

BREAKING ADVANCES

- 183** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 185** Landmark Study: The Relation of Solar Radiation to Cancer Mortality in North America
Joseph R. Bertino
- 186** Commentary on Huggins and Hodges: "Studies on Prostatic Cancer"
William G. Nelson

REVIEW

- 188** Lysyl Oxidase, a Targetable Secreted Molecule Involved in Cancer Metastasis
Thomas R. Cox, Alison Gartland, and Janine T. Erler

MEETING REPORT

- 193** Meeting Report Europhosphatase 2015: Phosphatases as Drug Targets in Cancer
Elmer Hoekstra, Maikel P. Peppelenbosch, and Gwenny M. Fuhler

PRIORITY REPORT

- 197** p73 and IGF1R Regulate Emergence of Aggressive Cancer Stem-like Features via miR-885-5p Control
Claudia Meier, Philip Hardtstock, Sophie Joost, Vijay Alla, and Brigitte M. Pützer
- Précis:* These findings offer major new insight into how the p53 family member p73 promotes the pathogenesis of highly malignant cancers, with implications for how to eradicate tumor-initiating cells and overcome drug resistance.

CLINICAL STUDIES

- 206** Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer
Jill A. Ohar, Mitchell Cheung, Jacqueline Talarchek, Suzanne E. Howard, Timothy D. Howard, Mary Hesdorffer, Hongzhuang Peng, Frank J. Rauscher, and Joseph R. Testa
- Précis:* BAP1 genetic testing may help identify individuals from families with a history of mesothelioma who are at higher risk of developing this cancer, but also with greater chances at long-term survival, an unusual pattern.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 216** Transcriptome Analysis of Recurrently Deregulated Genes across Multiple Cancers Identifies New Pan-Cancer Biomarkers
Bogumil Kaczkowski, Yuji Tanaka, Hideya Kawaji, Albin Sandelin, Robin Andersson, Masayoshi Itoh, Timo Lassmann, the FANTOM5 consortium, Yoshihide Hayashizaki, Piero Carninci, and Alistair R.R. Forrest

Précis: This genome-wide expression profiling approach identified new perspectives on DNA repetitive elements, often activated during cancer progression, as candidate biomarkers with pan-cancer potential.

MICROENVIRONMENT AND IMMUNOLOGY

- 227** Control of PD-L1 Expression by Oncogenic Activation of the AKT-mTOR Pathway in Non-Small Cell Lung Cancer
Kristin J. Lastwika, Willie Wilson III, Qing Kay Li, Jeffrey Norris, Haiying Xu, Sharon R. Ghazarian, Hiroshi Kitagawa, Shigeru Kawabata, Janis M. Taube, Sheng Yao, Linda N. Liu, Joell J. Gills, and Phillip A. Dennis
- Précis:* This study contributes to the rapidly accumulating evidence that oncogene signaling drives immune escape, implying that anti-oncogenic therapeutic strategies may be useful primarily for leveraging immunochemotherapy combinations.

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239 PD-1 Blunts the Function of Ovarian Tumor-Infiltrating Dendritic Cells by Inactivating NF- κ B

Lavakumar Karyampudi, Purushottam Lamichhane, James Krempski, Kimberly R. Kalli, Marshall D. Behrens, Doris M. Vargas, Lynn C. Hartmann, Jo Marie T. Janco, Haidong Dong, Karen E. Hedin, Allan B. Dietz, Ellen L. Goode, and Keith L. Knutson

Précis: These findings reveal how the immunosuppressive molecule PD-1 blunts the activity of tumor-infiltrating dendritic cells, with important implications for the ongoing development of therapeutic strategies to correct immune escape, including by re-engaging innate immune cells.

251 A Preclinical Model of Malignant Peripheral Nerve Sheath Tumor-like Melanoma Is Characterized by Infiltrating Mast Cells

Michael Hölzel, Jennifer Landsberg, Nicole Glodde, Tobias Bald, Meri Rogava, Stefanie Riesenberger, Albert Becker, Göran Jönsson, and Thomas Tüting

Précis: These findings highlight the ability to study human melanoma heterogeneity in a mouse model, revealing how melanocyte-immune cell interactions contribute to the development of distinct subsets of melanomas within a single individual.

264 Improved Treatment of Breast Cancer with Anti-HER2 Therapy Requires Interleukin-21 Signaling in CD8⁺ T Cells

Deepak Mittal, Franco Caramia, Stefan Michiels, Heikki Joensuu, Pirkko-Liisa Kellokumpu-Lehtinen, Christos Sotiriou, Sherene Loi, and Mark J. Smyth

Précis: These findings offer a preclinical rationale to boost IL21 signaling in HER2-positive breast cancer patients as a strategy to improve trastuzumab responses and limit the development of drug resistance.

275 PRC2 Epigenetically Silences Th1-Type Chemokines to Suppress Effector T-Cell Trafficking in Colon Cancer

Nisha Nagarsheth, Dongjun Peng, Ilona Kryczek, Ke Wu, Wei Li, Ende Zhao, Lili Zhao, Shuang Wei, Timothy Frankel, Linda Vatan, Wojciech Szeliga, Yali Dou, Scott Owens, Victor Marquez, Kaixiong Tao, Emina Huang, Guobin Wang, and Weiping Zou

Précis: A repressive epigenetic program that operates in colon cancer limits the efficiency of effector T cell trafficking to the tumor microenvironment, with implications for improving the efficacy of cancer immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

283 Combined MYC Activation and Pten Loss Are Sufficient to Create Genomic Instability and Lethal Metastatic Prostate Cancer

Gretchen K. Hubbard, Laura N. Mutton, May Khalili, Ryan P. McMullin, Jessica L. Hicks, Daniella Bianchi-Frias, Lucas A. Horn, Ibrahim Kulac, Michael S. Moubarek, Peter S. Nelson, Srinivasan Yegnasubramanian, Angelo M. De Marzo, and Charles J. Bieberich

Précis: The mouse model described can recapitulate key histopathologic and molecular features of human prostate cancer, including development of genomic instability and overt metastases to lymph nodes, liver, and lung.

293 HBXIP and LSD1 Scaffolded by lncRNA Hotair Mediate Transcriptional Activation by c-Myc

Yinghui Li, Zhen Wang, Hui Shi, Hang Li, Leilei Li, Runping Fang, Xiaoli Cai, Bowen Liu, Xiaodong Zhang, and Lihong Ye

Précis: This seminal study defines an oncogenic RNA/protein complex that serves as an effector for c-Myc in activating transcription of its target genes, illuminating long-standing questions concerning how c-Myc drives carcinogenesis.

305 EPHA2 Blockade Overcomes Acquired Resistance to EGFR Kinase Inhibitors in Lung Cancer

Katherine R. Amato, Shan Wang, Li Tan, Andrew K. Hastings, Wenqiang Song, Christine M. Lovly, Catherine B. Meador, Fei Ye, Pengcheng Lu, Justin M. Balko, Daniel C. Colvin, Justin M. Cates, William Pao, Nathanael S. Gray, and Jin Chen

Précis: Targeting a cell surface receptor kinase involved in cell-cell interactions appears to mitigate an important pathway of drug resistance in preclinical models of lung cancer, with immediate impact on clinical testing of the discovery.

319 Gender-Specific Molecular and Clinical Features Underlie Malignant Pleural Mesothelioma

Assunta De Rienzo, Michael A. Archer, Beow Y. Yeap, Nhien Dao, Daniele Sciaranghella, Antonios C. Sideris, Yifan Zheng, Alexander G. Holman, Yaoyu E. Wang, Paola S. Dal Cin, Jonathan A. Fletcher, Renee Rubio, Larry Croft, John Quackenbush, Peter E. Sugarbaker, Kiara J. Munir, Jesse R. Battilana, Corinne E. Gustafson, Lucian R. Chiriac, Soo Meng Ching, James Wong, Liang Chung Tay, Stephen Rudd, Robert Hercus, David J. Sugarbaker, William G. Richards, and Raphael Bueno

Précis: Novel molecular differences associated with gender and histology underlie the development of an asbestos-associated cancer of the outer epithelial lining of the lung, with implications for prognosing outcomes in patients.



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329 Cyclin D1 Promotes Androgen-Dependent DNA Damage Repair in Prostate Cancer Cells

Mathew C. Casimiro, Gabriele Di Sante, Xiaoming Ju, Zhiping Li, Ke Chen, Marco Crosariol, Ismail Yaman, Michael Gormley, Hui Meng, Michael P. Lisanti, and Richard G. Pestell

Précis: These findings shed light on how cyclin D1 promotes DNA damage repair mediated by androgens in the prostate, with potential clinical implications for treating therapy-resistant prostate cancer.

339 Obesity-Induced Colorectal Cancer Is Driven by Caloric Silencing of the Guanylin–GUCY2C Paracrine Signaling Axis

Jieru E. Lin, Francheska Colon-Gonzalez, Erik Blomain, Gilbert W. Kim, Amanda Aing, Brian Stoecker, Justin Rock, Adam E. Snook, Tingting Zhan, Terry M. Hyslop, Michal Tomczak, Richard S. Blumberg, and Scott A. Waldman

Précis: These seminal findings offer the first mechanistic connection between obesity and negation of a universal tumor suppressor pathway in colon tumorigenesis, with immediate implications for a hormone replacement strategy to prevent colorectal cancer in high-risk obese patients.

347 Peritoneal Dissemination Requires an Sp1-Dependent CXCR4/CXCL12 Signaling Axis and Extracellular Matrix–Directed Spheroid Formation

Yuta Kasagi, Yui Harada, Yosuke Morodomi, Toshiki Iwai, Satoru Saito, Kumi Yoshida, Eiji Oki, Hiroshi Saeki, Kippei Ohgaki, Masahiko Sugiyama, Mitsuo Onimaru, Yoshihiko Maehara, and Yoshikazu Yonemitsu

Précis: These findings illuminate mechanisms of peritoneal cancer dissemination, highlighting the Sp1/CXCR4/CXCL12 signaling axis as a rational target for the development of therapeutics to manage this intractable form of malignancy.

358 SKAP2 Promotes Podosome Formation to Facilitate Tumor-Associated Macrophage Infiltration and Metastatic Progression

Masamitsu Tanaka, Shintaro Shimamura, Sei Kuriyama, Daichi Maeda, Akiteru Goto, and Namiko Aiba

Précis: These findings reveal how macrophages infiltrate tumors and enhance metastasis, suggesting a new way to attenuate the tumor-promoting effects of this innate immune cell population in the tumor microenvironment.

PREVENTION AND EPIDEMIOLOGY

370 Skin Cancer Risk Is Modified by KIR/HLA Interactions That Influence the Activation of Natural Killer Immune Cells

Karin A. Vineretsky, Margaret R. Karagas, Brock C. Christensen, Jacquelyn K. Kuriger-Laber, Ann E. Perry, Craig A. Storm, and Heather H. Nelson

Précis: These findings reveal associations between keratinocyte-based cancers and activating signals for natural killer immune cells, demonstrating a role for natural killer cell tumor immunity in controlling the most common types of skin cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

377 Characterization of a c-Rel Inhibitor That Mediates Anticancer Properties in Hematologic Malignancies by Blocking NF- κ B–Controlled Oxidative Stress Responses

Yusuke Shono, Andrea Z. Tuckett, Hsiou-Chi Liou, Ekaterina Doubrovina, Enrico Derenzini, Samedy Ouk, Jennifer J. Tsai, Odette M. Smith, Emily R. Levy, Fabiana M. Kreines, Carly G.K. Ziegler, Mary I. Scallion, Mikhail Doubrovin, Glenn Heller, Anas Younes, Richard J. O'Reilly, Marcel R.M. van den Brink, and Johannes L. Zakrzewski

Précis: These results provide mechanistic insight and preclinical proof of concept for a novel small molecule to treat human lymphoid malignancies, with additional application in recipients of allogeneic bone marrow transplantations to ameliorate graft-versus-host disease, a major clinical challenge.

390 Maximizing the Efficacy of MAPK-Targeted Treatment in $PTEN^{LOF}/BRAF^{MUT}$ Melanoma through PI3K and IGF1R Inhibition

Barbara Herkert, Audrey Kauffmann, Sandra Mollé, Christian Schnell, Thomas Ferrat, Hans Voshol, Janina Juengert, Hélène Erasmus, Grégory Marszalek, Malika Kazic-Legueux, Eric Billy, David Ruddy, Mark Stump, Daniel Guthy, Mitko Ristov, Keith Calkins, Sauveur-Michel Maira, William R. Sellers, Francesco Hofmann, Michael N. Hall, and Saskia M. Brachmann

Précis: These findings reveal that the efficacy of MAPK inhibitors for the treatment of $PTEN$ -deficient and $BRAF$ mutant melanoma can be significantly improved by incorporating pharmacological strategies that also inhibit PI3K and IGF1R signaling.

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- 403** **An Anti-EGFR IgA That Displays Improved Pharmacokinetics and Myeloid Effector Cell Engagement *In Vivo***
Stefan Lohse, Saskia Meyer, Laura A.P.M. Meulenbroek, J.H. Marco Jansen, Maaïke Nederend, Anna Kretschmer, Katja Klausz, Uwe Möglinger, Stefanie Derer, Thies Rösner, Christian Kellner, Denis Schewe, Peter Sondermann, Sanjay Tiwari, Daniel Kolarich, Matthias Peipp, Jeanette H.W. Leusen, and Thomas Valerius
Précis: Monoclonal antibodies are generally engineered as IgG for therapeutic use, but this study makes a case for how the benefits of an IgA platform to engage myeloid effector cells may offer a useful format for therapeutic development.
- 418** **Neuropilin-2 Regulates Endosome Maturation and EGFR Trafficking to Support Cancer Cell Pathobiology**
Samikshan Dutta, Sohini Roy, Navatha S. Polavaram, Marissa J. Stanton, Heyu Zhang, Tanvi Bhola, Pia Hönscheid, Terrence M. Donohue Jr, Hamid Band, Surinder K. Batra, Michael H. Muders, and Kaustubh Datta
Précis: This study deepens the evidence that endocytotic processes, which serve as disease modifiers in cancer, offer candidate targets for broadly managing malignancy.
- 429** **Redirecting Transport of Nanoparticle Albumin-Bound Paclitaxel to Macrophages Enhances Therapeutic Efficacy against Liver Metastases**
Tomonori Tanei, Fransisca Leonard, Xuewu Liu, Jenolyn F. Alexander, Yuki Saito, Mauro Ferrari, Biana Godin, and Kenji Yokoi
Précis: A method for nanoparticle-mediated delivery of paclitaxel to macrophages within liver metastases can greatly enhance therapeutic efficacy, with immediate implications for clinical translation of the method to improve responses in patients with metastatic liver disease.
- 440** **Treatment of Triple-Negative Breast Cancer with TORC1/2 Inhibitors Sustains a Drug-Resistant and Notch-Dependent Cancer Stem Cell Population**
 Neil E. Bhola, Valerie M. Jansen, James P. Koch, Hua Li, Luigi Formisano, Janice A. Williams, Jennifer R. Grandis, and Carlos L. Arteaga
Précis: This study describes how triple-negative breast cancer stem-like cells evade killing by PI3K/mTOR inhibitors, highlighting the Notch1 signaling pathway as target to enhance responsiveness to these classes of targeted drugs.
- 453** **Effective Targeting of the Survivin Dimerization Interface with Small-Molecule Inhibitors**
Jing Qi, Zizheng Dong, Jianguo Liu, Robert C. Peery, Shaobo Zhang, Jing-Yuan Liu, and Jian-Ting Zhang
Précis: These results offer preclinical proof of concept for an anticancer agent that targets an important oncogenic driver, but more generally describes a set of novel in silico screening strategies to therapeutically target oncogenic target proteins that may be considered undruggable.
- 463** **Cancer Cell Dissemination and Homing to the Bone Marrow in a Zebrafish Model**
Antonio Sacco, Aldo M. Roccaro, Dongdong Ma, Jiantao Shi, Yuji Mishima, Michele Moschetta, Marco Chiarini, Nikhil Munshi, Robert I. Handin, and Irene M. Ghobrial
Précis: These findings validate zebrafish as a suitable model to monitor cancer cell dissemination and homing to bone marrow, a critical hematopoietic niche, enabling more accessible in vivo investigations of bone metastasis.
- 472** **Imaging, Biodistribution, and Dosimetry of Radionuclide-Labeled PD-L1 Antibody in an Immunocompetent Mouse Model of Breast Cancer**
Anders Josefsson, Jessie R. Nedrow, Sunju Park, Sangeeta Ray Banerjee, Andrew Rittenbach, Fabien Jammes, Benjamin Tsui, and George Sgouros
Précis: This study reports a method to image and evaluate the delivery of radiation combined with immune checkpoint therapy to tumors, and thus offers a novel approach for dynamically monitoring therapy responsiveness.

TUMOR AND STEM CELL BIOLOGY

- 480** **A Novel IL6 Antibody Sensitizes Multiple Tumor Types to Chemotherapy Including Trastuzumab-Resistant Tumors**
Haihong Zhong, April Davis, Maria Ouzounova, Rosa A. Carrasco, Cui Chen, Shannon Breen, Yong S. Chang, Jiaqi Huang, Zheng Liu, Yihong Yao, Elaine Hurt, Jacques Moisan, Michael Fung, David A. Tice, Shawn G. Clouthier, Zhan Xiao, Max S. Wicha, Hasan Korkaya, and Robert E. Hollingsworth
Précis: This study advances the concept that targeting the proinflammatory cytokine IL6 in breast cancers can heighten responses to therapy, including overcoming a major form of drug resistance in this disease, with an improved reagent that deserves clinical investigation.

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491 Interactions between Adipocytes and Breast Cancer Cells Stimulate Cytokine Production and Drive Src/Sox2/miR-302b-Mediated Malignant Progression



Manuel Picon-Ruiz, Chendong Pan, Katherine Drews-Elger, Kibeom Jang, Alexandra H. Besser, Dekuang Zhao, Cynthia Morata-Tarifa, Minsoon Kim, Tan A. Ince, Diana J. Azzam, Seth A. Wander, Bin Wang, Burcu Ergonul, Ram H. Datar, Richard J. Cote, Guy A. Howard, Dorraya El-Ashry, Pablo Torné-Poyatos, Juan A. Marchal, and Joyce M. Slingerland

Précis: This study identifies feed-forward signaling loops triggered by adipocyte-cancer cell interactions, driving inflammation and malignant growth and offering new therapeutic strategies to target breast cancers associated with obesity.

CORRECTION

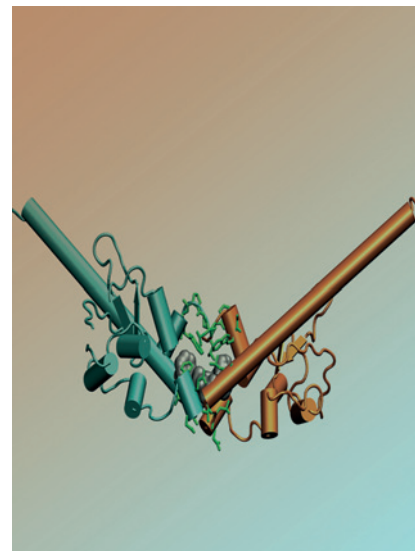
505 Correction: A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis

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ABOUT THE COVER

Overall structure of a survivin dimer with deeply buried dimerization core residues shown by their molecular surface in gray and noncore residues shown by sticks in green. Qi and colleagues show that the deeply buried dimerization core residues in undruggable oncogenic dimeric proteins can be targeted using computational approaches for drug discovery to destroy these proteins. Specifically, a lead small-molecule inhibitor LQZ-7F targeting the dimerization core residues of survivin was discovered that induced proteasome-dependent survivin degradation, mitotic arrest, apoptosis, and blocked the growth of human xenograft tumors. For details, see article by Qi and colleagues on page 453.



Cancer Research

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