

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
Wen-Yen Huang, Shih-Fan Lai, Hsien-Yi Chiu, Michael Chang, Maksim V. Plikus, Chih-Chieh Chan, You-Tzung Chen, Po-Nien Tsao, Tsung-Lin Yang, Hsuan-Shu Lee, Peter Chi, and Sung-Jan Lin
Précis: Hair follicles organize a regenerative adaptation to damage caused by chemotherapy or ionizing radiation.

- 6097** *Cic* Loss Promotes Gliomagenesis via Aberrant Neural Stem Cell Proliferation and Differentiation
Rui Yang, Lee H. Chen, Landon J. Hansen, Austin B. Carpenter, Casey J. Moure, Heng Liu, Christopher J. Pirozzi, Bill H. Diplas, Matthew S. Waitkus, Paula K. Greer, Huishan Zhu, Roger E. McLendon, Darell D. Bigner, Yiping He, and Hai Yan

Précis: Genetic inactivation of a transcriptional repression factor sheds light on the pathogenesis of oligodendrogliomas, with potential implications for therapeutic targeting of this type of brain tumor.

- 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 Fukuoka, 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 Kinoshita, Toshiaki Manabe, 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.

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TUMOR AND STEM CELL BIOLOGY

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 Vasmatazis, 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 Mechano-Signal Transduction in Mesenchymal Stem Cells Induces Prosaposin 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 prosaposin 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-GSK3 β -Nrf2* Signaling

Yong Teng, Huakan Zhao, Lixia Gao, Wenfa Zhang, Austin Y. Shull, and Chloe 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 Guang Yan, Rick F. Thorne, Richard A. Scolyer, Xu Dong Zhang, and Lei Jin

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.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6240 Copper Chelation Inhibits *BRAF*^{V600E}-Driven Melanomagenesis and Counters Resistance to *BRAF*^{V600E} 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 α* , 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 *PI3KII α* subtype-specific inhibitor for a target of long-standing potential in cancer therapy.

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

Vivek Shukla, Mahadev Rao, Hongen Zhang, Jeanette Beers, Darawalee Wangsa, Danny Wangsa, Floryne O. Buishand, Yonghong Wang, Zhiya Yu, Holly S. Stevenson, Emily S. Reardon, Kaitlin C. McLoughlin, Andrew S. Kaufman, Eden C. Payabyab, Julie A. Hong, Mary Zhang, Sean Davis, Daniel Edelman, Guokai Chen, Markku M. Miettinen, Nicholas P. Restifo, Thomas Ried, Paul A. Meltzer, and David S. Schrupp

Précis: Studies of a new 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

Suriyan Ponnusamy, Christopher C. Coss, Thirumagal Thiyagarajan, Kate Watts, Dong-Jin Hwang, Yali He, Luke A. Selth, Iain J. McEwan, Charles B. Duke, Jayaprakash Pagadala, Geetika Singh, Robert W. Wake, Christopher Ledbetter, Wayne D. Tilley, Tudor Moldoveanu, James T. Dalton, Duane D. Miller, and Ramesh Narayanan

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

6299 Bone-Induced Expression of Integrin $\beta 3$ Enables Targeted Nanotherapy of Breast Cancer Metastases

Michael H. Ross, Alison K. Esser, Gregory C. Fox, Anne H. Schmieder, Xiaoxia Yang, Grace Hu, Dipanjan Pan, Xinming Su, Yalin Xu, Deborah V. Novack, Thomas Walsh, Graham A. Colditz, Gabriel H. Lukaszewicz, Elizabeth Cordell, Joshua Novack, James A. J. Fitzpatrick, David L. Waning, Khalid S. Mohammad, Theresa A. Guise, Gregory M. Lanza, and Katherine N. Weilbaecher

Précis: These findings offer preclinical proof of concept that an integrin $\alpha\beta 3$ -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. Bieg-Bourme, Sherri 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 HIF2 α -Targeting Therapy for Renal Cell Carcinoma



Hirofumi Yoshino, Nijiro Nohata, Kazutaka Miyamoto, Masaya Yonemori, Takashi Sakaguchi, Satoshi Sugita, Toshihiko Itesako, 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 HIF2 α 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 PI3K α Inhibition Is Synergistic and Immunogenic in Triple-Negative Breast Cancer

Zhi Ling Teo, Stephanie Versaci, Sathana Dushyanthen, Franco Caramia, Peter Savas, Chris P. Mintoff, Magnus Zethoven, Balaji Virassamy, Stephen J. Luen, Grant A. McArthur, Wayne A. Phillips, Phillip K. Darcy, and Sherene Loi

Précis: Addition of immune checkpoint blockade to combined inhibition of CDK4/6 and PI3K α 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

Benjamin A. Kansy, Fernando Concha-Benavente, Raghvendra M. Srivastava, Hyun-Bae Jie, Gulidanna Shayan, Yu Lei, Jessica Moskovitz, Jennifer Moy, Jing Li, Sven Brandau, Stephan Lang, Nicole C. Schmitt, Gordon J. Freeman, William E. Gooding, David A. Clump, and Robert L. Ferris

Précis: These findings provide new insights into checkpoint receptor immunotherapy and characterize PD-1^{high}-expressing CD8⁺ T cells as dysfunctional and exhausted, as compared with PD-1^{low} populations, which associate with increased antitumor activity and better therapeutic outcomes

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6365 PD-1 Expression in Head and Neck Squamous Cell Carcinomas Derives Primarily from Functionally Anergic CD4⁺ TILs in the Presence of PD-L1⁺ TAMs

Austin K. Mattox, Jina Lee, William H. Westra, Robert H. Pierce, Ronald Ghossein, William C. Faquin, Thomas J. Diefenbach, Luc G. Morris, Derrick T. Lin, Lori J. Wirth, Armida Lefranc-Torres, Eiichi Ishida, Patrick D. Chakravarty, Lauren Johnson, Yang C. Zeng, Huabiao Chen, Mark C. Poznansky, Neil M. Iyengar, and Sara I. Pai

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.

6375 CD155TIGIT 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.

6389 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, Alesia Ivashkevich, 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.

6400 Inflammatory Monocytes Promote Perineural Invasion via CCL2-Mediated Recruitment and Cathepsin B Expression

Richard L. Bakst, Huizhong Xiong, Chun-Hao Chen, Sylvie Deborde, Anna Lyubchik, Yi Zhou, Shizhi He, William McNamara, Sei-Young Lee, Oakley C. Olson, Ingrid M. Leiner, Andrea R. Marcadis, James W. Keith, Hikmat A. Al-Ahmadie, Nora Katabi, Ziv Gil, Efsevia Vakiani, Johanna A. Joyce, Eric Pamer, and Richard J. Wong

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.

INTEGRATED SYSTEMS AND TECHNOLOGIES

6415 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.

6429 Multiscale Modeling of Inflammation-Induced Tumorigenesis Reveals Competing Oncogenic and Oncoprotective Roles for Inflammation

Yucheng Guo, Qing Nie, Adam L. MacLean, Yanda Li, Jinzhi Lei, and Shao Li

Précis: These findings explore the evolutionary dynamics of tumorigenesis from pathway mutation to abnormal population dynamics.

6442 In Silico Modeling of Immunotherapy and Stroma-Targeting Therapies in Human Colorectal Cancer



Jakob Nikolas Kather, Jan Poleszczuk, Meggy Suarez-Carmona, Johannes Krisam, Pomnimol Charoentong, Nektarios A. Valous, Cleo-Aron Weis, Luca Tavernar, Florian Leiss, Esther Herpel, Fee Klupp, Alexis Ulrich, Martin Schneider, Alexander Marx, Dirk Jäger, and Niels Halama

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.

6453 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.

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PREVENTION AND EPIDEMIOLOGY

6462 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

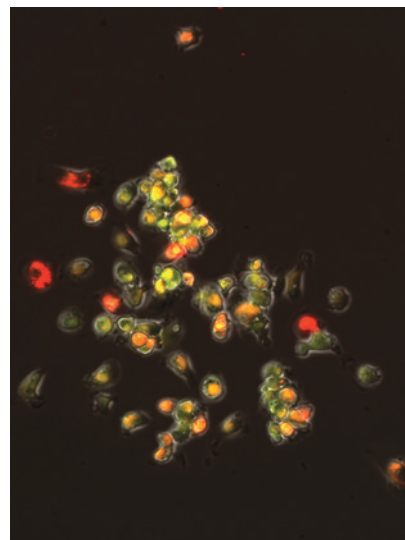
6470 Correction: Breast Tumor Kinase Phosphorylates p190RhoGAP to Regulate Rho and Ras and Promote Breast Carcinoma Growth, Migration, and Invasion

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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.



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