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.

5216 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.

MICROENVIRONMENT AND IMMUNOLOGY

5229 Lack of p53 Augments Antitumor Functions in Cytolytic T Cells
Précis: These findings suggest that p53 regulates glycolytic commitment and TGFβ 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
Emerick Limagne, Romain Euvrard, Marion Thibaudin, Cédric Rébé, Valentin Derangé, Angélique Cheviaux, Romain Boidot, Frédérique Végran, Nathalie Bornefroy, Julie Vincent, Leila Bengrine-le-Fevere, 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 Gátjen, Franziska Brand, Michael Grau, Kerstin Gerlach, Ralph Kettiritz, 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 Yamachi, 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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<td>Tissue Stiffness and Hypoxia Modulate the Integrin-Linked Kinase ILK to Control Breast Cancer Stem-like Cells</td>
<td>Mei-Fong Pang, Michael J. Siedlik, Siyang Han, Melody Stallings-Mann, Derek C. Radisky, and Celeste M. Nelson</td>
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<td><strong>Précis:</strong> These results show how an important mechanotransducer controls the development of breast cancer stem-like cells in response to tissue stiffness and oxygen tension.</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>5302</td>
<td>Monocyte Induction of E-Selectin-Mediated Endothelial Activation Releases VE-Cadherin Junctions to Promote Tumor Cell Extravasation in the Metastasis Cascade</td>
<td>Irina Hauselmann, Marko Roblek, Darya Protsyuk, Volker Huck, Lucija Knoplova, Sandra Grasel, Alexander T. Bauer, Stefan W. Schneider, and Lubor Bonsig</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>5313</td>
<td>Endosialin-Expressing Pericytes Promote Metastatic Dissemination</td>
<td>Carmen Viski, Courtney König, Magdalena Kijewska, Carolin Mogler, Clare M. Hacke, and Hellmut G. Augustin</td>
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<td><strong>Précis:</strong> This study shows how primary tumor-associated pericytes promote tumor cell intravasation, resulting in elevated numbers of circulating tumor cells and enhanced metastasis.</td>
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<td>5326</td>
<td>Identification of a Natural Killer Cell Receptor Allele That Prolongs Survival of Cytomegalovirus-Positive Glioblastoma Patients</td>
<td>Mervin Dominguez-Valentin, Andrea Grz Navarro, Aminur Mohummad Rahman, Surentran Kumar, Christèle Retiere, Elling Ulvestad, Vessela Kristensen, Morten Lund-Johansen, Benedicte Alexandra Lie, Per Øyvind Enger, Gro Njølstad, Einar Kristoffersen, Stein Atle Lie, and Martha Chekenya</td>
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<td><strong>Précis:</strong> 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.</td>
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### MOLECULAR AND CELLULAR PATHOBIOLOGY

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<td>Jak1–STAT3 Signals Are Essential Effectors of the USP6/TRE17 Oncogene in Tumorigenesis</td>
<td>Laura Quirk, Robert Young, Ian C. Henrich, Xiaoke Wang, Yan W. Asmann, Andre M. Oliveira, and Margaret M. Chou</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>5348</td>
<td>Calcium-Sensing Receptor Promotes Breast Cancer by Stimulating Intracrine Actions of Parathyroid Hormone–Related Protein</td>
<td>Wonnam Kim, Farzin M. Takyar, Karena Swan, Jaekwang Jeong, Joshua VanHouten, Catherine Sullivan, Pamela Dann, Herbert Yu, Nathalie Fiaschi-Taesch, Wenhan Chang, and John Wysolomdenki</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>Long Noncoding RNA GCASPC, a Target of miR-17-3p, Negatively Regulates Pyruvate Carboxylase–Dependent Cell Proliferation in Gallbladder Cancer</td>
<td>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</td>
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<td><strong>Précis:</strong> 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.</td>
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<td>5372</td>
<td>Differential Effects of IL6 and Activin A in the Development of Cancer-Associated Cachexia</td>
<td>Justin L. Chen, Kelly L. Walton, Hongwei Qian, Timothy D. Colgan, Adam Hagg, Matthew J. Watt, Craig A. Harrison, and Paul Gregorevic</td>
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<td><strong>Précis:</strong> This study presents a useful model to deconstruct the common muscle-wasting condition associated with cancer called cachexia, with immediate clinical implications on how to block or slow this devastating condition in cancer patients.</td>
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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. Riuavets, 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, Yong Peng Lam, George D.D. Jones, Nickolai 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.

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 III α 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.
5501  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.

5509  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.

5512  JARID1B Enables Transit between Distinct States of the Stem-like Cell Population in Oral Cancers

Nicole D. Facompre, Kayla M. Harmsen, Xavier Sole, Sheshenvar 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 Warmann, Joerg Fuchs, Silvia Vetter, Dennis Thiele, Maike Nieser, Meltem Avci-Adali, Yulia Skokowa, Ludger Schöls, 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 Piovan, Rosaria Orlandi, Ambra V. Guadani, 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 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 IxBα Inhibitor Causes Leukemia Cell Death through a p38 MAP Kinase-dependent, NF-κB-independent Mechanism

ABOUT THE COVER

Nestin, a type VI intermediate filament protein, plays a critical role in the tumorigenesis of hedgehog pathway-driven medulloblastoma. Loss of Nestin dramatically inhibited proliferation and promoted differentiation of medulloblastoma cells. By counterstaining with DAPI, no tumor mass was found in the cerebella of immunocompromised mice after transplantation with Nestin-deficient medulloblastoma cells. For details, see article by Li and colleagues on page 5573.