BREAKING ADVANCES

5187  Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY

COMMENTARIES

5189  p21(WAF1) Mediates Cell-Cycle Inhibition, Relevant to Cancer Suppression and Therapy
Wafik S. El-Deiry

5192  Commentary on "Recombinant Humanized Anti-HER2 Antibody (Herceptin) Enhances the Antitumor Activity of Paclitaxel and Doxorubicin against HER2/neu Overexpressing Human Breast Cancer Xenografts" (A Follow Up)
John Mendelsohn

REVIEWS

5195  Molecular or Metabolic Reprograming: What Triggers Tumor Subtypes?
Katherine Eason and Anguraj Sadanandam

5201  Metabolic Plasticity as a Determinant of Tumor Growth and Metastasis
Camille Lehu, Fanny Dupuy, Rebecca Rabinovitch, Russell G. Jones, and Peter M. Siegel

INTEGRATED SYSTEMS AND TECHNOLOGIES

5209  Enhanced Survival with Implantable Scaffolds That Capture Metastatic Breast Cancer Cells In Vivo
Précis: Microscaffolds to absorb metastatic cells in the circulation can be used to detect these cells and even reduce tumor burden in solid organs to enhance survival after resection of a primary tumor.

5219  JNK Pathway Activation Modulates Acquired Resistance to EGFR/HER2-Targeted Therapies
Simin Manole, Edward J. Richards, and Aaron S. Meyer
Précis: These findings suggest immediate repositioning for clinical evaluation of JNK kinase inhibitors, which have found few useful applications in the clinic as yet, in drug combinations to limit acquired resistance, which arise commonly in patients treated with tyrosine kinase inhibitors.

5229  Lack of p53 Augments Antitumor Functions in Cytolytic T Cells
Précis: These findings suggest that p53 regulates glycolytic commitment and TGFß signaling in T cells, such that inhibiting p53 could improve T-cell persistence and tumor control in adoptive immunotherapy.

5241  Accumulation of MDSC and Th17 Cells in Patients with Metastatic Colorectal Cancer Predicts the Efficacy of a FOLFOX-Bevacizumab Drug Treatment Regimen
Emeric Limagne, Romain Euvrard, Marion Thibaudin, Cédric Rébé, Valentin Derangère, Angélique Cheviaux, Romain Boidot, Frédérique Végran, Nathalie Bornefoy, Julie Vincent, Leila Bengrine-Lefèvre, Sylvain Ladoire, Dominique Delmas, Lionel Apestoh, and François Ghiringhelli
Précis: This study provides a clinical rationale to combine FOLFOX-bevacizumab chemotherapy with inhibitors of ATP ectonucleotidases and PD-1/PD-L1 checkpoint inhibitors to more effectively treat metastatic colorectal cancer.

5253  Splenic Marginal Zone Granulocytes Acquire an Accentuated Neutrophil B-Cell Helper Phenotype in Chronic Lymphocytic Leukemia
Marcel Gätjen, Franziska Brand, Michael Grau, Kerstin Gerlach, Ralph Kettirits, Jörg Westermann, Ioannis Anagnostopoulos, Peter Lenz, Georg Lenz, Uta E. Höpken, and Armin Rehm
Précis: These results suggest that targeting aberrant neutrophil differentiation and restoring myeloid cell homeostasis could limit the formation of survival niches for chronic B lymphocytic leukemia cells, with implications for therapeutic management.

5266  In Vivo FRET Imaging of Tumor Endothelial Cells Highlights a Role of Low PKA Activity in Vascular Hyperpermeability
Fumio Yamauchi, Yuji Kamioka, Tetsuya Yano, and Michiyuki Matsuda
Précis: These findings suggest that VEGF signaling increases vascular permeability by reducing endothelial PKA activity in tumor tissue, at least in part.
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5277 Tissue Stiffness and Hypoxia Modulate the Integrin-Linked Kinase ILK to Control Breast Cancer Stem-like Cells
Mei-Fong Pang, Michael J. Siedlik, Siyang Han, Melody Stallings-Mann, Derek C. Radisky, and Celeste M. Nelson
Précis: These results show how an important mechanotransducer controls the development of breast cancer stem-like cells in response to tissue stiffness and oxygen tension.

5288 Assessing Immune-Related Adverse Events of Efficacious Combination Immunotherapies in Preclinical Models of Cancer
Jing Liu, Stephen J. Blake, Heidi Harjumää, Kirsten A. Fairfax, Michelle C.R. Yong, Stacey Allen, Holbrook E. Kuhl, Kazuyoshi Takeda, Mark J. Smyth, and Michele W.L. Teng
Précis: This study reports the development of a useful mouse model to preclinically assess the therapeutic window of novel immunotherapy combinations, to better understand the balance between their mechanisms of action and safety.

5302 Monocyte Induction of E-Selectin–Mediated Endothelial Activation Releases VE-Cadherin Junctions to Promote Tumor Cell Extravasation in the Metastasis Cascade
Irina Hauselmann, Marko Roblek, Darya Protsyuk, Volker Huck, Lucia Knoplova, Sandra Gräsle, Alexander T. Bauer, Stefan W. Schneider, and Lubor Borsig
Précis: These findings provide mechanistic insight into how activated endothelial cells recruit inflammatory monocytes to promote tumor cell extravasation by loosening a specific class of tight junctions.

5313 Endosialin-Expressing Pericytes Promote Metastatic Dissemination
Carmen Viski, Courtney König, Magdalena Kijewska, Carolin Mogler, Clare M. Hackett, and Hellmut G. Augustin
Précis: This study shows how primary tumor-associated pericytes promote tumor cell intravasation, resulting in elevated numbers of circulating tumor cells and enhanced metastasis.

5326 Identification of a Natural Killer Cell Receptor Allele That Prolongs Survival of Cytomegalovirus-Positive Glioblastoma Patients
Mev Dominguez–Valentin, Andrea Gras Navarro, Aminur Mohummad Rahman, Surendra Kumar, Christèle Retière, Elbing Ulvestad, Vessela Kristensen, Morten Lund-Johansen, Benedicte Alexandra Lie, Per Øyvind Enger, Gro Njølstad, Einar Kristoffersen, Stein Atle Lie, and Martha Chekenya
Précis: These findings identify a specific genetic allele of a natural killer immune cell receptor that may provide a biomarker of intrinsically milder forms of glioblastoma.

5337 Jak1–STAT3 Signals Are Essential Effectors of the USP6/TRE17 Oncogene in Tumorigenesis
Laura Quick, Robert Young, Ian C. Henrich, Xiaoke Wang, Yan W. Asmann, Andre M. Oliveira, and Margaret M. Chou
Précis: In defining Jak1 as one of the first substrates for the oncoprotein USP6, this study offers a mechanistic rationale to clinically explore Jak and STAT3 inhibitors to treat bone and soft tissue tumors, which are driven by activated USP6.

5348 Calcium-Sensing Receptor Promotes Breast Cancer by Stimulating Intracrine Actions of Parathyroid Hormone–Related Protein
Wonnam Kim, Farzin M. Takyar, Karena Swan, Jae-kwang Jeong, Joshua VanHouten, Catherine Sullivan, Pamela Dann, Herbert Yu, Nathalie Fiaschi-Taesch, Wenhan Chang, and John Wysolomdenki
Précis: These findings define a novel locus for the development of therapeutic agents to limit bone metastasis, a feature of many advanced cancers lacking effective tools for clinical management.

5351 Long Noncoding RNA GCASPC, a Target of miR-17-3p, Negatively Regulates Pyruvate Carboxylase–Dependent Cell Proliferation in Gallbladder Cancer
Ming-zhe Ma, Yan Zhang, Ming-zhe Weng, Shou-hua Wang, Ye Hu, Zhao-yuan Hou, Yi-yu Qin, Wei Gong, Yong-Jie Zhang, Xiang Kong, Jian-dong Wang, and Zhi-wei Quan
Précis: Results define a novel mechanism of cell proliferation regulated by a long noncoding RNA in gallbladder cancer, illuminating a new basis to understand its aggressive pathogenicity.

5372 Differential Effects of IL6 and Activin A in the Development of Cancer-Associated Cachexia
Justin L. Chen, Kelly L. Walton, Hongwei Qian, Timothy D. Colgan, Adam Hagg, Matthew J. Watt, Craig A. Harrison, and Paul Gregorevic
Précis: This study presents a useful model to deconstruct the complex muscle-wasting condition associated with cancer called cachexia, with immediate clinical implications on how to block or slow this devastating condition in cancer patients.
The NSL Chromatin-Modifying Complex Subunit KANSL2 Regulates Cancer Stem–like Properties in Glioblastoma That Contribute to Tumorigenesis
Nazarena E. Ferreyra Solari, Fiorella S. Belforte, Lucia Canedo, Guillermo A. Videla-Richardson, Joaquin M. Espinosa, Mario Rossi, Eva Serna, Miguel A. Riusavets, Horacio Martinetto, Gustavo Sevlever, and Carolina Perez-Castro

Précis: This finding describes how a protein involved in epigenetic program regulates the development of cancer stem-like cells in glioblastoma, with possible implications for development of clinical prognostic biomarker.

Cancer-Associated Fibroblasts in Pancreatic Cancer Are Reprogrammed by Tumor-Induced Alterations in Genomic DNA Methylation
Qian Xiao, Donger Zhou, Agnieszka A. Rucki, Jamila Williams, Jiaojiao Zhou, Guanglan Mo, Adrian Murphy, Kenji Fujiwara, Jennifer Kleponis, Bulent Salman, Christopher L. Wolfgang, Robert A. Anders, Shu Zheng, Elizabeth M. Jaffee, and Lei Zheng

Précis: These results illuminate how pancreatic cancer cells program cancer-associated fibroblasts to direct tumor-stromal interactions in the tumor microenvironment.

BTK Modulates p53 Activity to Enhance Apoptotic and Senescent Responses
Mohammad Althubiti, Miran Rada, Jesvin Samuel, Josep M. Escorsa, Hishyar Najeeb, Koon-Guan Lee, Kong-Peng Lam, George D.D. Jones, Nikolai A. Barlev, and Salvador Macip

Précis: This study raises some concern about using Bruton's tyrosine kinase inhibitors to treat leukemia, based on the finding that BTK stimulates p53 activity and reinforces tumor suppression.

Exercise and Prognosis on the Basis of Clinicopathologic and Molecular Features in Early-Stage Breast Cancer: The LACE and Pathways Studies
Lee W. Jones, Marilyn L. Kwan, Erin Weltzien, Sarat Chandrarapaty, Barbara Sternfeld, Carol Sweeney, Philip S. Bernard, Adrienne Castillo, Laurel A. Habel, Candye H. Kroenke, Bryan M. Langholz, Charles P. Queensberry Jr., Chau Dang, Britta Weigelt, Lawrence H. Kushi, and Bette J. Caan

Précis: These findings support the assertion that exercise positively influences cancer outcomes in early-stage breast cancer patients, but variably based on differences in pathologic and molecular features between individuals.

Plasma 25-Hydroxyvitamin D and Risk of Breast Cancer in Women Followed over 20 Years

Précis: This study examines the association between circulating levels of 25-hydroxyvitamin D, a biomarker of vitamin D status, and breast cancer risk, as well as tumor expression of the vitamin D receptor that is key to the biologic activity of this biomarker.

Inhibiting Mitochondrial DNA Ligase IIIα Activates Caspase 1–Dependent Apoptosis in Cancer Cells
Anahita Sallmyr, Yoshihiro Matsumoto, Vera Roginskaya, Bennett Van Houten, and Alan E. Tomkinson

Précis: These results offer evidence that a specific mechanism of mitochondrial DNA metabolism can serve as a therapeutic target for cancer treatment.

SMAC Mimetic Birinapant plus Radiation Eradicates Human Head and Neck Cancers with Genomic Amplifications of Cell Death Genes FADD and BIRC2

Précis: These provocative findings support the evaluation of genomic alterations for a class of targeted apoptosis-inducing drugs to improve the response of head-and-neck cancers to irradiation.

An In Vivo Reporter to Quantitatively and Temporally Analyze the Effects of CDK4/6 Inhibitor-Based Therapies in Melanoma
Jessica L.F. Teh, Timothy J. Purwin, Evan J. Greenawalt, Inna Chervoneva, Allison Goldberg, Michael A. Davies, and Andrew E. Aplin

Précis: The results of this study may inform ongoing and future clinical trials utilizing CDK4/6 inhibitors for the treatment of cutaneous melanoma.
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5467 SIRT2 Deacetylates and Inhibits the Peroxidase Activity of Peroxiredoxin-1 to Sensitize Breast Cancer Cells to Oxidant Stress-Inducing Agents
Warren Fiskus, Veena Coothankandawamy, Jianguang Chen, Hongwei Ma, Kyungsoo Ha, Dyana T. Saenz, Stephanie S. Kriegier, Christopher P. Mill, Basuha Sun, Peng Huang, Jeffrey S. Mummm, Ari M. Melnick, and Kapil N. Bhalla
Précis: These findings show that by undermining the function of peroxiredoxin-1, SIRT2 unleashes a critical pro-oxidant function responsible for sensitizing breast cancer cells to reactive oxygen species, suggesting a new target to attack for therapeutic purposes.

5479 A Cell-Penetrating Peptide Targeting AAC-11 Specifically Induces Cancer Cells Death
Léonard Jagot-Lacoussière, Ewa Kotula, Bruno O. Villoutreix, Heriberto Bruzzoni-Giovanelli, and Jean-Luc Poyer
Précis: This study provides preclinical evidence for the cancer therapeutic value of a cell-penetrating peptide that targets the scaffolding function of a little-understood antiapoptotic protein.

5491 A Small-Molecule Antagonist of HIF2α Is Efficacious in Preclinical Models of Renal Cell Carcinoma
Précis: This important study offers preclinical proof of concept for a mechanistically novel class of therapeutics to treat kidney cancers, validating HIF2α as a pathogenic driver and demonstrating efficacy as well as reduced cardiovascular risk relative to other existing agents that target the VEGF pathway.

5501 NUDT15 Hydrolyzes 6-Thio-DeoxyGTP to Mediate the Anticancer Efficacy of 6-Thioguanine
Précis: These results define an important mechanism of response to thiopurines, a class of cancer chemotherapy used commonly to treat childhood leukemia, and how certain genetic variants in patients confer sensitivity to thiopurine treatment, providing insights into how to extend cures in these pediatric diseases.

5512 Decoding Intratumoral Heterogeneity of Breast Cancer by Multiparametric In Vivo Imaging: A Translational Study
Précis: In presenting the potential of hybrid PET/MRI imaging to decode tumor heterogeneity noninvasively, this translational study shows that it may be possible to diagnose cancers in a more comprehensive as well as noninvasive manner.

5523 Integrative Genome-Scale Analysis Identifies Epigenetic Mechanisms of Transcriptional Deregulation in Unfavorable Neuroblastomas
Kai-Oliver Henrich, Sebastian Bender, Maral Saadati, Daniel Dreidax, Moritz Gartguber, Chunxuan Shao, Carl Herrmann, Manuel Wiesendarth, Martha Parzonka, Lea Wehrmann, Matthias Fischer, David J. Duffy, Emma Bell, Alica Torkov, Peter Schneer, Christoph Plass, Thomas Höfer, Axel Benner, Stefan M. Pfister, and Frank Westermann
Précis: As shown in this study, epigenetic deregulation contributes to the development of high-risk neuroblastomas through repression of differentiation programs via PRC2 hyperactivity and aberrant methylation of regulatory DNA elements including intragenic enhancers.

5538 JARID1B Enables Transit between Distinct States of the Stem-like Cell Population in Oral Cancers
Nicole D. Facompre, Kayla M. Harmeyer, Xavier Sole, Shereeyar Kabraji, Zachary Belden, Varun Sahu, Kelly Whelan, Koji Tanaka, Gregory S. Weinstein, Kathleen T. Montone, Alexander Roesch, Phyllis A. Gimotty, Meenhard Herlyn, Anil K. Rustgi, Hiroshi Nakagawa, Sridhar Ramaswamy, and Devraj Basu
Précis: This study of a quiescent subset of oral cancer cells that can acquire stem-like cell markers offers a new conceptual basis to understand the plasticity and heterogeneity of stem-like cells in cancer, with implications for their therapeutic targeting.
Inducing Differentiation of Premalignant Hepatic Cells as a Novel Therapeutic Strategy in Hepatocarcinoma
Benita Wolf, Kathrin Krieg, Christine Falk, Kai Breuhahn, Hildegard Keppeler, Tilo Biedermann, Evi Schmid, Steven Warnmann, Joerg Fuchs, Silvia Vetter, Dennis Thiele, Maike Nieser, Meltem Avci-Adali, Yulia Skokowa, Ludger Schols, Stefan Hauser, Marc Ringelhan, Tetyana Yevsa, Mathias Heikenwalder, and Uta Kossatz-Boehlert

Précis: This study offers a mechanistic rationale for a combinational therapeutic approach to deplete liver tumor-initiating cells arrested in G1 phase of the cell cycle.

miR-9 and miR-200 Regulate PDGFRβ-Mediated Endothelial Differentiation of Tumor Cells in Triple-Negative Breast Cancer
Elvira D’Ippolito, Ilaria Plantamura, Lucia Bongiovanni, Patrizia Casalini, Sara Baroni, Claudia Piован, Rosaria Orlandi, Ambra V. Guademi, Annunziata Gloghini, Anna Rossini, Sara Cresta, Anna Tessari, Filippo De Braud, Gianpiero Di Leva, Claudio Tripodo, and Marilena V. Iorio

Précis: Results suggest a strategy to block tumor vascularization and bypass resistance to antiangiogenic therapies in aggressive triple-negative breast cancers, by attacking tumor-to-endothelial transdifferentiation.

Nestin Mediates Hedgehog Pathway Tumorigenesis
Peng Li, Eric H. Lee, Fang Du, Renata E. Gordon, Larra W. Yuelling, Yongqiang Liu, Jessica M.Y. Ng, Hao Zhang, Jinhua Wu, Andrey Korshunov, Stefan M. Pfister, Tom Curran, and Zeng-jie Yang

Précis: Beyond serving as a biomarker for cancer stem-like cells, Nestin is shown in this study to drive hedgehog pathway-associated cancers such as medulloblastoma, one type of poorly managed brain tumor.

Correction: An IkBα Inhibitor Causes Leukemia Cell Death through a p38 MAP Kinase-dependent, NF-κB-independent Mechanism