

BREAKING INSIGHTS

- 2087** Highlights from Recent Cancer Literature

OBITUARY

- 2089** Arthur B. Pardee: In Memoriam (1921–2019)
Judith Campisi, Khandan Keyomarsi, and Heide L. Ford

REVIEW

- 2091** BRCA1—No Matter How You Splice It
Dan Li, Lisa M. Harlan-Williams, Easwari Kumaraswamy,
and Roy A. Jensen

CANCER RESEARCH HIGHLIGHTS

- 2099** Nischarin Regulates Secretion of Exosomes and Cancer Progression
Kathleen M. McAndrews and Raghu Kalluri
See related article, p. 2152
- 2102** Stromal Support of Metabolic Function through Mitochondrial Transfer in Multiple Myeloma
Lawrence H. Boise and Mala Shanmugam
See related article, p. 2285
- 2104** Role of Apelin in Glioblastoma Vascularization and Invasion after anti-VEGF Therapy: What Is the Impact on the Immune System?
Zohreh Amoozgar, Rakesh K. Jain, and Dan G. Duda
See related article, p. 2298

CONTROVERSY AND CONSENSUS

- 2107** The Physics of Cancer
Forest M. White, Robert A. Gatenby, and
Claudia Fischbach

GENOME AND EPIGENOME

- 2111** Intratumoral Genetic and Functional Heterogeneity in Pediatric Glioblastoma
Mary Hoffman, Aaron H. Gillmor, Daniel J. Kunz, Michael J. Johnston, Ana Nikolic, Kiran Narta, Mehdi Zarrei, Jennifer King, Katrina Ellestad, Ngoc Ha Dang, Florence M.G. Cavalli, Michelle M. Kushida, Fiona J. Coutinho, Yuankun Zhu, Betty Luu, Yussanne Ma, Andrew J. Mungall, Richard Moore, Marco A. Marra, Michael D. Taylor, Trevor J. Pugh, Peter B. Dirks, Douglas Strother, Lucie Lafay-Cousin, Adam C. Resnick, Stephen Scherer, Donna L. Senger, Benjamin D. Simons, Jennifer A. Chan, A. Sorana Morrissy, and Marco Gallo

Significance: This work challenges several assumptions regarding the genetic organization of pediatric GBM and highlights mutagenic programs that start during early prenatal development.

- 2124** Oncogenic Properties of the Antisense lncRNA COMET in BRAF- and RET-Driven Papillary Thyroid Carcinomas
Roberta Esposito, Daniela Esposito, Pierlorenzo Pallante, Alfredo Fusco, Alfredo Ciccodicola, and Valerio Costa
Significance: These results highlight the oncogenic role of lncRNA COMET in thyroid and indicate it as a potential new target to overcome vemurafenib resistance in BRAF-mutated and MET-addicted carcinomas.

METABOLISM AND CHEMICAL BIOLOGY

- 2136** Enhanced Fatty Acid Scavenging and Glycerophospholipid Metabolism Accompany Melanocyte Neoplasia Progression in Zebrafish
Fiona Henderson, Hannah R. Johnston, Andrew P. Badrock, Emrys A. Jones, Duncan Forster, Raghavendar T. Nagaraju, Christos Evangelou, Jivko Kamarashev, Michael Green, Michael Fairclough, Irene Barinaga-Rementeria Ramirez, Shuning He, B. Ewa Snaar-Jagalska, Katherine Hollywood, Warwick B. Dunn, Herman P. Spaink, Michael P. Smith, Paul Lorigan, Emmanuelle Claude, Kaye J. Williams, Adam W. McMahon, and Adam Hurlstone
Significance: These findings demonstrate the translational potential of monitoring fatty acid uptake and identify lipoprotein lipase as a potential therapeutic target in melanoma.

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MOLECULAR CELL BIOLOGY

2152 Exosomes from Nischarin-Expressing Cells Reduce Breast Cancer Cell Motility and Tumor Growth

Mazvita Maziveyi, Shengli Dong, Somesh Baranwal, Ali Mehrnezhad, Rajamani Rathinam, Thomas M. Huckaba, Donald E. Mercante, Kidong Park, and Suresh K. Alahari

Significance: Regulation of Nischarin-mediated exosome secretion by Rab14 seems to play an important role in controlling tumor growth and migration.

See related commentary, p. 2099

2167 Negative Regulation of p53-Induced Senescence by N-WASP Is Crucial for DMBA/TPA-Induced Skin Tumor Formation

Hui Li, Simon Petersen, Alberto Garcia Mariscal, and Cord Brakebusch

Significance: These findings demonstrate that N-WASP regulates p53-dependent senescence in keratinocytes in vitro and in vivo.

2182 AQP4 Aggregation State Is a Determinant for Glioma Cell Fate

Laura Simone, Francesco Pisani, Maria G. Mola, Manuela De Bellis, Giuseppe Merla, Lucia Micalé, Antonio Frigeri, Angelo L. Vescovi, Maria Svelto, and Grazia P. Nicchia

Significance: This study demonstrates how AQP4 aggregation influences plasma membrane dynamics to alter cell proliferation, invasiveness, migration, and apoptotic potential in glioma cells.

2195 Combined Menin and EGFR Inhibitors Synergize to Suppress Colorectal Cancer via EGFR-Independent and Calcium-Mediated Repression of SKP2 Transcription

Bryson W. Katona, Rebecca A. Glynn, Kayla E. Paulosky, Zijie Feng, Caroline I. Davis, Jian Ma, Corbett T. Berry, Katherine M. Szigety, Smita Matkar, Yuanyuan Liu, Haoren Wang, Yuan Wu, Xin He, Bruce D. Freedman, Donita C. Brady, and Xianxin Hua

Significance: Menin acts as a calcium-responsive regulator of SKP2 expression, and small molecule EGFR inhibitors, which induce calcium release, synergize with Menin inhibition to reduce SKP2 expression and suppress colorectal cancer.

2208 Myc and Loss of p53 Cooperate to Drive Formation of Choroid Plexus Carcinoma

Jun Wang, Diana M. Merino, Nicholas Light, Brian L. Murphy, Yong-Dong Wang, Xiaohui Guo, Andrew P. Hodges, Lianne Q. Chau, Kun-Wei Liu, Girish Dhall, Shahab Asgharzadeh, Erin N. Kiehna, Ryan J. Shirey, Kim D. Janda, Michael D. Taylor, David Malkin, David W. Ellison, Scott R. VandenBerg, Charles G. Eberhart, Rosalie C. Sears, Martine F. Roussel, Richard J. Gilbertson, and Robert J. Wechsler-Reya

Significance: This study describes new mouse models of choroid plexus carcinoma and uses them to investigate the biology and therapeutic responsiveness of this highly malignant pediatric brain tumor.

2220 CD317 Activates EGFR by Regulating Its Association with Lipid Rafts

Guizhong Zhang, Xin Li, Qian Chen, Junxin Li, Qingguo Ruan, Youhai H. Chen, Xiaolu Yang, and Xiaochun Wan

Significance: Activation of EGFR by CD317 in hepatocellular carcinoma cells suggests CD317 as an alternative target for treating EGFR-dependent tumors.

2232 Epigenetic Regulation of the PTEN-AKT-RAC1 Axis by G9a Is Critical for Tumor Growth in Alveolar Rhabdomyosarcoma

Akshay V. Bhat, Monica Palanichamy Kala, Vinay Kumar Rao, Luca Pignata, Huey Jin Lim, Sudha Suriyamurthy, Kenneth T. Chang, Victor K. Lee, Ernesto Guccione, and Reshma Taneja

Significance: These findings demonstrate that RAC1 is an effector of G9a oncogenic functions and highlight the potential of G9a inhibitors in the treatment of ARMS.

2244 Resistance to MAPK Inhibitors in Melanoma Involves Activation of the IGF1R-MEK5-Erk5 Pathway

Lucía Benito-Jardón, Marta Díaz-Martínez, Nohemi Arellano-Sánchez, Paloma Vaquero-Morales, Azucena Esparís-Ogando, and Joaquín Teixidó

Significance: Activation of the IGF1R-MEK5-Erk5 signaling pathway opposes pharmacologic inhibition of Erk1/2 in melanoma, leading to the reactivation of cell proliferation and acquired resistance.

2257 EBF1-Mediated Upregulation of Ribosome Assembly Factor PNO1 Contributes to Cancer Progression by Negatively Regulating the p53 Signaling Pathway

Aling Shen, Youqin Chen, Liya Liu, Yue Huang, Hongwei Chen, Fei Qi, Jiumao Lin, Zhiqing Shen, Xiangyan Wu, Meizhu Wu, Qiongyu Li, Liman Qiu, Na Yu, Thomas J. Sferri, and Jun Peng

Significance: This study identifies the ribosome assembly factor PNO1 as a potential oncogene involved in tumor growth and progression of colorectal cancer.

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TUMOR BIOLOGY AND IMMUNOLOGY

2271 Collagen Remodeling in the Hypoxic Tumor-Mesothelial Niche Promotes Ovarian Cancer Metastasis



Suchitra Natarajan, Kaitlyn M. Foreman, Michaela I. Soriano, Ninna S. Rossen, Hussein Shehade, Daniel R. Fregoso, Joshua T. Eggold, Venkatesh Krishnan, Oliver Dorigo, Adam J. Krieg, Sarah C. Heilshorn, Subarna Sinha, Katherine C. Fuh, and Erinn B. Rankin

Significance: This study identifies HIF/LOX signaling as a potential therapeutic target to inhibit collagen remodeling and tumor progression in HGSOC.

2285 CD38-Driven Mitochondrial Trafficking Promotes Bioenergetic Plasticity in Multiple Myeloma

Christopher R. Marlein, Rachel E. Piddock, Jayna J. Mistry, Lyubov Zaitseva, Charlotte Hellmich, Rebecca H. Horton, Zhigang Zhou, Martin J. Auger, Kristian M. Bowles, and Stuart A. Rushworth

Significance: Multiple myeloma relies on both oxidative phosphorylation and glycolysis following acquisition of mitochondria from its bone marrow microenvironment.

See related commentary, p. 2102

2298 Targeting APLN/APLNR Improves Antiangiogenic Efficiency and Blunts Proinvasive Side Effects of VEGFA/VEGFR2 Blockade in Glioblastoma

Giorgia Mastrella, Mengzhuo Hou, Min Li, Veit M. Stoecklein, Nina Zdouc, Marie N.M. Volmar, Hrvoje Miletic, Sören Reinhard, Christel C. Herold-Mende, Susanne Kleber, Katharina Eisenhut, Gaetano Gargiulo, Michael Synowitz, Angelo L. Vescovi, Patrick N. Harter, Josef M. Penninger, Ernst Wagner, Michel Mittelbronn, Rolf Bjerkvig, Dolores Hambardzumyan, Ulrich Schüller, Jörg-Christian Tonn, Josefine Radke, Rainer Glass, and Roland E. Kälin

Significance: Pharmacological targeting of the APLNR acts synergistically with established anti-angiogenic treatments in glioblastoma and blunts therapy resistance to current strategies for antiangiogenesis.

See related commentary, p. 2104

2314 Inhibition of miR-328-3p Impairs Cancer Stem Cell Function and Prevents Metastasis in Ovarian Cancer

Amit K. Srivastava, Ananya Banerjee, Tiantian Cui, Chunhua Han, Shurui Cai, Lu Liu, Dayong Wu, Ri Cui, Zaibo Li, Xiaoli Zhang, Guozhen Xie, Karuppayiah Selvendiran, Srinivas Patnaik, Adam R. Karpf, Jinsong Liu, David E. Cohn, and Qi-En Wang

Significance: These findings present inhibition of miR-328 as a novel strategy for efficient elimination of CSC to prevent tumor metastasis and recurrence in patients with epithelial ovarian cancer.

TRANSLATIONAL SCIENCE

2327 Selective EGLN Inhibition Enables Ablative Radiotherapy and Improves Survival in Unresectable Pancreatic Cancer



Tara N. Fujimoto, Lauren E. Colbert, Yanqing Huang, Jessica M. Molkentine, Amit Deorukhkar, Laura Baseler, Marimar de la Cruz Bonilla, Meifang Yu, Daniel Lin, Sonal Gupta, Peter K. Cabeceiras, Charles V. Kingsley, Ramesh C. Tailor, Gabriel O. Sawakuchi, Eugene J. Koay, Helen Piwnica-Worms, Anirban Maitra, and Cullen M. Taniguchi

Significance: Selective protection of the intestinal tract by EGLN inhibition enables potentially definitive doses of radiation therapy. This might allow radiation to be a surgical surrogate for unresectable pancreatic cancer.

2339 Bcl-2 Is a Therapeutic Target for Hypodiploid B-Lineage Acute Lymphoblastic Leukemia

Ernesto Diaz-Flores, Evan Q. Comeaux, Kailyn L. Kim, Ella Melnik, Kyle Beckman, Kara L. Davis, Kevin Wu, Jon Akutagawa, Olga Bridges, Roberta Marino, Margo Wohlfeil, Benjamin S. Braun, Charles G. Mullighan, and Mignon L. Loh

Significance: These results demonstrate the efficacy of ABT-199 in vivo and provide encouraging preclinical data of Bcl-2 as a potential target for the treatment of hypodiploid B-ALL.

2352 A Functional Landscape of Resistance to MEK1/2 and CDK4/6 Inhibition in NRAS-Mutant Melanoma

Tikvah K. Hayes, Flora Luo, Ofir Cohen, Amy B. Goodale, Yenarae Lee, Sasha Pantel, Mukta Bagul, Federica Piccioni, David E. Root, Levi A. Garraway, Matthew Meyerson, and Cory M. Johannessen

Significance: These findings reveal that NRAS-mutant melanomas can acquire resistance to genetic ablation of NRAS or combination MEK1/2 and CDK4/6 inhibition by upregulating activity of the RTK-RAS-RAF and RTK-PI3K-AKT signaling cascade.

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- 2367** **Preclinical Efficacy of Covalent-Allosteric AKT Inhibitor Borussertib in Combination with Trametinib in KRAS-Mutant Pancreatic and Colorectal Cancer**
 Jörn Weisner, Ina Landel, Christoph Reintjes, Niklas Uhlenbrock, Marija Trajkovic-Arsic, Niklas Dienstbier, Julia Hardick, Svetlana Ladigan, Marius Lindemann, Steven Smith, Lena Quambusch, Rebekka Scheinplug, Laura Depta, Rajesh Gontla, Anke Unger, Heiko Müller, Matthias Baumann, Carsten Schultz-Fademrecht, Georgia Günther, Abdelouahid Maghnoij, Matthias P. Müller, Michael Pohl, Christian Teschendorf, Heiner Wolters, Richard Viebahn, Andrea Tannapfel, Waldemar Uhl, Jan G. Hengstler, Stephan A. Hahn, Jens T. Siveke, and Daniel Rauh
Significance: Borussertib, a first-in-class covalent-allosteric AKT inhibitor, displays antitumor activity in combination with the MEK inhibitor trametinib in patient-derived xenograft models and provides an excellent starting point for further pharmacokinetic/dynamic optimization.
- 2379** **Genome-Wide RNAi Screen Identifies PMPCB as a Therapeutic Vulnerability in EpCAM⁺ Hepatocellular Carcinoma**
 Atsushi Takai, Hien Dang, Naoki Oishi, Subreen Khatib, Sean P. Martin, Dana A. Dominguez, Ji Luo, Rachel Bagni, Xiaolin Wu, Katie Powell, Qing-Hai Ye, Hu-Liang Jia, Lun-Xiu Qin, Jinqiu Chen, Gary A. Mitchell, Xiaoling Luo, Snorri S. Thorgeirsson, and Xin Wei Wang
Significance: This study identifies PMPCB as critical to mitochondrial homeostasis and as a synthetic lethal candidate that selectively kills highly resistant EpCAM⁺ HCC tumors by inactivating the Wnt/ β -catenin signaling pathway.
- 2392** **Spindle Assembly Checkpoint Inhibition Can Resensitize p53-Null Stem Cells to Cancer Chemotherapy**
 Changlong Liu, Carolyn E. Banister, and Phillip J. Buckhaults
Significance: These findings show that inhibition of spindle assembly checkpoints and chromosomal organizing centers may provide a new way to treat p53-deficient cancer cells with standard chemotherapy drugs.
- 2404** **MDM2 and MDM4 Are Therapeutic Vulnerabilities in Malignant Rhabdoid Tumors**
 Thomas P. Howard, Taylor E. Arnoff, Melinda R. Song, Andrew O. Giacomelli, Xiaofeng Wang, Andrew L. Hong, Neekesh V. Dharia, Su Wang, Francisca Vazquez, Minh-Tam Pham, Ann M. Morgan, Franziska Wachter, Gregory H. Bird, Guillaume Kugener, Elaine M. Oberlick, Matthew G. Rees, Hong L. Tiv, Justin H. Hwang, Katherine H. Walsh, April Cook, John M. Krill-Burger, Aviad Tsherniak, Prafulla C. Gokhale, Peter J. Park, Kimberly Stegmaier, Loren D. Walensky, William C. Hahn, and Charles W.M. Roberts
Significance: This study identifies two targets, MDM2 and MDM4, as vulnerabilities in a deadly pediatric cancer and provides preclinical evidence that compounds inhibiting these proteins have therapeutic potential.
- 2415** **Inhibition of NF- κ B-Dependent Signaling Enhances Sensitivity and Overcomes Resistance to BET Inhibition in Uveal Melanoma**
 Grazia Ambrosini, Catherine Do, Benjamin Tycko, Ronald B. Realubit, Charles Karan, Elgilda Musi, Richard D. Carvajal, Vivian Chua, Andrew E. Aplin, and Gary K. Schwartz
Significance: These findings provide evidence that inhibitors of NF- κ B signaling synergize with BET inhibition in in vitro and in vivo models, suggesting a clinical utility of these targeted therapies in patients with uveal melanoma.
- 2426** **Picosecond Infrared Laser Desorption Mass Spectrometry Identifies Medulloblastoma Subgroups on Intrасurgical Timescales**
 Michael Woolman, Claudia M. Kuzan-Fischer, Isabelle Ferry, Taira Kiyota, Betty Luu, Megan Wu, David G. Munoz, Sunit Das, Ahmed Aman, Michael D. Taylor, James T. Rutka, Howard J. Ginsberg, and Arash Zarrine-Afsar
Significance: This study demonstrates that laser-extracted lipids allow immediate grading of medulloblastoma tumors into prognostically important subgroups in 10 seconds, providing medulloblastoma pathology in an actionable manner during surgery.
- 2435** **Susceptibility Perturbation MRI Maps Tumor Infiltration into Mesorectal Lymph Nodes**
 Inês Santiago, João Santinha, Andrada Ianus, Antonio Galzerano, Rita Theias, Joana Maia, Maria J. Barata, Nuno Loução, Bruno Costa-Silva, Antonio Beltran, Celso Matos, and Noam Shemesh
Significance: These findings introduce an MRI methodology tailored to detect magnetic susceptibility perturbations induced by subtle alterations in tissue microstructure.

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ABOUT THE COVER

Pediatric glioblastoma harbors an unexpected degree of intratumoral genetic heterogeneity. The coexistence of genetic subclones is here represented as branches of a tree with cells/leaves of different colors. Some of these subclones are more ancestral than others, as represented by their earlier branching points. Subclonal compartments are fueled by slow-cycling cancer stem cells, which are represented as the roots of the tree. Four cancer stem cells (pink, orange, blue, and yellow) each generated branches (or subclones) of the same color. However, one cancer stem cell (black) is mostly dormant and will produce its progeny at relapse. The cancer stem cell architecture of pediatric glioblastoma may explain why the genetic makeup of diagnostic and relapse samples are widely different. For details, see article by Hoffman and colleagues on page 2111.

