

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 Reprogramming: What Triggers Tumor Subtypes?
Katherine Eason and Anguraj Sadanandam
- 5201** Metabolic Plasticity as a Determinant of Tumor Growth and Metastasis
Camille Lehuédé, 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*
Shreyas S. Rao, Grace G. Bushnell, Samira M. Azarin, Graham Spicer, Brian A. Aguado, Jenna R. Stoehr, Eric J. Jiang, Vadim Backman, Lonnie D. Shea, and Jacqueline S. Jeruss
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.

MICROENVIRONMENT AND IMMUNOLOGY

- 5229** Lack of p53 Augments Antitumor Functions in Cytolytic T Cells
Anirban Banerjee, Krishnamurthy Thyagarajan, Shilpak Chatterjee, Paramita Chakraborty, Pravin Kesarwani, Myroslawa Soloshchenko, Mazen Al-Hommrani, Kristina Andrijauskaite, Kelly Moxley, Harinarayanan Janakiraman, Matthew J. Scheffel, Kristi Helke, Kent Armenson, Viswanathan Palanisamy, Mark P. Rubinstein, Elizabeth-Garrett Mayer, David J. Cole, Chrystal M. Paulos, Christina Voelkel-Johnson, Michael I. Nishimura, and Shikhar Mehrotra
Précis: These findings suggest that p53 regulates glycolytic commitment and TGF β 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 Chevriaux, Romain Boidot, Frédérique Végran, Nathalie Bonnefoy, Julie Vincent, Leila Bengrine-Lefevre, Sylvain Ladoire, Dominique Delmas, Lionel Apetoh, 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 Kettritz, 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.

Table of Contents

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 Harjunpää, Kirsten A. Fairfax, Michelle C.R. Yong, Stacey Allen, Holbrook E. Kohrt, 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 Häuselmann, Marko Roblek, Darya Protsyuk, Volker Huck, Lucia Knopfova, Sandra Grässle, 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. Isacke, 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, Elling 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

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, Jaekwang Jeong, Joshua VanHouten, Catherine Sullivan, Pamela Dann, Herbert Yu, Nathalie Fiaschi-Taesch, Wenhan Chang, and John Wysolmerski

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.

5361 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 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.

Table of Contents

5383 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, Lucía Canedo, Guillermo A. Videla-Richardson, Joaquín M. Espinosa, Mario Rossi, Eva Serna, Miguel A. Riudavets, 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.

5395 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.

5405 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, 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.

PREVENTION AND EPIDEMIOLOGY

5415 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 Chandralapaty, Barbara Sternfeld, Carol Sweeney, Philip S. Bernard, Adrienne Castillo, Laurel A. Habel, Candyce 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.

5423 Plasma 25-Hydroxyvitamin D and Risk of Breast Cancer in Women Followed over 20 Years

A. Heather Eliassen, Erica T. Warner, Bernard Rosner, Laura C. Collins, Andrew H. Beck, Liza M. Quintana, Rulla M. Tamimi, and Susan E. Hankinson

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.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5431 Inhibiting Mitochondrial DNA Ligase III α Activates Caspase 1-Dependent Apoptosis in Cancer Cells

Annahita 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.

5442 SMAC Mimetic Birinapant plus Radiation Eradicates Human Head and Neck Cancers with Genomic Amplifications of Cell Death Genes *FADD* and *BIRC2*

Danielle F. Eytan, Grace E. Snow, Sophie Carlson, Adeeb Derakhshan, Anthony Saleh, Stephen Schiltz, Hui Cheng, Suresh Mohan, Shaleeka Cornelius, Jamie Coupar, Anastasia L. Sowers, Lidia Hernandez, James B. Mitchell, Christina M. Annunziata, Zhong Chen, and Carter Van Waes

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.

5455 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.

Table of Contents

5467 SIRT2 Deacetylates and Inhibits the Peroxidase Activity of Peroxiredoxin-1 to Sensitize Breast Cancer Cells to Oxidant Stress-Inducing Agents

Warren Fiskus, Veena Coothankandaswamy, Jianguang Chen, Hongwei Ma, Kyungsoo Ha, Dyana T. Saenz, Stephanie S. Krieger, Christopher P. Mill, Baohua Sun, Peng Huang, Jeffrey S. Mumm, 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-Lacoussiere, Ewa Kotula, Bruno O. Villoutreix, Heriberto Bruzzoni-Giovanelli, and Jean-Luc Poyet

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 HIF2 α Is Efficacious in Preclinical Models of Renal Cell Carcinoma



Eli M. Wallace, James P. Rizzi, Guangzhou Han, Paul M. Wehn, Zhaodan Cao, Xinlin Du, Tzuling Cheng, Robert M. Czerwinski, Darryl D. Dixon, Barry S. Goggin, Jonas A. Grina, Megan M. Halfmann, Melissa A. Maddie, Sarah R. Olive, Stephen T. Schlachter, Huiling Tan, Bin Wang, Keshi Wang, Shanhai Xie, Rui Xu, Hanbiao Yang, and John A. Josey

Précis: This important study offers preclinical proof of concept for a mechanistically novel class of therapeutics to treat kidney cancers, validating HIF2 α 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

Nicholas C.K. Valerie, Anna Hagenkort, Brent D.G. Page, Geoffrey Masuyer, Daniel Rehling, Megan Carter, Luka Bevc, Patrick Herr, Evert Homan, Nina G. Sheppard, Pål Stenmark, Ann-Sofie Jemth, and Thomas Helleday

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.

TUMOR AND STEM CELL BIOLOGY

5512 Decoding Intratumoral Heterogeneity of Breast Cancer by Multiparametric *In Vivo* Imaging: A Translational Study

Jennifer Schmitz, Julian Schwab, Johannes Schwenck, Qian Chen, Leticia Quintanilla-Martinez, Markus Hahn, Beate Wietek, Nina Schwenzer, Annette Staebler, Ursula Kohlhofer, Olulana H. Aina, Neil E. Hubbard, Gerald Reischl, Alexander D. Borowsky, Sara Brucker, Konstantin Nikolaou, Christian la Fougère, Robert D. Cardiff, Bernd J. Pichler, and Andreas M. Schmid

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 Gartlgruber, Chunxuan Shao, Carl Herrmann, Manuel Wiesenfarth, Martha Parzonka, Lea Wehrmann, Matthias Fischer, David J. Duffy, Emma Bell, Alica Torkov, Peter Schmezer, 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, Sheheryar 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.

Table of Contents

5550 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, Maïke 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.

5562 miR-9 and miR-200 Regulate PDGFR β -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. Gualeni, 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.

5573 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

5584 Correction: An I κ B α Inhibitor Causes Leukemia Cell Death through a p38 MAP Kinase-dependent, NF- κ B-independent Mechanism

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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.

