Highlights from Recent Cancer Literature

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 Banafshé 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, Victor G. Martínez, Ana Estrella, Gustavo J. Melen, Andrew S. MacDonald, Alexander Phythin-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.

Molecular Homology and Difference between Spontaneous Canine Mammary Cancer and Human Breast Cancer
Katherine T. Ostapoff, Bercin Kutluk Cenik, Miao Wang, Rissheng Ye, Xiaoqiong Xu, Desiree Nugent, Moriah M. Hagopian, Mary Topalovski, Lee B. Rivera, Kyla D. Carroll, and Rolf A. Brekken

This study demonstrates that TGFβ signaling in stromal cells directly affects tumor cell plasticity and the metastatic capacity of pancreatic tumors.

Neutralizing Murine TGFβR2 Promotes a Differentiated Tumor Cell Phenotype and Inhibits Pancreatic Cancer Metastasis
Rosa Anna DeFilippis, Colleen Fordyce, Kelley Patten, Hang Chang, Jianxin Zhao, Gerald V. Fontenay, Karla Kerlikowske, Bahram Parvin, and Thea D. Tlsty

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.

Molecular Homology and Difference between Spontaneous Canine Mammary Cancer and Human Breast Cancer
Delil Liu, Huan Xiong, Angela E. Ellis, Nicole C. Northrup, Carlos O. Rodriguez Jr, Ruth M. O’Regan, Stephen Dalton, and Shaying Zhao

This study of spontaneous mammary cancers that arise in dogs offers a novel perspective on critical questions in breast cancer research.
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<td>CSF1/CSF1R Blockade Reprograms Tumor-Infiltrating Macrophages and Improves Response to T-cell Checkpoint</td>
<td>Yu Zhu, Brett L. Knolhoff, Melissa A. Meyer, Timothy M. Nywening, Brian L. West, Jingxin Luo, Andrea Wang-Cillam, S. Peter Goedegebuure, David C. Linehan, and David G. DeNardo</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>Macrophage Inflammatory Protein Derivative ECI301 Enhances the Alarmin-Associated Abscopal Benefits of Tumor Radiotherapy</td>
<td>Shiro Kanegasaki, Kouji Matsushima, Kenshiro Shiraiishi, Keichi Nakagawa, and Tomoko Tsuchiya</td>
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<td><strong>Précis:</strong> 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.</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>5091</td>
<td>BMP4 Inhibits Breast Cancer Metastasis by Blocking Myeloid-Derived Suppressor Cell Activity</td>
<td>Yuan Cao, Clare Y. Slaney, Bradley N. Bidwell, Belinda S. Parker, Cameron N. Johnstone, Jai Rautela, Bedrich L. Eckhardt, and Robin L. Anderson</td>
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<td><strong>Précis:</strong> This study demonstrates that BMP4 can inhibit metastasis by reducing NF-kB 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.</td>
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<td>5103</td>
<td>A Novel Wnt Regulatory Axis in Endometrioid Endometrial Cancer</td>
<td>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</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>Natural Allelic Variations in Glutathione Peroxidase-1 Affect Its Subcellular Localization and Function</td>
<td>Soumen Ber, Frank Weinberg, Dede N. Ekoue, Kristine Asenberger-Fricano, Mao Mao, Marcelo G. Bonini, and Alan M. Diamond</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>TIGAR Has a Dual Role in Cancer Cell Survival through Regulating Apoptosis and Autophagy</td>
<td>Jia-Ming Xie, Bin Li, Hong-Pei Yu, Guan-Geng Gao, Wei Li, Hao-Rong Wu, and Zheng-Hong Qin</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>Validation and Structural Characterization of the LEDGF/p75–MLL Interface as a New Target for the Treatment of MLL-Dependent Leukemia</td>
<td>Kateřina Cermáková, Petr Tesina, Jonas Demeuzeleemster, Sara El Ashkar, Hélène Mérreau, Juerg Schwaller, Pavlina Režáčová, Václav Veverka, and Jan De Rijck</td>
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<td><strong>Précis:</strong> This study identifies a potential molecular foothold in epigenetic therapy aimed at altering transcriptional programs in cancer cells to selectively trigger their demise.</td>
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Armed Oncolytic Virus Enhances Immune Response

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

Preciso: This preclinical study provides a rationale to target the oncolytic 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.

RPA Inhibition Increases Replication Stress and Suppresses Tumor Growth

Jason G. Glanzer, Shengqin Liu, Ling Wang, Adam Mosel, Aimin Peng, and Greg C. Oakley

Preciso: 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, Naveedep Saini, Richard C. Koya, Thiele Chodon, Antoni Ribas, Owen N. Witte, and Donald B. Kohn

Preciso: 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

Preciso: 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 Diacoum, Hao Liu, Vincenzo Cerullo, Ignazio Caruana, Valentina Hoyos, Lisa Boucher-Hayes, Barbara Savoldo, and Gianpiero Dotti

Preciso: 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. Leahy, and Donald Small

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

Preciso: 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.

5-Lipoxygenase Is a Candidate Target for 5-lipoxygenases may help eradicate cancer stem cell–like cells in acute myeloid leukemias, with immediate implications for clinical evaluation in patients.

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, Mi-Chie Hung, and Yuh-Pyng Sher

Preciso: 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 Steinhardt, Ingrid Fleming, Thorsten J. Maier, and Martin Ruthardt

Preciso: 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 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, XiuXia 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

Enhancing Reproducibility in Cancer Drug Screening: How Do We Move Forward?

For more information please visit www.aacrjournals.org
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.