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  

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 Banañesh Larijani

MICROENVIRONMENT AND IMMUNOLOGY

4996 Neutralizing Murine TGFβR2 Promotes a Differentiated Tumor Cell Phenotype and Inhibits Pancreatic Cancer Metastasis  
Katherine T. Ostapoff, Bercin Kutluk Cenik, Miao Wang, Risheeng Ye, Xiaohong Xu, Desiree Nugent, Moriah M. Hagopian, Mary Topalovski, Lee B. Rivera, Kyla D. Carroll, and Rolf A. Brekken

5008 TLR7 Promotes Tumor Progression, Chemotherapy Resistance, and Poor Clinical Outcomes in Non–Small Cell Lung Cancer  
Saradiya Chatterjee, Lucie 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

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 Phytyian-Adams, Rosa Sacedón, Eugene Maraskovsky, Jonathan Cebon, Manuel Ramírez, Angeles Vicente, and Alberto Varas

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 Theo D. Tlsty

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

Precíos: 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 EC1301 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-DerivedSuppressor 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.

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.

5113  Natural Allelic Variations in Glutathione Peroxidase-1 Affect Its Subcellular Localization and Function
Soumen Bera, Frank Weinberg, Dede N. Ekoue, Kristine Aasenberger-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
Katěrina Cermáková, Petr Tesina, Jonas Demeulemeester, Sara El Ashkar, Hélène Méreau, Juerg Schwaller, Pavlina 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.
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

TUMOR AND STEM CELL BIOLOGY

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

armed tumors.
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 Muller, and Monilola A. Olayioye

Preciso: 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 Delzenne-Goette, Sjalin H. Naik, Ji-Ying Song, Jan-Herman Dannenberg, Jacob B. Hansen, and Hein te Riele

Preciso: 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

Preciso: 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, Xiaoxia Liu, Jun Lei, Wuhua Guo, Linquan Wu, Kui Hong, and Jianghua Shao

Preciso: 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.

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, Huanmin Wang, Zobeida Cruz-Monserrate, and Craig D. Logsdon

Preciso: 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.

TALEN-Mediated Somatic Mutagenesis in Murine Models of Cancer
Shuyuan Zhang, Lin Li, Sara L. Kendrick, Robert D. Gerard, and Hao Zhu

Preciso: These results document new methods of interrogating cancer genes, advancing genome editing to study somatic mutations in vivo.

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, IL-Ke Nalbantoglu, Sekhar Dharmarajan, and Nicholas O. Davidson

Preciso: These results provide novel insight into the role of the ubiquitous RNA binding protein HuR as an oncogenic modifier of colon tumor susceptibility.

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

Preciso: 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

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 \[^{18}F\text{-FHBG}\] 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.