

Cancer Research

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BREAKING ADVANCES

- 4953 **Highlights from Recent Cancer Literature**

REVIEWS

- 4955 **Emerging Potential of Therapeutic Targeting of Ubiquitin-Specific Proteases in the Treatment of Cancer**

Anupama Pal, Matthew A. Young, and Nicholas J. Donato

- 4967 **Sonic Hedgehog Signaling in Basal Cell Nevus Syndrome**

Mohammad Athar, Changzhao Li, Arianna L. Kim, Vladimir S. Spiegelman, and David R. Bickers

PERSPECTIVE

- 4976 **Obesity, Cholesterol Metabolism, and Breast Cancer Pathogenesis**

Donald P. McDonnell, Sunghee Park, Matthew T. Goulet, Jeff Jasper, Suzanne E. Wardell, Ching-yi Chang, John D. Norris, John R. Guyton, and Erik R. Nelson

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4983 **High-Throughput Time-Resolved FRET Reveals Akt/PKB Activation as a Poor Prognostic Marker in Breast Cancer**



Selvaraju Veeriah, Pierre Leboucher, Julien de Naurois, Nirmal Jethwa, Emma Nye, Tamara Bunting, Richard Stone, Gordon Stamp, Véronique Calleja, Stefanie S. Jeffrey, Peter J. Parker, and Banafshé Larijani

Précis: Using a novel quantitative imaging platform to determine the status of an activated biomarker in cancer patients may better identify high-risk patients who could benefit from a suitable targeted drug therapy.

MICROENVIRONMENT AND IMMUNOLOGY

- 4996 **Neutralizing Murine TGF β R2 Promotes a Differentiated Tumor Cell Phenotype and Inhibits Pancreatic Cancer Metastasis**

Katherine T. Ostapoff, Bercin Kutluk Cenic, Miao Wang, Risheng Ye, Xiaohong Xu, Desiree Nugent, Moriah M. Hagopian, Mary Topalovski, Lee B. Rivera, Kyla D. Carroll, and Rolf A. Brekken

Précis: This study demonstrates that TGF β signaling in stromal cells directly affects tumor cell plasticity and the metastatic capacity of pancreatic tumors.

- 5008 **TLR7 Promotes Tumor Progression, Chemotherapy Resistance, and Poor Clinical Outcomes in Non-Small Cell Lung Cancer**



Saradiya Chatterjee, Lucile Crozet, Diane Damotte, Kristina Iribarren, Catherine Schramm, Marco Alifano, Audrey Lupo, Julien Cherfils-Vicini, Jeremy Goc, Sandrine Katsahian, Mohammad Younes, Marie Caroline Dieu-Nosjean, Wolf Herman Fridman, Catherine Sautès-Fridman, and Isabelle Cremer

Précis: Activation of an immune stimulatory molecule, TLR7, studied mainly in immune cells but also highly expressed in human lung carcinoma cells, confers powerful tumor growth advantage that may be mediated in part by NF- κ B, perhaps helping explain its contributions to cancer.

- 5019 **Optimal Effector Functions in Human Natural Killer Cells Rely upon Autocrine Bone Morphogenetic Protein Signaling**

Neil C. Robson, Laura Hidalgo, Tristan McAlpine, Heng Wei, Víctor G. Martínez, Ana Entrena, Gustavo J. Melen, Andrew S. MacDonald, Alexander Phythian-Adams, Rosa Sacedón, Eugene Maraskovsky, Jonathan Cebon, Manuel Ramírez, Angeles Vicente, and Alberto Varas

Précis: The TGF β superfamily members BMP-2 and BMP-6 are produced by and are required to support the optimal functions of natural killer immune cells, suggesting new ways to enhance the powerful capability of these cells to eradicate tumors.

- 5032 **Stress Signaling from Human Mammary Epithelial Cells Contributes to Phenotypes of Mammographic Density**

Rosa Anna DeFilippis, Colleen Fordyce, Kelley Patten, Hang Chang, Jianxin Zhao, Gerald V. Fontenay, Karla Kerlikowske, Bahram Parvin, and Thea D. Tlsty

Précis: These findings provide new insights into how high mammographic density arises in the breast and why this condition is associated with breast cancer risk, with implications for the definition of novel intervention targets to prevent breast cancer.

- 5045 **Molecular Homology and Difference between Spontaneous Canine Mammary Cancer and Human Breast Cancer**


Deli Liu, Huan Xiong, Angela E. Ellis, Nicole C. Northrup, Carlos O. Rodriguez Jr, Ruth M. O'Regan, Stephen Dalton, and Shaying Zhao

Précis: This study of spontaneous mammary cancers that arise in dogs offers a novel perspective on critical questions in breast cancer research.

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- 5057** **CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint Immunotherapy in Pancreatic Cancer Models**
Yu Zhu, Brett L. Knolhoff, Melissa A. Meyer, Timothy M. Nywening, Brian L. West, Jingqin Luo, Andrea Wang-Gillam, S. Peter Goedegebuure, David C. Linehan, and David G. DeNardo
Précis: These preclinical findings offer a rationale to empower therapeutic effects of T-cell checkpoint-based immunotherapeutics that block PD-1 and CTLA-4 by reprogramming of immunosuppressive myeloid cells that are abundant in the tumor microenvironment.

- 5070** **Macrophage Inflammatory Protein Derivative ECI301 Enhances the Alarmin-Associated Abscopal Benefits of Tumor Radiotherapy**
Shiro Kanegasaki, Kouji Matsushima, Kenshiro Shiraishi, Keiichi Nakagawa, and Tomoko Tsuchiya
Précis: This study suggests mechanistic insights into a long recognized but little understood phenomenon in radiotherapy, the abscopal effect, which refers to antitumor benefits outside the irradiated field.

- 5079** **Natural Killer Cells Eradicate Galectin-1-Deficient Glioma in the Absence of Adaptive Immunity**
 Gregory J. Baker, Peter Chockley, Viveka Nand Yadav, Robert Doherty, Michael Ritt, Sivaraj Sivaramakrishnan, Maria G. Castro, and Pedro R. Lowenstein
Précis: Blocking an important mechanism of immune escape in glioma mediated by galectin-1 overexpression may be sufficient to restore the ability of natural killer cells to eradicate this type of brain cancer, without the need of adaptive immune functions.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5091** **BMP4 Inhibits Breast Cancer Metastasis by Blocking Myeloid-Derived Suppressor Cell Activity**
Yuan Cao, Clare Y. Slaney, Bradley N. Bidwell, Belinda S. Parker, Cameron N. Johnstone, Jai Rautela, Bedrich L. Eckhardt, and Robin L. Anderson
Précis: This study demonstrates that BMP4 can inhibit metastasis by reducing NF- κ B activity in tumor cells, leading to a suppression of G-CSF secretion and a consequential reduction in the number of metastases promoting myeloid-derived suppressor cells.

- 5103** **A Novel Wnt Regulatory Axis in Endometrioid Endometrial Cancer**
Yu Zhao, Yihua Yang, Jone Trovik, Kun Sun, Liang Zhou, Peiyong Jiang, Tat-San Lau, Erling A. Hovivik, Helga B. Salvesen, Hao Sun, and Huating Wang
Précis: These findings establish a novel Wnt/ β -catenin regulatory axis that involves a tumor suppressive member of the cadherin family, protocadherin-10, and a noncoding RNA, MALAT1, that supports the development of a subtype of endometrial cancer.

- 5118** **Natural Allelic Variations in Glutathione Peroxidase-1 Affect Its Subcellular Localization and Function**
Soumen Bera, Frank Weinberg, Dede N. Ekoue, Kristine Ansenberger-Fricano, Mao Mao, Marcelo G. Bonini, and Alan M. Diamond
Précis: Genetic variations in glutathione peroxidase-1 that affect the risk of several types of cancer are shown here to affect the function of this enzyme, with implications for understanding its fundamental roles in cancer pathophysiology.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 5127** **TIGAR Has a Dual Role in Cancer Cell Survival through Regulating Apoptosis and Autophagy**
Jia-Ming Xie, Bin Li, Hong-Pei Yu, Quan-Geng Gao, Wei Li, Hao-Rong Wu, and Zheng-Hong Qin
Précis: These results illuminate a new mechanism by which a key inhibitor of cell death helps regulate the response of cancer cells to chemotherapeutic drugs, with possible implications as a drug response biomarker.


- 5139** **Validation and Structural Characterization of the LEDGF/p75-MLL Interface as a New Target for the Treatment of MLL-Dependent Leukemia**
 Kateřina Čermáková, Petr Tesina, Jonas Demeulemeester, Sara El Ashkar, Hélène Méreau, Juerg Schwaller, Pavlína Řezáčová, Vaclav Veverka, and Jan De Rijck
Précis: This study identifies a potential molecular foothold in epigenetic therapy aimed at altering transcriptional programs in cancer cells to selectively trigger their demise.

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- 5152 AXL Mediates Resistance to Cetuximab Therapy**
Toni M. Brand, Mari Iida, Andrew P. Stein, Kelsey L. Corrigan, Cara M. Braverman, Neha Luthar, Mahmoud Toulany, Parkash S. Gill, Ravi Salgia, Randall J. Kimple, and Deric L. Wheeler

Précis: *This preclinical study provides a rationale to target the oncogenic receptor kinase AXL in cancers that exhibit intrinsic or acquired resistance to the anti-EGFR drug cetuximab, with immediate implications for the clinical evaluation of AXL inhibitors in cetuximab-resistant cancers.*

- 5165 RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth**

Jason G. Glanzer, Shengqin Liu, Ling Wang, Adam Mosel, Aimin Peng, and Greg G. Oakley

Précis: *By targeting a lynchpin of DNA replication, a compound that heightens DNA replication stress in cancer cells may offer a broadly useful new strategy for treatment.*

- 5173 HSV-sr39TK Positron Emission Tomography and Suicide Gene Elimination of Human Hematopoietic Stem Cells and Their Progeny in Humanized Mice**

Eric H. Gschwend, Melissa N. McCracken, Michael L. Kaufman, Michelle Ho, Roger P. Hollis, Xiaoyan Wang, Navdeep Saini, Richard C. Koya, Thinle Chodon, Antoni Ribas, Owen N. Witte, and Donald B. Kohn

Précis: *These results support the clinical development of a dual use imaging-suicide gene in immunotherapy and provide insights into the reversible engraftment of human hematopoietic stem cells.*

- 5184 Quantitative Optical Imaging of Primary Tumor Organoid Metabolism Predicts Drug Response in Breast Cancer**

Alex J. Walsh, Rebecca S. Cook, Melinda E. Sanders, Luigi Aurisicchio, Gennaro Ciliberto, Carlos L. Arteaga, and Melissa C. Skala

Précis: *This study demonstrates that cellular-level optical imaging of metabolic coenzymes resolves early, heterogeneous drug responses within primary tumor organoid cultures that are consistent with long-term in vivo tumor response.*

- 5195 Armed Oncolytic Virus Enhances Immune Functions of Chimeric Antigen Receptor-Modified T Cells in Solid Tumors**

Nobuhiro Nishio, Iulia Diaconu, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Bouchier-Hayes, Barbara Savoldo, and Gianpietro Dotti

Précis: *The cytokine/chemokine-armed virus described in this report may improve the effectiveness of CAR T-cell therapy in solid tumors, where this therapy has not been nearly as effective as in liquid tumors.*

- 5206 FLT3 Kinase Inhibitor TTT-3002 Overcomes Both Activating and Drug Resistance Mutations in FLT3 in Acute Myeloid Leukemia**

Hayley S. Ma, Bao Nguyen, Amy S. Duffield, Li Li, Allison Galanis, Allen B. Williams, Patrick A. Brown, Mark J. Levis, Daniel J. Leahy, and Donald Small

Précis: *A new small molecule inhibitor of FLT3, which can overcome all mutations documented to date, in this driver of acute myeloid leukemia, also exhibits superior pharmacologic properties that lend appeal for this agent as an effective next-generation therapeutic in this setting.*

- 5218 TLR9 Is Critical for Glioma Stem Cell Maintenance and Targeting**

Andreas Herrmann, Gregory Cherryholmes, Anne Schroeder, Jillian Phallen, Darya Alizadeh, Hong Xin, Tianyi Wang, Heehyoung Lee, Christoph Lahtz, Piotr Swiderski, Brian Armstrong, Claudia Kowolik, Gary L. Gallia, Michael Lim, Christine Brown, Behnam Badie, Stephen Forman, Marcin Kortylewski, Richard Jove, and Hua Yu

Précis: *The discovery that the toll-like receptor TLR9 is expressed in stem-like cells in an aggressive brain cancer may offer a useful tool for treatment strategies in this setting.*

TUMOR AND STEM CELL BIOLOGY

- 5229 ADAM9 Promotes Lung Cancer Metastases to Brain by a Plasminogen Activator-Based Pathway**

Chen-Yuan Lin, Hung-Jen Chen, Cheng-Chung Huang, Liang-Chuan Lai, Tzu-Pin Lu, Guan-Chin Tseng, Ting-Ting Kuo, Qian-Yu Kuok, Jennifer L. Hsu, Shian-Ying Sung, Mien-Chie Hung, and Yuh-Pyng Sher

Précis: *These findings highlight the integrated view for ADAM9 in lung cancer brain metastases and indicate that targeting of ADAM9-regulated pathways may be a rational approach to inhibit cancer metastases.*

- 5244 5-Lipoxygenase Is a Candidate Target for Therapeutic Management of Stem Cell-like Cells in Acute Myeloid Leukemia**

Jessica Roos, Claudia Oancea, Maria Heinssmann, Dilawar Khan, Hannelore Held, Astrid S. Kahnt, Ricardo Capelo, Estel la Buscató, Ewgenij Proschak, Elena Puccetti, Dieter Steinhilber, Ingrid Fleming, Thorsten J. Maier, and Martin Ruthardt

Précis: *These findings suggest that targeting the 5-lipoxygenases may help eradicate cancer stem cell-like cells in acute myeloid leukemias, with immediate implications for clinical evaluation in patients.*

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- 5256** **miR149 Functions as a Tumor Suppressor by Controlling Breast Epithelial Cell Migration and Invasion**
Annabell Bischoff, Bettina Huck, Bettina Keller, Michaela Strotbek, Simone Schmid, Melanie Boerries, Hauke Busch, Dafne Müller, and Monilola A. Olayioye
Précis: These findings define the molecular function of miR-149, which is downregulated in aggressive and often untreatable basal-like breast cancers, with potential implications for the design of future miRNA-based therapeutics in this disease setting.
- 5266** **RB Family Tumor Suppressor Activity May Not Relate to Active Silencing of E2F Target Genes**
Tinke L. Vormer, Kamila Wojciechowicz, Marleen Dekker, Sandra de Vries, Anja van der Wal, Elly Delzenne-Goette, Sjalín H. Naik, Ji-Ying Song, Jan-Hermen Dannenberg, Jacob B. Hansen, and Hein te Riele
Précis: These provocative findings suggest that RB tumor suppressor activity does not require interaction with LxCxE-containing proteins, implying it may not involve silencing of E2F target genes as previously thought.
- 5277** **Runx2 Is a Novel Regulator of Mammary Epithelial Cell Fate in Development and Breast Cancer**
Thomas W. Owens, Renee L. Rogers, Sarah A. Best, Anita Ledger, Anne-Marie Mooney, Alison Ferguson, Paul Shore, Alexander Swarbrick, Christopher J. Ormandy, Peter T. Simpson, Jason S. Carroll, Jane E. Visvader, and Matthew J. Naylor
Précis: These results establish a novel function for Runx2 of mammary cell fate and breast cancer that may offer a novel generalized route for therapeutic interventions in this malignancy.
- 5287** **Ubiquitin-like Protein FAT10 Promotes the Invasion and Metastasis of Hepatocellular Carcinoma by Modifying β -Catenin Degradation**
Rongfa Yuan, Kai Wang, Junwen Hu, Chen Yan, Ming Li, Xin Yu, Xiuxia Liu, Jun Lei, Wuhua Guo, Linquan Wu, Kui Hong, and Jianghua Shao
Précis: These findings link two drivers of invasion and metastasis in liver cancer and identify a novel pathway for β -catenin control that may have relevance in other cancers.
- 5301** **Cell Surface Lactate Receptor GPR81 Is Crucial for Cancer Cell Survival**
Christina L. Roland, Thiruvengadam Arumugam, Defeng Deng, Shi He Liu, Bincy Philip, Sobeyda Gomez, William R. Burns, Vijaya Ramachandran, Huamin Wang, Zobeida Cruz-Monserrate, and Craig D. Logsdon
Précis: Lactate metabolic changes alter cancer cell survival, and this study suggests a highly targetable G-protein coupled receptor on the cancer cell surface as a novel generalized antimetabolic therapy cancer treatment.
- 5311** **TALEN-Mediated Somatic Mutagenesis in Murine Models of Cancer**
Shuyuan Zhang, Lin Li, Sara L. Kendrick, Robert D. Gerard, and Hao Zhu
Précis: These results document new methods of interrogating cancer genes, advancing genome editing to study somatic mutations in vivo.
- 5322** **Intestinal Epithelial HuR Modulates Distinct Pathways of Proliferation and Apoptosis and Attenuates Small Intestinal and Colonic Tumor Development**
Antonina Giammanco, Valerie Blanc, Grace Montenegro, Coen Klos, Yan Xie, Susan Kennedy, Jianyang Luo, Sung-Hee Chang, Timothy Hla, ILKe Nalbantoglu, Sekhar Dharmarajan, and Nicholas O. Davidson
Précis: These results provide novel insight into the role of the ubiquitous RNA binding protein HuR as an oncogenic modifier of colon tumor susceptibility.
- 5336** **Genetic Ablation of Metadherin Inhibits Autochthonous Prostate Cancer Progression and Metastasis**
Liling Wan, Guohong Hu, Yong Wei, Min Yuan, Roderick T. Bronson, Qifeng Yang, Javed Siddiqui, Kenneth J. Pienta, and Yibin Kang
Précis: A poorly understood gene that is overexpressed widely in human cancer is shown to support malignant progression, providing a foundation to justify studies that could elucidate its molecular function and potential as a therapeutic target.

CORRECTION

- 5348** **Correction: Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?**

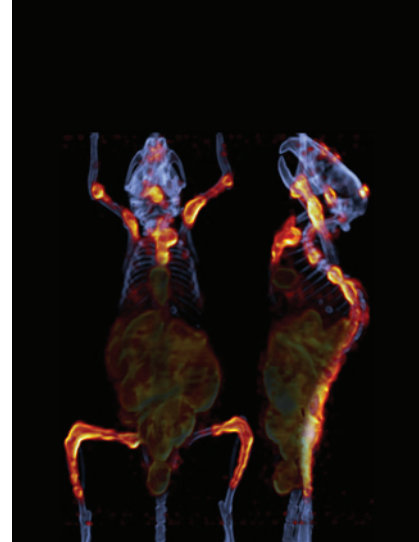
 AC icon indicates Author Choice

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ABOUT THE COVER

Non-invasive *in vivo* imaging of gene-modified human hematopoietic stem cells and their progeny can be achieved using positron image tomography (PET), shown here as coronal and sagittal plane overlays on X-ray computed tomography scans. Imaging after systemically administered [^{18}F]-FHBG reveals accumulation of probe localized to areas of hematopoietic engraftment such as the humerus, tibia, femur, vertebrae, sternum, and thymus. Background probe uptakes in the gastrointestinal tract and gall bladder, present in non-humanized NSG and mock-transduced humanized mice have been artificially masked for clarity. For details, see article by Gschwend on page 5173.



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