REVIEWS

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

PERSPECTIVE

Obesity, Cholesterol Metabolism, and Breast Cancer Pathogenesis

INTEGRATED SYSTEMS AND TECHNOLOGIES

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 Banañsh 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

Neutralizing Murine TGFβR2 Promotes a Differentiated Tumor Cell Phenotype and Inhibits Pancreatic Cancer Metastasis
Katherine T. Ostapoff, Bercin Kutluk Cenik, 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 TGFβ signaling in stromal cells directly affects tumor cell plasticity and the metastatic capacity of pancreatic tumors.
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.

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 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.

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 Dememelester, Sara El Askar, Hélène Méréau, 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.
Armed Oncolytic Virus Enhances Immune Tumor Response.

Functionality of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors

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

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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

5165 RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth
Jason G. Glanzer, Shengqin Liu, Ling Wang, Adam Mosel, Ainmeng Peng, and Greg C. Oakley

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

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 Auriisicchio, Gennaro Ciliberto, Carlos L. Arteaga, and Melissa C. Skala

5195 Armed Oncolytic Virus Enhances Immune Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors
 Nobuhiro Nishio, Jula D'Acoum, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Bouchier-Hayes, Barbara Savoldo, and Gianpietro Dotti

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

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 Kovolik, Gary L. Gallia, Michael Lim, Christine Brown, Behnam Badie, Stephen Forman, Marcin Kortylewski, Richard Jove, and Hua Yu

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

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

5256 Functions of Chimeric Antigen Receptor–Modified T Cells in Solid Tumors
Nobuhiro Nishio, Jula D’Acoum, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Bouchier-Hayes, Barbara Savoldo, and Gianpietro Dotti

5261 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.
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, Sjalin H. Naik, Ji-Ying Song, Jan-Hermer 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
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, Xixia 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 TALEN-Mediated Somatic Mutagenesis in Murine Models of Cancer
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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.