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

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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

### PERSPECTIVE

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. Rodríguez 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.
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.

Macrophage Inflammatory Protein Derivative EC1301 Enhances the Alarmin-Associated Abscopal Benefits of Tumor Radiotherapy
Shiro Kanegasaki, Kouji Matsushima, Kenshiro Shiromaishi, 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.

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.

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-κB activity in tumor cells, leading to a suppression of G-CSF secretion and a consequent reduction in the number of metastases promoting myeloid-derived suppressor cells.

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. Hoivik, 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.

Natural Allelic Variations in Glutathione Peroxidase-1 Affect Its Subcellular Localization and Function
Soumen Bera, Frank Weinberg, Dede N. Ekoue, Kristine A. Asenberger-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.

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.

Validation and Structural Characterization of the LEDGF/p75–MLL Interface as a New Target for the Treatment of MLL-Dependent Leukemia
Kateřina Cermáková, Petr Tesina, Jonas Demeulemeester, Sara El Ashkar, Hélène Méreau, Juerg Schwaller, Pavlína Rezáčová, Václav 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.
<table>
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<th>5152</th>
<th>AXL Mediates Resistance to Cetuximab Therapy</th>
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<td>Toni M. Brand, Mari Iida, Andrew P. Stein, Kelsey L. Corrigan, Cara M. Braverman, Neha Lurham, Mahmoud Toulany, Parkash S. Gill, Ravi Salgia, Randall J. Kimple, and Deric L. Wheeler</td>
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**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.

<table>
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<tr>
<th>5165</th>
<th>RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth</th>
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<td>Jason G. Glanzer, Shengjin Liu, Ling Wang, Adam Mosel, Aimin Peng, and Greg G. Oakley</td>
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**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.

<table>
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<tr>
<th>5173</th>
<th>HSV-sr39TK Positron Emission Tomography and Suicide Gene Elimination of Human Hematopoietic Stem Cells and Their Progeny in Humanized Mice</th>
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<tr>
<td>Eric H. Gschwend, Melissa N. McCracken, Michael L. Kaufman, Michelle Ho, Roger P. Hollis, Xiaoyan Wang, Navdeep Saini, Richard C. Koya, Thinkle Chodon, Antoni Ribas, Owen N. Witte, and Donald B. Kohn</td>
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**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.

<table>
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<th>5184</th>
<th>Quantitative Optical Imaging of Primary Tumor Organoid Metabolism Predicts Drug Response in Breast Cancer</th>
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<tr>
<td>Alex J. Walsh, Rebecca S. Cook, Melinda E. Sanders, Luigi Aurisicchio, Gennaro Ciliberto, Carlos L. Arteaga, and Melissa C. Skala</td>
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**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.

<table>
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<th>5195</th>
<th>Armed Oncolytic Virus Enhances Immune Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors</th>
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<tr>
<td>Nobuhiro Nishio, Jula D'aconou, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Boucher-Hayes, Barbara Savoldo, and Gianpietro Dotti</td>
<td></td>
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**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.

<table>
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<tr>
<th>5206</th>
<th>FLT3 Kinase Inhibitor TTT-3002 Overcomes Both Activating and Drug Resistance Mutations in FLT3 in Acute Myeloid Leukemia</th>
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<tr>
<td>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</td>
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**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.

<table>
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<th>5218</th>
<th>TLR9 is Critical for Glioma Stem Cell Maintenance and Targeting</th>
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<td>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</td>
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**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

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<th>5229</th>
<th>ADAM9 Promotes Lung Cancer Metastases to Brain by a Plasminogen Activator-Based Pathway</th>
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<td>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</td>
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**Précis:** These findings highlight the integrated view for ADAM9 in lung cancer brain metastasizes and indicate that targeting of ADAM9-regulated pathways may be a rational approach to inhibit cancer metastases.

<table>
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<tr>
<th>5244</th>
<th>5-Lipoxygenase Is a Candidate Target for Therapeutic Management of Stem Cell–like Cells in Acute Myeloid Leukemia</th>
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<tr>
<td>Jessica Roos, Claudia Oancea, Maria Heineßmann, Dilawar Khan, Hannelore Held, Astrid S. Kahnt, Ricardo Capelo, Estel la Buscató, Ewgenij Proschak, Elena Puccetti, Dieter Steinbüchler, Ingrid Fleming, Thorsten J. Maier, and Martin Ruthardt</td>
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**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.
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. Olajide

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.

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 Delzerme-Goette, Sjalin H. Nalik, 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.

Runx2 Is a Novel Regulator of Mammary Epithelial Cell Fate in Development and Breast Cancer


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.

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, Xiaxia 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.

CORRECTION

Correction: Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?
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 Gschweng on page 5173.