Emerging Potential of Therapeutic Targeting of Ubiquitin-Specific Proteases in the Treatment of Cancer
Anupama Pal, Matthew A. Young, and Nicholas J. Donato

Sonic Hedgehog Signaling in Basal Cell Nevus Syndrome
Mohammad Athar, Changzhao Li, Arianna L. Kim, Vladimir S. Spiegelman, and David R. Bickers

Obesity, Cholesterol Metabolism, and Breast Cancer Pathogenesis

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 Banaftshé Larijani

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.

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

The TGFβ 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.

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 invention targets to prevent breast cancer.

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

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

5118  Natural Allelic Variations in Glutathione Peroxidase-1 Affect Its Subcellular Localization and Function
Soumen Bera, Frank Weinberg, Dede N. Ekoue, Kristine Amsenberger-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 Cermáková, Petr Tesina, Jonas Demoulemeester, Sara El Ashkar, Hélène Méreau, Juerg Schwaller, Pavlína Rezáčová, 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.
Armed Oncolytic Virus Enhances Immune Quantitative Optical Imaging of Primary HSV-sr39TK Positron Emission Tomography RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth HSV-sr39TK Positron Emission Tomography and Suicide Gene Elimination of Human Hematopoietic Stem Cells and Their Progeny in Humanized Mice Quantitative Optical Imaging of Primary Tumor Organoid Metabolism Predicts Drug Response in Breast Cancer Armed Oncolytic Virus Enhances Immune Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors

FLT3 Kinase Inhibitor TTT-3002 Overcomes Both Activating and Drug Resistance Mutations in FLT3 in Acute Myeloid Leukemia TLR9 Is Critical for Glioma Stem Cell Maintenance and Targeting ADAM9 Promotes Lung Cancer Metastases to Brain by a Plasminogen Activator-Based Pathway 5-Lipoxygenase Is a Candidate Target for Therapeutic Management of Stem Cell–like Cells in Acute Myeloid Leukemia

CTD2015-0421 3500 TUMOR AND STEM CELL BIOLOGY

5299 ADAM9 Promotes Lung Cancer Metastases to Brain by a Plasminogen Activator-Based Pathway

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

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

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

5124 Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors

5152 AXL Mediates Resistance to Cetuximab Therapy

5165 RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth

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

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

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

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

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

5218 TLR9 Is Critical for Glioma Stem Cell Maintenance and Targeting

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

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

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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.

RB Family TumorSuppressor 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, Sjalin 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.

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, Xuxia 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.