Highlights from Recent Cancer Literature

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. Cholewa, Xiaosu 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 Yeheskell, Addie Dvir, Lior Soussan-Gutman, Dinath Jeselsohn, Myles Brown, Vincent A. Miller, David Sarid, Shulamith Rizel, Baruch Klein, Tami Rubinek, 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 Rebecchi, Inna V. Fedorenko, Jane L. Messina, Rahel Mathew, Silvya S. Marta-Engler, David Basanta, Keiran S.M. Smalley, 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 Hessev, Alkaterini Pipili, Veronica Mariotti, Bharath Buchupalli, Katie Foster, Dominique Bonnet, Agamemnon Grigoriadis, Pranela Rameshvar, 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
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Carbon Monoxide Expedites Metabolic Exhaustion to Inhibit Tumor Growth
Barbara Wegiel, David Gallo, Eva Csizmadia, Clair Harris, John Belcher, Gregory M. Vercellotti, Leszek Helcynski, Tumor and Stem Cell Biology

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

PTEN Loss Mitigates the Response of Medulloblastoma to Hedgehog Pathway Inhibition

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

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, Huiping Gao, Shun Lu, Ming Yao, Ying Mao, Hong-Yang Wang, Shengli Yang, Jianren Gu, Chuanyuan Li, and Zonghai Li

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

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

Generation of Prostate Tumor–Initiating Cells Is Associated with Elevation of Reactive Oxygen Species and IL-6/STAT3 Signaling
Yi Qu, Anne Margrete Oyan, Ruhui Liu, Yaping Hua, Jiqiang 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 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.

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

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

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.

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.

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.
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

Precis: 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.

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

Precis: 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.

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

Precis: 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.

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 Byzantsev, Alfred Au, Janet H. Scott, and John W. Park

Precis: 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.

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

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.