Tumor–Stroma Interaction: Revealing Fibroblast-Secreted Exosomes as Potent Regulators of Wnt-Planar Cell Polarity Signaling in Cancer Metastasis
Valbona Luga and Jeffrey L. Wrana

The Role of Polo-like Kinase 1 in Carcinogenesis: Cause or Consequence?
Brian D. Choława, Xiaoqi Liu, and Nihal Ahmad

D538G Mutation in Estrogen Receptor-α: A Novel Mechanism for Acquired Endocrine Resistance in Breast Cancer
Keren Merenbakh-Lamin, Noa Ben-Baruch, Adva Yeheskel, Addie Dvir, Lior Soussan-Gutman, Rinath Jeselsohn, Roman Yelensky, Myles Brown, Vincent A. Miller, David Sarid, Shulamith Rizel, Baruch Klein, Tami Rubinék, and Ido Wolf

Free Somatostatin Receptor Fraction Predicts the Antiproliferative Effect of Octreotide in a Neuroendocrine Tumor Model: Implications for Dose Optimization
Pedram Heidari, Eric Wehrenberg-Klee, Peiman Habibollahi, Daniel Yokell, Matthew Kulke, and Umar Mahmood

Senescent Fibroblasts in Melanoma Initiation and Progression: An Integrated Theoretical, Experimental, and Clinical Approach
Eunjung Kim, Vito Rebeccia, Inna V. Fedorenko, Jane L. Messina, Rahel Mathew, Silvya S. Marta-Engleis, David Basanta, Keiran S.M. Smallley, and Alexander R.A. Anderson

A Novel Model of Dormancy for Bone Metastatic Breast Cancer Cells
Rebecca Marlow, Gabriella Honeth, Sara Lombardi, Massimiliano Cariati, Sonya Hessey, Alkaterini Pipili, Veronica Mariotti, Bharath Buchupalli, Katie Foster, Dominique Bonnet, Agamemnon Grigoriadis, Pranela Rameshwar, Anand Purushotham, Andrew Tutt, and Gabriela Dontu

Therapeutic PD-1 Pathway Blockade Augments with Other Modalities of Immunotherapy T-Cell Function to Prevent Immune Decline in Ovarian Cancer
Jaikumar Duraiswamy, Gordon J. Freeman, and George Coukos

Precis: These findings developed by in silico modeling reinforce an alternative perspective on cancer, in which senescent fibroblasts create the core conditions required to license the ability of cancer cell mutations to promote malignancy, reinforcing a greater therapeutic focus on the tumor microenvironment as a cause of cancer.
MOLECULAR AND CELLULAR PATHOBIOLOGY

6913
Low PIP4K2B Expression in Human Breast Tumors Correlates with Reduced Patient Survival: A Role for PIP4K2B in the Regulation of E-Cadherin Expression
Willem-Jan Keune, Andrew H. Sims, David R. Jones, Yvette Bulsma, James T. Lynch, Karin Jirstrom, Goran Landberg, and Nullin Divecha
Précis: An enzyme that regulates second messengers in lipid signaling impacts the survival of breast cancer patients by modifying a pivotal tumor suppressor function.

6926
Skin Tumorigenesis Stimulated by Raf Inhibitors Relies Upon Raf Functions That Are Dependent and Independent of ERK
Eszter Doma, Christian Rupp, Andrea Varga, Florian Kern, Bettina Riegler, and Manuela Baccarini
Précis: Provocative preclinical results suggest that B-Raf inhibitors being used currently in the clinic to treat melanoma may not only trigger development of cutaneous skin tumors, a known side effect, but also gastric tumors, which are far less manageable.

6938
TRAF4 Is a Critical Molecule for Akt Activation in Lung Cancer
Wei Li, Cong Peng, Mee-Hyun Lee, DoYoung Lim, Feng Zhu, Yang Fu, Ge Yang, Yuqiao Sheng, Lanbo Xiao, Xin Dong, WeiYa Ma, Ann M. Bode, Ya Cao, and Zigang Dong
Précis: These findings reveal a pivotal role for a ubiquitlation enzyme in Akt control and lung cancer pathophysiology, suggesting its role as a candidate molecular target for lung cancer prevention and therapy.

6951
SHON Is a Novel Estrogen-Regulated Oncogene in Mammary Carcinoma That Predicts Patient Response to Endocrine Therapy
Yewon Jung, Tarek M.A. Abdel-Fatah, Stephen Y.T. Chan, Christopher C. Nolan, Andrew R. Green, Ian O. Ellis, Lili Li, Baiqi Huang, Jun Lu, Bing Xu, Longxin Chen, Runlin Z. Ma, Min Zhang, Jingru Wang, ZhengSheng Wu, Tao Zhu, Jo K. Perry, Peter E. Lobie, and Dong-Xu Liu
Précis: These findings identify a human oncogene that may serve as a simple biomarker to predict the therapeutic efficacy of antiestrogen therapy in ER⁺ breast tumors.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6963
Androgen Glucuronidation: An Unexpected Target for Androgen Deprivation Therapy, with Prognosis and Diagnostic Implications
Laurent Grosse, Sophie Páquet, Patrick Caron, Ladan Fazli, Paul S. Rennie, Alain Bélanger, and Olivier Barbier
Précis: These findings reveal a local pathway of androgen metabolism in prostate cells that can antagonize the effects of androgen deprivation therapy in prostate cancer.

6972
miRNA-95 Mediates Radioresistance in Tumors by Targeting the Sphingolipid Phosphatase SGPP1
Xiaoyong Huang, Samira Taeb, Sahar Jahangiri, Urban Emmenegger, Elisa Tran, Jeff Bruce, Aruz Mesci, Elina Korpela, Danny Vesprini, C. Shun Wong, Robert G. Bristow, Fei-Fei Liu, and Stanley K. Liu
Précis: This seminal report identifies a little-studied microRNA as a major mediator of radiation resistance in tumors, also showing how resistance can be reversed with a clinically approved inhibitor of sphingosine-1-phosphate signaling.

6987
Supramolecular Nanoparticles That Target Phosphoinositide-3-Kinase Overcome Insulin Resistance and Exert Pronounced Antitumor Efficacy
Précis: This study provides a preclinical foundation for the use of supramolecular nanochemistry to overcome current challenges associated with PI3K inhibitors and also offers a more general paradigm for the development of molecular targeted therapeutics for cancer treatment.

6998
Contribution of Bcl-2 Phosphorylation to Bak Binding and Drug Resistance
Haiming Dai, Husheng Ding, X. Wei Meng, Sun-Hee Lee, Paula A. Schneider, and Scott H. Kaufmann
Précis: These findings offer a mechanistic basis to understand the enhanced antiapoptotic activity of phosphorylated Bcl-2, along with the ability of BH3 mimetics to enhance cancer cell sensitivity to taxanes.
Carbon Monoxide Expedites Metabolic Exhaustion to Inhibit Tumor Growth
Barbara Wegiel, David Gallo, Eva Csizmadia, Clair Harris, John Belcher, Gregory M. Vercellotti, Nuno Penacho, Pier Paolo Pandolfi, Pankaj Seth, Vikas Sukhatme, Asif Ahmed, Anders Bjartell, Jenny Liao Persson, and Leo E. Otterbein

Precise: Clinical trials of carbon monoxide that are being conducted as a strategy for chemosensitization may benefit from mechanistic insights into CO-induced cancer cell death provided in this study.

The HSP90 Inhibitor Ganetespib Synergizes with the MET Kinase Inhibitor Crizotinib in both Crizotinib-Sensitive and -Resistant MET-Driven Tumor Models
Naoto Miyajima, Shinji Tsutsumi, Carole Sourbier, Kristin Beebe, Mehdi Mollapour, Candy Rivas, Soichiro Yoshida, Jane B. Trepel, Ying Huang, Manabu Tatokoro, Nobuo Shinohara, Katsuya Nonomura, and Len Neckers

Precise: Hsp90 inhibition synergizes with MET tyrosine kinase inhibition and restores sensitivity to drug-resistant MET mutants.

PTEN Loss Mitigates the Response of Medulloblastoma to Hedgehog Pathway Inhibition

Precise: This study offers new insights into the potential efficacy of Hedgehog pathway inhibitors being tested clinically against a common pediatric cancer.

Antitumor Activity of the Selective Pan-RAF Inhibitor TAK-632 in BRAF Inhibitor-Resistant Melanoma
Akiito Nakamura, Takeo Arita, Shuntaro Tsuichya, Jill Donelan, Yoshua Chouitair, Elizabeth Carideo, Katherine Galvin, Masanori Okaniwa, Tomoyasu Ishikawa, and Sei Yoshida

Precise: This pan-RAF inhibitor may offer needed therapeutic options for patients with NRAS- or BRAF-driven melanomas that are refractory to BRAF inhibitor treatment.

A Novel EGFR Isoform Confers Increased Invasiveness to Cancer Cells
Min Zhou, Hai Wang, Keke Zhou, Xiaoying Luo, Xiaorong Pan, Bizhi Shi, Hua Jiang, Jiqin Zhang, Kesang Li, Hua-Mao Wang, Huijing Gao, Shun Lu, Ming Yao, Ying Mao, Hong-Yang Wang, Shengli Yang, Jianren Gu, Chuanxuian Li, and Zonghai Li

Precise: These findings reveal a novel mechanism through which dysregulated EGFR signaling drives cancer cell invasion and poor prognosis, in glioma and other cancers, with implications for new prognosis and treatment paradigms involving this core pathway in cancer.

Silencing of the miR-17~92 Cluster Family Inhibits Medulloblastoma Progression
Brian L. Murphy, Susanna Obad, Laure Bihannic, Olivier Ayrault, Frederique Zindy, Sakari Kauppinen, and Martine F. Roussel

Precise: This study highlights the therapeutic utility achieved by systemic delivery of a drug-like antisense molecule directed against microRNAs, termed tiny LNAs, to suppress tumor progression.

Glioblastoma Stem Cells Are Regulated by Interleukin-8 Signaling in a Tumoral Perivascular Niche
David W. Infanger, Youjin Cho, Brina S. Lopez, Sunish Mohanan, S. Chris Liu, Demirkan Gursel, John A. Boockvar, and Claudia Fischbach

Precise: This study demonstrates the impact that a 3D tumor environment exerts on chemokine-mediated signals needed to maintain cancer stem-like cells, with broader implications for illustrating the important role of 3D culture models in gaining a better understanding of cancer pathogenesis.

Generation of Prostate Tumor-Initiating Cells Is Associated with Elevation of Reactive Oxygen Species and IL-6/STAT3 Signaling
Yi Qu, Anne Margrete Oyan, Runhui Liu, Yaping Hua, Jigang Zhang, Randi Hovland, Mihaela Popa, Xiaojun Liu, Karl A. Brokstad, Ronald Simon, Anders Molven, Biaoyang Lin, Wei-dong Zhang, Emmet McCormack, Karl-Henning Kalland, and Xi-Song Ke

Precise: A novel stepwise-generated model of human prostate carcinogenesis reveals an intrinsic association of ROS and IL-6/STAT3 signaling, illuminating this relationship and defining therapeutic targets in this setting.
7101 In Vivo MAPK Reporting Reveals the Heterogeneity in Tumoral Selection of Resistance to RAF Inhibitors
Kevin J. Basile, Ethan V. Abel, Neda Dadpey, Edward J. Hartsough, Paolo Fortina, and Andrew E. Aplin
Précis: This article describes a novel in vivo system for noninvasive evaluation of a kinase-mediated mechanism of acquired resistance to BRAF-targeting drugs, an area of present clinical challenge for treating metastatic melanoma.

7111 Neuropilin-2 Is Upregulated in Lung Cancer Cells during TGF-β1–Induced Epithelial–Mesenchymal Transition
Patrick Nasarre, Robert M. Gemmill, Vincent A. Potiron, Joëlle Roche, Xian Lu, Anna E. Barón, Christopher Korch, Elizabeth Garrett-Mayer, Alessandro Lagana, Philip H. Howe, and Harry A. Drabkin
Précis: These findings provide insights into how TGF-β1 mediates invasion and tumorigenesis and identify a novel therapeutic target that may prevent or reverse EMT associated with metastatic progression.

7122 BCCIP Suppresses Tumor Initiation but Is Required for Tumor Progression
Yi-Yuan Huang, Li Dai, Dakim Gaines, Roberto Droz-Rosario, Huimei Lu, Jingmei Liu, and Zhiyuan Shen
Précis: This study describes a paradoxical tumor suppressor that can also promote cancer progression, serving as a prototype for a class of suppressors that does not need to be permanently inactivated to trigger tumorigenesis.

7134 Molecular Profiling of Tumor Cells in Cerebrospinal Fluid and Matched Primary Tumors from Metastatic Breast Cancer Patients with Leptomeningeal Carcinomatosis
Mark Jesus M. Magbanua, Michelle Melisko, Ritu Roy, Eduardo V. Sosa, Louai Hauranieh, Andrea Kablanian, Lauren E. Eisenbud, Artem Byazantsev, Alfred Au, Janet H. Scott, and John W. Park
Précis: This study describes a method for molecular analysis of tumor cells isolated from cerebrospinal fluid, shedding light on their molecular characteristics and suggesting candidate biomarkers and therapeutic targets relevant to metastatic spread in the central nervous system.

LETTERS TO THE EDITOR

7144 Benefits of Vascular Normalization Are Dose and Time Dependent—Letter
Yuhui Huang, Triantafyllos Stylianos, Dan G. Duda, Dai Fukumura, and Rakesh K. Jain

7147 Bevacizumab-Induced Vessel Normalization Hampers Tumor Uptake of Antibodies—Response
Marlous Arjaans, Sjoukje F. Oosting, Carolina P. Schröder, and Elisabeth G.E. de Vries

ABOUT THE COVER
Carbon monoxide (CO) at therapeutic concentrations induces growth arrest of lung and prostate cancer cell lines and tumors. CO is generated endogenously as a bioactive signaling molecule by the cytoprotective gene heme oxygenase-1 (HO-1). In cancer cells, HO-1 activity, and thus endogenous CO levels, is decreased and can be rescued by delivery of exogenous CO. Astonishingly, CO sensitizes cancer cells to chemotherapeutic agents while simultaneously protecting normal cells from genotoxin-induced cell death. The mechanism of CO involves its propensity to bind to heme-containing oxidases in mitochondria. Shown here are prostate cancer cells (PC3) exposed to CO in the presence of the genotoxin doxorubicin, which resulted in a dramatic shift in mitochondrial membrane potential and metabolic collapse driven by an anti-Warburg effect. Using MitoTracker Red CMXRos staining (red), which fluoresces when a cell is actively respiring, Wegiel and colleagues observed that CO decreased respiration and mitochondrial membrane potential, indicative of mitochondrial failure. Nuclei were stained with Hoechst (blue). For details, see article by Wegiel and colleagues on page 7009.

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