dong Zhang, and Lei Lin
Précis: These findings identify a critical regulatory pathway for upregulation of a pathway that helps protect dNTP pools in cancer cells from oxidative damage, with potential implications for improving cancer therapeutic targeting.

6240 Copper Chelation Inhibits BRAFV600E-Driven Melanomagenesis and Counters Resistance to BRAFV600E and MEK1/2 Inhibitors
Donita C. Brady, Matthew S. Crowe, Danielle N. Greenberg, and Christopher M. Counter
Précis: These preclinical findings offer an immediately translatable clinical rationale to re-purpose approved copper chelators for the treatment of therapy-resistant melanomas.

6253 PI-273, a Substrate-Competitive, Specific Small-Molecule Inhibitor of PI4KII, Inhibits the Growth of Breast Cancer Cells
Jiangmei Li, Zhen Gao, Dan Zhao, Lunfeng Zhang, Xinhua Qiao, Yingying Zhao, Hong Ding, Panpan Zhang, Junyan Lu, Jia Liu, Hualiang Jiang, Cheng Luo, and Chang Chen
Précis: These findings validate the first PI4KIIa subtype-specific inhibitor for a target of long-standing potential in cancer therapy.
Table of Contents

6267 ASXL3 Is a Novel Pluripotency Factor in Human Respiratory Epithelial Cells and a Potential Therapeutic Target in Small Cell Lung Cancer

Précis: Studies of a novel model of human lung-derived induced pluripotent stem cells (iPSC) reveal the PRC2-binding protein ASXL3 as a novel candidate factor in development of small cell lung carcinoma.

6282 Novel Selective Agents for the Degradation of Androgen Receptor Variants to Treat Castration-Resistant Prostate Cancer

Précis: These findings characterize next-generation drug candidate molecules for the treatment of advanced castration-resistant prostate cancers.

6299 Bone-Induced Expression of Integrin β3 Enables Targeted Nanotherapy of Breast Cancer Metastases

Précis: These findings offer preclinical proof of concept that an integrin αvβ3-targeted drug-filled nanoparticle can safely and effectively target breast cancer bone metastases, addressing an acute therapeutic need.

6313 Next-Generation Sequencing in the Clinical Setting Clarifies Patient Characteristics and Potential Actionability
Cheyennedra C. Berg-Bourne, Sheri Z. Millis, David E. Piccioni, Paul T. Fanta, Michael E. Goldberg, Juliann Chmielecki, Barbara A. Parker, and Razelle Kurzrock

Précis: Genomic profiling of >1000 patients by next-generation sequencing reveals the enormous complexity and heterogeneity of human cancer, deepening and extending perspectives gained from clinical histopathological studies.

6321 PHGDH as a Key Enzyme for Serine Biosynthesis in HIF2α-Targeting Therapy for Renal Cell Carcinoma
Hiroyumi Yoshino, Nijiro Nohata, Kazutaka Miyamoto, Masaya Yonemori, Takashi Sakaguchi, Satoshi Sugita, Toshikiko Iesako, Satoshi Kofuji, Masayuki Nakagawa, Rajvir Dahiya, and Hideki Enokida

Précis: These findings identify the serine biosynthesis pathway as a source of candidate therapeutic targets to eradicate advanced or metastatic clear cell renal cancers resistant to HIF2α antagonists.

6330 Genome-Wide CRISPR Screen for Essential Cell Growth Mediators in Mutant KRAS
Colorectal Cancers
Edwin H. Yau, Indrasena Reddy Kummetha, Gianluigi Lichinchi, Rachel Tang, Yunlin Zhang, and Tariq M. Rana

Précis: Using an in vivo application of the CRISPR-Cas9 system, this study identifies new targetable enzymes critical for the growth of mutant KRAS-driven colorectal and pancreatic cancers.

6340 Combined CDK4/6 and PI3Kα Inhibition Is Synergistic and Immunogenic in Triple-Negative Breast Cancer

Précis: Addition of immune checkpoint blockade to combined inhibition of CDK4/6 and PI3Kα elicits a durable antitumor response in triple-negative breast cancers modeled preclinically in mice.

MICROENVIRONMENT AND IMMUNOLOGY

6353 PD-1 Status in CD8+ T Cells Associates with Survival and Anti-PD-1 Therapeutic Outcomes in Head and Neck Cancer

Précis: These findings provide new insights into checkpoint receptor immunotherapy and characterize PD-1high-expressing CD8+ T cells as dysfunctional and exhausted, as compared with PD-1low populations, which associate with increased antitumor activity and better therapeutic outcomes.
PD-1 Expression in Head and Neck Squamous Cell Carcinomas Derives Primarily from Functionally Anergic CD4⁺ TILs in the Presence of PD-L1⁺ TAMs

Précis: These results point to the importance of CD4⁺ T helper cells as pivotal regulators of PD-L1 levels in determining the response of a common type of head and neck cancers to PD1 immune checkpoint therapy.

CD155/TIGIT Signaling Regulates CD8⁺ T-cell Metabolism and Promotes Tumor Progression in Human Gastric Cancer
Weiling He, Hui Zhang, Fei Han, Xinlin Chen, Run Lin, Wei Wang, Haibo Qiu, Zhenhong Zhuang, Qi Liao, Weijing Zhang, Qinbo Cai, Yongmei Cui, Wenting Jiang, Han Wang, and Zunfu Ke

Précis: Gastric cancer cells negatively regulate CD8 T-cell metabolism and induce functional exhaustion of CD8 T cells via the CD155/TIGIT interaction in the tumor microenvironment.

Localized Synchrotron Irradiation of Mouse Skin Induces Persistent Systemic Genotoxic and Immune Responses
Jessica Ventura, Pavel N. Lobachevsky, Jason S. Palazzolo, Helen Forrester, Nicole M. Haynes, Alezia Vashkevich, Andrew W. Stevenson, Christopher J. Hall, Andreas Ntargaras, Vasilis Kotsaris, Gerasimos Ch. Pollakis, Gianna Potsi, Konstantinos Skordylis, Georgia Terzoudi, Ioannis S. Pateras, Vassilis G. Gorgoulis, Alexandros G. Georgakilas, Carl N. Sprung, and Olga A. Martin

Précis: Brief low-dose exposures or ablative doses of radiation induce persistent biological effects in off-target tissues.

Inflammatory Monocytes Promote Perineural Invasion via CCL2-Mediated Recruitment and Cathepsin B Expression

Précis: These findings show how subversion of a nerve repair program mediates pathogenesis of peripheral nerve invasion by tumors, an ominous sign of poor prognosis, and suggest new targeted strategies to prevent or reverse this process.

Survival Outcomes in Cancer Patients Predicted by a Partial EMT Gene Expression Scoring Metric
Jason T. George, Mohit Kumar Jolly, Shengnan Xu, Jason A. Somarelli, and Herbert Levine

Précis: This study highlights a valuable gene signature tool that may help illuminate malignant progression and clinical outcomes.

In Silico Modeling of Immunotherapy and Stroma-Targeting Therapies in Human Colorectal Cancer

Précis: This study provides sound guidance for designing effective clinical immunotherapy for colorectal cancer, in showing the importance of targeting the stroma along with activating the adaptive immune system.

Mitosis-Mediated Intravasation in a Tissue-Engineered Tumor–Microvessel Platform
Andrew D. Wong and Peter C. Searson

Précis: Direct observation of intravasation provides a framework for understanding the physical and biological factors involved in mediating this process.
Type II Diabetes and Incidence of Estrogen Receptor Negative Breast Cancer in African American Women

Julie R. Palmer, Nelsy Castro-Webb, Kimberly Bertrand, Traci N. Bethea, and Gerald V. Denis

Précis: Analysis of a large cohort study reveals that African American women with type 2 diabetes have a 40% increased incidence of ER– breast cancer independent of obesity as a risk factor.

Correction: Breast Tumor Kinase Phosphorylates p190RhoGAP to Regulate Rho and Ras and Promote Breast Carcinoma Growth, Migration, and Invasion

ABOUT THE COVER

Apoptotic cells are known to get engulfed by immune cells. However, apoptotic cancer stem cells that resurrect by reconstructing themselves from apoptotic bodies (called blebbishields; red fluorescence) evade phagocytosis by immune cells (green fluorescence) through blebbishield-immune cell fusion to generate hybrid cells (termed PBSHMS cells; cover image was imaged at 1 week after fusion). PBSHMS cells exhibit chromosomal instability and are capable of tumorigenesis, and metastasis in nude mice demonstrates that these hybrids are not the product of phagocytosis. For details, see article by Jinesh and Kamat on page 6144.