

## BREAKING ADVANCES

- 2773** Highlights from Recent Cancer Literature

## REVIEWS

- 2775** TAM Receptor Tyrosine Kinases in Cancer Drug Resistance

Mikaella Vouri and Sassan Hafizi

- 2779** Therapeutic IgE Antibodies: Harnessing a Macrophage-Mediated Immune Surveillance Mechanism against Cancer

Sophia N. Karagiannis, Debra H. Josephs, Heather J. Bax, and James F. Spicer

## PERSPECTIVE

- 2784** Widespread Use of Misidentified Cell Line KB (HeLa): Incorrect Attribution and Its Impact Revealed through Mining the Scientific Literature

Liwen Vaughan, Wolfgang Glänzel, Christopher Korch, and Amanda Capes-Davis

## CLINICAL STUDIES

- 2789** BRCA2 Hypomorphic Missense Variants Confer Moderate Risks of Breast Cancer

Hermela Shimelis, Romy L.S. Mesman, Catharina Von Nicolai, Asa Ehlen, Lucia Guidugli, Charlotte Martin, Fabienne M.G.R. Calléja, Huong Meeks, Emily Hallberg, Jamie Hinton, Jenna Lilyquist, Chunling Hu, Cora M. Aalfs, Kristiina Aittomäki, Irene Andrulis, Hoda Anton-Culver, Volker Arndt, Matthias W. Beckmann, Javier Benitez, Natalia V. Bogdanova, Stig E. Bojesen, Manjeet K. Bolla, Anne-Lise Borresen-Dale, Hiltrud Brauch, Paul Brennan, Hermann Brenner, Annegien Broeks, Barbara Brouwers, Thomas Brüning, Barbara Burwinkel, Jenny Chang-Claude, Georgia Chenevix-Trench, for kConFab/AOCS Investigators, Ching-Yu Cheng, Ji-Yeob Choi, J. Margriet Collée, Angela Cox, Simon S. Cross, Kamila Czene, Hatem Darabi, Joe Dennis, Thilo Dörk, Isabel dos-Santos-Silva, Alison M. Dunning, Peter A. Fasching, Jonine Figueroa, Henrik Flyger, Montserrat García-Closas, Graham G. Giles, Gord Glendon, Pascal Guénel, Christopher A. Haiman, Per Hall, Ute Hamann, Mikael Hartman,

Frans B. Hogervorst, Antoinette Hollestelle, John L. Hopper, Hidemi Ito, Anna Jakubowska, Daehae Kang, Veli-Matti Kosma, Vessela Kristensen, for NBCS Collaborators, Kah-Nyin Lai, Diether Lambrechts, Loic Le Marchand, Jingmei Li, Annika Lindblom, Aritaya Lophatananon, Jan Lubinski, Eva Machackova, Arto Mannermaa, Sara Margolin, Frederik Marme, Keitaro Matsuo, Hui Miao, Kyriaki Michailidou, Roger L. Milne, Kenneth Muir, Susan L. Neuhausen, Heli Nevanlinna, Janet E. Olson, Curtis Olsword, Jan J.C. Oosterwijk, Ana Osorio, Paolo Peterlongo, Julian Peto, Paul D.P. Pharoah, Katri Pylkäs, Paolo Radice, Muhammad Usman Rashid, Valerie Rhenius, Anja Rudolph, Suleeporn Sangrajrang, Elinor J. Sawyer, Marjanka K. Schmidt, Minouk J. Schoemaker, Caroline Seynaeve, Mitul Shah, Chen-Yang Shen, Martha Shrubsole, Xiao-Ou Shu, Susan Slager, Melissa C. Southey, Daniel O. Stram, Anthony Swerdlow, Soo H. Teo, Ian Tomlinson, Diana Torres, Thérèse Truong, Christi J. van Asperen, Lizet E. van der Kolk, Qin Wang, Robert Winqvist, Anna H. Wu, Jyh-Cherng Yu, Wei Zheng, Ying Zheng, Jennifer Leary, Logan Walker, Lenka Foretova, Florentia Fostira, Kathleen B.M. Claes, Liliana Varesco, Setareh Moghadasi, Douglas F. Easton, Amanda Spurdle, Peter Devilee, Harry Vrieling, Alvaro N.A. Monteiro, David E. Goldgar, Aura Carreira, Maaïke P.G. Vreeswijk, and Fergus J. Couch

*Précis:* These results show how BRCA2 missense variants that partially influence protein function can confer clinically relevant increased risks of breast cancer, with potential implications for risk management of women who harbor specific variants.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 2800** Mathematical Modeling Links Pregnancy-Associated Changes and Breast Cancer Risk
- Daniel Temko, Yu-Kang Cheng, Kornelia Polyak, and Franziska Michor

*Précis:* A simple mathematical model demonstrates that pregnancy-associated reduction in p27<sup>+</sup> cell frequency in human breast can explain the protective effect of pregnancy against ER<sup>+</sup> breast cancer.

- 2810** Tissue-Specific Signaling Networks Rewired by Major Somatic Mutations in Human Cancer Revealed by Proteome-Wide Discovery
- Junfei Zhao, Feixiong Cheng, and Zhongming Zhao


*Précis:* This systematic oncoproteomics analysis of kinase phosphorylation site mutations illustrates new capabilities to speed the development of precision oncology.

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**2822** Variability in Chromatin Architecture and Associated DNA Repair at Genomic Positions Containing Somatic Mutations

Byungho Lim, Jihyeob Mun, Yong Sung Kim, and Seon-Young Kim

*Précis:* These findings increase our knowledge surrounding mutational processes and the identification of cancer type-specific mutations within the tissue-specific epigenomic landscape.

**2869**  Multidrug Analyses in Patients Distinguish Efficacious Cancer Agents Based on Both Tumor Cell Killing and Immunomodulation

Jason P. Frazier, Jessica A. Bertout, William S. Kerwin, Alicia Moreno-Gonzalez, Joey R. Casalini, Marc O. Grenley, Emily Beirne, Kori L. Watts, Andy Keener, Derek J. Thirstrup, Ilona Tretyak, Sally H. Ditzler, Chelsea D. Tripp, Kevin Choy, Sarah Gillings, Megan N. Breit, Karri A. Meleo, Vanessa Rizzo, Chamisa L. Herrera, James A. Perry, Ravi K. Amaravadi, James M. Olson, and Richard A. Klinghoffer

*Précis:* Growing evidence suggests that targeted therapies, which are highly efficacious in patients, are likely assisted by occult recruitment of the host immune system, generally by unknown mechanisms, a problem illuminated by a nongenomic method introduced by this study (CIVO), which is used to probe responses in a diverse set of patients.

## MICROENVIRONMENT AND IMMUNOLOGY

**2834** SETD1B Activates iNOS Expression in Myeloid-Derived Suppressor Cells

Priscilla S. Redd, Mohammed L. Ibrahim, John D. Klement, Sarah K. Sharman, Amy V. Paschall, Dafeng Yang, Asha Nayak-Kapoor, and Kebin Liu

*Précis:* Tactics to blunt myeloid-derived suppressor cells in cancer are provided by this study, which shows that iNOS expression in such cells normally controlled by IRF8 under physiological conditions is bypassed by tumor cells through an alternate epigenetic pathway under pathological conditions.

**2844** GAD1 Upregulation Programs Aggressive Features of Cancer Cell Metabolism in the Brain Metastatic Microenvironment

Patricia M. Schnepf, Dennis D. Lee, Ian H. Guldner, Treasa K. O'Tighearnaigh, Erin N. Howe, Bhavana Palakurthi, Kaitlyn E. Eckert, Tiffany A. Toni, Brandon L. Ashfeld, and Siyuan Zhang

*Précis:* These results show how epigenetic changes in GAD1 expression alter local glutamate metabolism in the brain metastatic microenvironment, contributing to a metabolic adaptation that facilitates metastasis outgrowth in that setting, with potential implications for repurposing certain clinical drugs to eradicate brain metastases.

**2857** Targeting Autocrine CCL5-CCR5 Axis Reprograms Immunosuppressive Myeloid Cells and Reinforces Antitumor Immunity

Yi Ban, Junhua Mai, Xin Li, Marisa Mitchell-Flack, Tuo Zhang, Lixing Zhang, Lotfi Chouchane, Mauro Ferrari, Haifa Shen, and Xiaojing Ma

*Précis:* This study offers preclinical proof of concept for therapeutic targeting of the CCL5-CCR5 signaling pathway in myeloid cells as a promising target for cancer immunotherapy.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

**2881** NRF2 Induction Supporting Breast Cancer Cell Survival Is Enabled by Oxidative Stress-Induced DPP3-KEAP1 Interaction

Kevin Lu, Allen L. Alcivar, Jianglin Ma, Tzeh Keong Foo, Susan Zywea, Amar Mahdi, Yanying Huo, Thomas W. Kensler, Michael L. Gatzka, and Bing Xia

*Précis:* New insights into the control of the pivotal stress-regulated transcription factor NRF2 in cancer suggest new biomarkers for prognosis and treatment.

**2893** A PET Imaging Strategy to Visualize Activated T Cells in Acute Graft-versus-Host Disease Elicited by Allogeneic Hematopoietic Cell Transplant

John A. Ronald, Byung-Su Kim, Gayatri Gowrishankar, Mohammad Namavari, Israt S. Alam, Aloma D'Souza, Hidekazu Nishikii, Hui-Yen Chuang, Ohad Ilovich, Chih-Feng Lin, Robert Reeves, Adam Shuhendler, Aileen Hoehne, Carmel T. Chan, Jeanette Baker, Shahriar S. Yaghoubi, Henry F. VanBrocklin, Randall Hawkins, Benjamin L. Franc, Salma Jivan, James B. Slater, Emily F. Verdin, Kenneth T. Gao, Jonathan Benjamin, Robert Negrin, and Sanjiv Sam Gambhir

*Précis:* A radiotracer compound developed from the T-cell targeted cancer drug arabinofuranosylguanine (AraG) can be used for noninvasive PET imaging to detect activated donor T cells prior to overt clinical symptoms of graft-versus-host disease, a common dangerous side-effect of T-cell transplant immunotherapy strategies used to eradicate leukemia and other cancers.

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**2903** Metabolic Markers and Statistical Prediction of Serous Ovarian Cancer Aggressiveness by Ambient Ionization Mass Spectrometry Imaging

Marta Sans, Kshipra Gharpure, Robert Tibshirani, Jialing Zhang, Li Liang, Jinsong Liu, Jonathan H. Young, Robert L. Dood, Anil K. Sood, and Livia S. Eberlin

*Précis:* A rapid mass spectrometry method reveals distinct metabolic signatures in different ovarian tissue types, allowing diagnosis of specific types of ovarian cancer with an overall accuracy of <95% compared with traditional histopathological grading.

**2914** Cellular Prion Protein PrP<sup>C</sup> and Ecto-5'-Nucleotidase Are Markers of the Cellular Stress Response to Aneuploidy

Patrícia H. Domingues, Lalitha S.Y. Nanduri, Katarzyna Seget, Sharavan V. Venkateswaran, David Agorku, Cristina Viganó, Conrad von Schubert, Erich A. Nigg, Charles Swanton, Rocío Sotillo, Andreas Bosio, Zuzana Storchová, and Olaf Hardt

*Précis:* A comprehensive atlas of cell surface marker expression in multiple models of aneuploidy offers a tool to analyze cells with aneuploid chromosome settings and consequential cellular stress responses.

**2927** CIC-DUX4 Induces Small Round Cell Sarcomas Distinct from Ewing Sarcoma

Toyoki Yoshimoto, Miwa Tanaka, Mizuki Homme, Yukari Yamazaki, Yutaka Takazawa, Cristina R. Antonescu, and Takuro Nakamura

*Précis:* This study reports a useful mouse model for a highly aggressive type of soft tissue sarcoma, distinct from but similar to Ewing's sarcoma, offering a new tool to explore biomarkers and therapies for this recently defined disease.

## PREVENTION AND EPIDEMIOLOGY

**2938** Spermidine Prolongs Lifespan and Prevents Liver Fibrosis and Hepatocellular Carcinoma by Activating MAP1S-Mediated Autophagy

Fei Yue, Wenjiao Li, Jing Zou, Xianhan Jiang, Guibin Xu, Hai Huang, and Leyuan Liu

*Précis:* This exciting and potentially seminal study offers a preclinical proof of concept for orally administered spermidine as a safe and cost-effective strategy to prevent liver fibrosis and hepatocellular carcinoma, and also to extend lifespan.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**2952** Tumor-Localized Secretion of Soluble PD1 Enhances Oncolytic Virotherapy

Mee Y. Barteo, Katherine M. Dunlap, and Eric Barteo

*Précis:* Soluble PD1 secretion from oncolytic myxoma virus improves response rates to checkpoint blockade, which could significantly improve immunotherapy against a variety of malignancies.

**2964** A Squalene-Based Nanomedicine for Oral Treatment of Colon Cancer

Larissa Kotelevets, Eric Chastre, Joachim Caron, Julie Mougin, Gerard Bastian, Alain Pineau, Francine Walker, Therese Lehy, Didier Desmaële, and Patrick Couvreur

*Précis:* These results offer preclinical validation of a nanocarrier formulation of cisplatin for colon cancer treatment, which can safely improve efficacy, address drug resistance issues potentially, and improve compliance by enabling oral administration.

**2976** Preclinical Characterization of BET Family Bromodomain Inhibitor ABBV-075 Suggests Combination Therapeutic Strategies

Mai H. Bui, Xiaoyu Lin, Daniel H. Albert, Leiming Li, Lloyd T. Lam, Emily J. Faivre, Scott E. Warder, Xiaoli Huang, Denise Wilcox, Cherrie K. Donawho, George S. Sheppard, Le Wang, Steve Fidanze, John K. Pratt, Dachun Liu, Lisa Hasvold, Tamar Uziel, Xin Lu, Fred Kohlhapp, Guowei Fang, Steven W. Elmore, Saul H. Rosenberg, Keith F. McDaniel, Warren M. Kati, and Yu Shen

*Précis:* Distinct proapoptotic activities of a BET inhibitor in clinical trials to treat hematological cancers may have uses to treat solid tumors in combination with anti-BH3 therapies.

**2990** SFK/FAK Signaling Attenuates Osimertinib Efficacy in Both Drug-Sensitive and Drug-Resistant Models of EGFR-Mutant Lung Cancer



Eiki Ichihara, David Westover, Catherine B. Meador, Yingjun Yan, Joshua A. Bauer, Pengcheng Lu, Fei Ye, Amanda Kulick, Elisa de Stanchina, Robert McEwen, Marc Ladanyi, Darren Cross, William Pao, and Christine M. Lovly


*Précis:* These findings identify SFK/FAK family member upregulation as a mechanism of resistance to the recently approved EGFR inhibitor osimertinib, enabling physicians and researchers to design clinical trials to overcome resistance.

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- 3001** Modulation of Bax and mTOR for Cancer Therapeutics  
Rui Li, Chunyong Ding, Jun Zhang, Maohua Xie, Dongkyoo Park, Ye Ding, Guo Chen, Guojing Zhang, Melissa Gilbert-Ross, Wei Zhou, Adam I. Marcus, Shi-Yong Sun, Zhuo G. Chen, Gabriel L. Sica, Suresh S. Ramalingam, Andrew T. Magis, Haian Fu, Fadlo R. Khuri, Walter J. Curran, Taofeek K. Owonikoko, Dong M. Shin, Jia Zhou, and Xingming Deng  
*Précis:* These findings provide preclinical evidence for a pharmacologic combination of Bax activation and mTOR inhibition as a rational strategy to improve lung cancer treatment.

- 3013** Expression of Neuroendocrine Factor VGF in Lung Cancer Cells Confers Resistance to EGFR Kinase Inhibitors and Triggers Epithelial-to-Mesenchymal Transition  
Wen Hwang, Yu-Fan Chiu, Ming-Han Kuo, Kuan-Lin Lee, An-Chun Lee, Chia-Cherng Yu, Junn-Liang Chang, Wen-Chien Huang, Shih-Hsin Hsiao, Sey-En Lin, and Yu-Ting Chou  
*Précis:* When upregulated in lung cancer cells, a neuropeptide cleaved into multiple hormone-like factors promotes energy production and confers aggressive features, with possible implications for prognosis and therapy in this setting.


- 3027** E3 Ligase cIAP2 Mediates Downregulation of MRE11 and Radiosensitization in Response to HDAC Inhibition in Bladder Cancer  
Judith Nicholson, Sarah J. Jevons, Blaz Groselj, Sophie Ellermann, Rebecca Konietzny, Martin Kerr, Benedikt M. Kessler, and Anne E. Kiltie  
*Précis:* These findings identify MRE11 as a substrate of cIAP2-mediated ubiquitination and open new routes towards defining bladder cancer biomarkers and improving chemoradiation strategies.

- 3040** ATM Deficiency Is Associated with Sensitivity to PARP1 and ATR Inhibitors in Lung Adenocarcinoma  
 Anna Schmitt, Gero Knittel, Daniela Welcker, Tsun-Po Yang, Julie George, Michael Nowak, Uschi Leaser, Reinhard Büttner, Sven Perner, Martin Peifer, and Hans Christian Reinhardt  
*Précis:* The results of this preclinical study provide a functional rationale to profile KRAS-mutant human tumors for disabling mutations in the DNA damage response kinase ATM, which increase sensitivity to inhibitors of topoisomerase II, PARP1, and ATR.

- 3057** Integrative Cancer Pharmacogenomics to Infer Large-Scale Drug Taxonomy  
Nehme El-Hachem, Deena M.A. Gendoo, Laleh Soltan Ghorai, Zhaleh Safikhani, Petr Smirnov, Christina Chung, Kenan Deng, Ailsa Fang, Erin Birkwood, Chantal Ho, Ruth Isserlin, Gary D. Bader, Anna Goldenberg, and Benjamin Haibe-Kains  
*Précis:* The Drug Network Fusion approach predicts mechanism of action of poorly characterized compounds and highlights the potential to repurpose approved drugs with new anticancer indications.

## TUMOR AND STEM CELL BIOLOGY

- 3070** Combination Therapy Targeting BCL6 and Phospho-STAT3 Defeats Intratumor Heterogeneity in a Subset of Non-Small Cell Lung Cancers  
Dhruba Deb, Satwik Rajaram, Jill E. Larsen, Patrick D. Dospoy, Rossella Marullo, Long Shan Li, Kimberley Avila, Fengtian Xue, Leandro Cerchietti, John D. Minna, Steven J. Altschuler, and Lani F. Wu  
*Précis:* A comprehensive atlas of cell surface marker expression in multiple models of aneuploidy offers a tool to analyze cells with aneuploid chromosome settings and consequential cellular stress responses.
- 3082** NOTCH1 Signaling Regulates Self-Renewal and Platinum Chemoresistance of Cancer Stem-like Cells in Human Non-Small Cell Lung Cancer  
Yun Zhang, Wei Xu, Huiqin Guo, Yanmei Zhang, Yuexi He, Sau Har Lee, Xin Song, Xiaoyan Li, Yongqing Guo, Yunlong Zhao, Cheng Ding, Fei Ning, Yuanyuan Ma, Qun-Ying Lei, Xiaoyu Hu, Shengnan Li, and Wei Guo  
*Précis:* These results define the pathogenic character of a cancer stem-like subpopulation in lung cancers, the targeting of which may relieve platinum resistance in this disease.

- 3092** The p53/p21 Complex Regulates Cancer Cell Invasion and Apoptosis by Targeting Bcl-2 Family Proteins  
 Eun Mi Kim, Chan-Hun Jung, Jongdoo Kim, Sang-Gu Hwang, Jong Kuk Park, and Hong-Duck Um  
*Précis:* These findings provide a new foundation for understanding aberrant p53 signaling processes that lead to tumor progression and therapy resistance.

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**3101** Disrupting Androgen Receptor Signaling Induces Snail-Mediated Epithelial–Mesenchymal Plasticity in Prostate Cancer

Lu Miao, Lin Yang, Rui Li, Daniel N. Rodrigues, Mateus Crespo, Jer-Tsong Hsieh, Wayne D. Tilley, Johann de Bono, Luke A. Selth, and Ganesh V. Raj

*Précis:* This seminal report shows how targeting the androgen receptor may lead to undesirable phenotypic plasticity in prostate cancer cells, suggesting a general mechanism of resistance to hormonal therapies in prostate and breast cancers.

**3113** Multinuclear NMR and MRI Reveal an Early Metabolic Response to mTOR Inhibition in Sarcoma



Valentina Di Galleonardo, Hannah N. Aldeborgh, Vesselin Miloushev, Kelly M. Folkers, Kristin Granlund, William D. Tap, Jason S. Lewis, Wolfgang A. Weber, and Kayvan R. Keshari

*Précis:* These results illustrate the use of hyperpolarized MRI as a sensitive technique to monitor drug-induced perturbation of the PI3K/mTOR pathway in sarcomas, with implications for use in recruiting responsive patients to rapalog clinical trials.

**3123** Water Concentration Analysis of the Surgical Margin—Response

Gerwin J. Puppels

## CORRECTIONS

**3124** Correction: Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer

**3125** Correction: Chromosome Instability Modulated by BMI1–AURKA Signaling Drives Progression in Head and Neck Cancer

**3127** Correction: Connective Tissue Growth Factor Activates Pluripotency Genes and Mesenchymal–Epithelial Transition in Head and Neck Cancer Cells

## LETTERS TO THE EDITOR

**3121** Water Concentration Analysis of the Surgical Margin—Letter

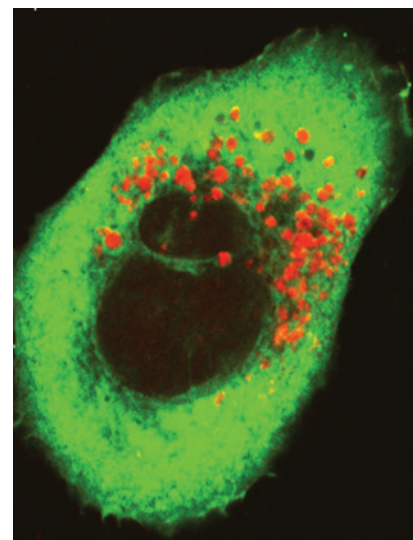
C. Murali Krishna and Aditi Sahu

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## ABOUT THE COVER

Autophagy is a major pathway for degradation of dysfunctional organelles and misfolded or aggregated proteins, and its defects trigger oxidative stresses to induce cell death, promote liver fibrosis and HCC, and reduce lifespans. Natural component spermidine enhances autophagy flux by depleting cytosolic histone deacetylase 4 and reducing its interaction with autophagy activator microtubule-associated protein MAP1S to dramatically expand lifespans and to prevent liver fibrosis and hepatocellular carcinomas. For details, see article by Yue and colleagues on page 2938.



# Cancer Research

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