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.

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 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.

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 Deemeulemeester, Sara El Ashkar, Hélène Méreau, Juerg Schwaller, Pavlina 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.
RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth
Jason G. Glanzer, Shengqin Liu, Ling Wang, Adam Mosel, Aimin Peng, and Greg G. Oakley

Precise: 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.

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, Thine Chodon, Antonio Ribas, Owen N. Witte, and Donald B. Kohn

Precise: 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.

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

Precise: 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.

Armed Oncolytic Virus Enhances Immune Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors
Nobuhiro Nishio, Jula Dtaconu, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Bouchier-Hayes, Barbara Savoldo, and Gianpietro Dotti

Precise: 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.

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. Lealy, and Donald Small

Precise: 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.

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

Precise: 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.

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

Precise: 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.

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, Evgenij Proschak, Elena Puccetti, Dieter Steinhilber, Ingrid Fleming, Thorsten J. Maier, and Martin Ruthardt

Precise: 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. 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 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-Hermen Danenberg, 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?

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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 Gschweng on page 5173.