BREAKING ADVANCES

1 Highlights from Recent Cancer Literature

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4 Tumor Heterogeneity—A ‘Contemporary Concept’ Founded on Historical Insights and Predictions
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18 A New View of Ras Isoforms in Cancers
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PRIORITY REPORTS

24 A Sucrose-Enriched Diet Promotes Tumorigenesis in Mammary Gland in Part through the 12-Lipoxygenase Pathway
Yan Jiang, Yong Pan, Patrea R. Rhea, Lin Tan, Mihai Gagea, Lorenzo Cohen, Susan M. Fischer, and Peiyang Yang
Précis: Results offer preclinical evidence that fructose derived from dietary sugar increases risks of breast cancer development and metastasis via production of pro-inflammatory lipids.

30 Mitochondrial DNA Repair through OGG1 Activity Attenuates Breast Cancer Progression and Metastasis
Larysa V. Yuzevovych, Andrea G. Kahn, Michele A. Schuler, Lars Eide, Ritu Arora, Glenn L. Wilson, Ming Tan, and Lyudmila I. Rachek
Précis: These findings show that DNA damage in mitochondria promotes breast cancer progression and metastasis, offering a preclinical rationale to promote DNA repair in this organelle.

35 M-CSF and GM-CSF Receptor Signaling Differentially Regulate Monocyte Maturation and Macrophage Polarization in the Tumor Microenvironment
Eva Van Overmeire, Benoît Stijlemans, Felix Heymann, Jiri Keirse, Yannick Morias, Yvon Elkrin, Lea Brys, Chloé Abels, Qods Lahmar, Can Ergen, Lars Vereecke, Frank Tacke, Patrick De Baetserier, Jo A Van Ginderachter, and Damya Laoui
Précis: Myeloid colony-stimulating factors exert opposing effects in regulating the phenotype of tumor-associated macrophages, with potentially important implications for the development of cancer immunotherapies targeting innate immune cells.

43 Noninvasive Quantification of 2-Hydroxyglutarate in Human Gliomas with IDH1 and IDH2 Mutations
Uzay E. Emir, Sarah J. Larkin, Nick de Pennington, Natalie Voets, Puneet Plaha, Richard Stacey, Khalid Al-Qahtani, James McCullagh, Christopher J. Schofield, Stuart Clare, Peter Jezzard, Tom Cadoux-Hudson, and Olaf Ansonge
Précis: A rapid, noninvasive, and quantitative detection method for 2-hydroxyglutarate in human glioblastomas can distinguish IDH1 and IDH2 mutations in vivo, with implications for improving diagnosis and therapeutic monitoring of this disease.

MICROENVIRONMENT AND IMMUNOLOGY

50 Radiotherapy Combined with Novel STING-Targeting Oligonucleotides Results in Regression of Established Tumors
Jason R. Baird, David Friedman, Benjamin Cottam, Thomas W. Dubensky, Jr., David B. Kanne, Shelly Bambina, Keith Bahajat, Marka R. Crittenden, and Michael J. Gough
Précis: These exciting findings offer a preclinical rationale to immediately investigate in clinic the powerful properties of a novel ligand of STING—one of the most provocative immunotherapeutic targets at present—in enhancing the efficacy of neoadjuvant or adjuvant radiotherapy for human cancers.
62 Immunotargeting of Antigen xCT Attenuates Stem-like Cell Behavior and Metastatic Progression in Breast Cancer
Stefania Lanzardo, Laura Conti, Ronald Rooke, Roberto Ruiu, Nathalie Accart, Elisabetta Bolli, Maddalena Arigoni, Marco Macagno, Giuseppina Barrera, Stefania Pizzimenti, Luigi Aurisicchio, Raffaele Adolfo Calogero, and Federica Cavallo
Précis: Immunotargeting of breast cancer stem-like cells can sensitize them to chemotherapy, offering an effective strategy to overcome drug resistance and to limit metastatic progression.

73 An Effective Immuno-PET Imaging Method to Monitor CD8-Dependent Responses to Immunotherapy
Richard Tavare, Helena Escuin-Ordinas, Stephen Mok, Melissa N. McCracken, Kirstin A. Zettlitz, Felix B. Salazar, Owen N. Witte, Antoni Ribas, and Anna M. Wu
Précis: A sensitive noninvasive method to detect endogenous CD8⁺ cytotoxic T cells offers a tool to evaluate the response to many cancer immunotherapies.

83 Ubiquitin-Specific Protease 4-Mediated Deubiquitination and Stabilization of PRL-3 Is Required for Potentiating Colorectal Oncogenesis
Cheng Xing, Xing-Xing Lu, Peng-Da Guo, Tong Shen, Shen Zhang, Xiao-Shun He, Wen-Juan Gan, Xiu-Ming Li, Jing-Ru Wang, Yuan-Yuan Zhao, Hua Wu, and Jian-Ming Li
Précis: Proteolytic degradation pathways, which exert oncogenic effects in colorectal cancer, suggest a new class of therapeutic targets that are aberrantly expressed in that disease setting.

96 PLAC8 Localizes to the Inner Plasma Membrane of Pancreatic Cancer Cells and Regulates Cell Growth and Disease Progression through Critical Cell-Cycle Regulatory Pathways
Précis: A multifunctional protein absent from healthy or chronically inflamed pancreatic tissues, but widely expressed in most pancreatic cancers, is found to be a pivotal regulator of cell growth and progression in this disease.

108 Identification of Novel Fusion Genes in Testicular Germ Cell Tumors
Andreas M. Hoff, Sharmini Alagaratnam, Sen Zhao, Jarle Bruun, Peter W. Andrews, Raghlaid A. Lothe, and Rolf I. Skotheim
Précis: This study identifies genetic drivers of malignancy and biomarkers of disease progression in testicular tumors, specifically revealing fusion oncogenes that have not been described previously in this disease.

117 Multikinase Inhibitors Induce Cutaneous Toxicity through OAT6-Mediated Uptake and MAP3K7-Driven Cell Death
Précis: The mechanism underlying a side effect of multikinase inhibitors affecting the skin suggests a rational basis for therapeutic management of this condition.

127 Identification and Characterization of Tyrosine Kinase Nonreceptor 2 Mutations in Leukemia through Integration of Kinase Inhibitor Screening and Genomic Analysis
Julia E. Maxson, Melissa L. Abel, Jinhua Wang, Xianming Deng, Sina Reckel, Samuel B. Luty, Hua Huang Sun, Julie Gorenstein, Seamus B. Hughes, Daniel Bottomly, Beth Wilmot, Shannon K. McWreney, Jared Radich, Oliver Hantschel, Richard E. Middleton, Nathanael S. Gray, Brian J. Drucker, and Jeffrey W. Tyner
Précis: A new method to identify and prioritize functionally important genetic mutations in leukemia highlights TNK2 as an actionable therapeutic target.

139 Connexin 43 Inhibition Sensitizes Chemoresistant Glioblastoma Cells to Temozolomide
Susan F. Murphy, Robin T. Varghese, Samy Lamouille, Sujuan Guo, Kevin J. Pridham, Pratik Kanabur, Alyssa M. Osmani, Shaan Sharma, Jane Jourdan, Cara M. Rodgers, Gary R. Simonds, Robert G. Gourdie, and Zhi Sheng
Précis: A cell-cell communication channel may offer a theranostic biomarker to predict survival of certain glioblastoma patients who are resistant to temozolomide, a standard-of-care drug used widely for treatment.

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TUMOR AND STEM CELL BIOLOGY

150 Establishment and Characterization of an In Vitro Model of Ovarian Cancer Stem-like Cells with an Enhanced Proliferative Capacity

Précis: These findings highlight a new method to culture human ovarian stem-like cells, defining a reciprocal relationship between established regulators, which impact malignant progression in this disease setting.

161 H3K27 Demethylase JMJD3 Employs the NF-κB and BMP Signaling Pathways to Modulate the Tumor Microenvironment and Promote Melanoma Progression and Metastasis
Woo-Yong Park, Beom-Jin Hong, Jungsul Lee, Chulhee Choi, and Mi-Young Kim

Précis: This study focuses on a histone demethylase that appears to be critical for shaping a favorable tumor microenvironment for invasion and metastasis, with implications for broadly undercutting local tissue supports for malignant progression in a disease-selective manner.

171 Eva1 Maintains the Stem-like Character of Glioblastoma-Initiating Cells by Activating the Noncanonical NF-κB Signaling Pathway
Naoki Ohtsu, Yuka Nakatani, Daisuke Yamashita, Shiro Ohue, Takanori Ohnishi, and Toru Kondo

Précis: These findings define a new theranostic marker of glioblastoma-initiating cells and offer a preclinical rationale for its further exploration in targeted therapeutic strategies.

CORRECTION

182 Correction: miR326 Maturation Is Crucial for VEGF-C–Driven Cortactin Expression and Esophageal Cancer Progression

ABOUT THE COVER

Cyclic dinucleotides injected into tumors result in rapid hemorrhagic necrosis by activating the sensor STING. To examine expression of STING in the tumor environment, Panc02 pancreatic adenocarcinoma tumors grown in immune competent mice were stained for the macrophage marker F4/80 (red), STING (green), and the DAPI nuclear counterstain (blue). Both the cancer cells and the tumor stroma, including F4/80+ tumor macrophages, expressed STING; however, in STING−/− mice, cyclic dinucleotides had no effect, indicating that it is the stromal rather than cancer expression of STING that mediates this effect. For details, see article by Baird and colleagues on page 50.