

BREAKING INSIGHTS

- 5189** Highlights from Recent Cancer Literature

REVIEW

- 5191** Treg Destabilization and Reprogramming: Implications for Cancer Immunotherapy
David H. Munn, Madhav D. Sharma, and Theodore S. Johnson

CANCER RESEARCH HIGHLIGHTS

- 5200** An Interleukin-1 Signature in Breast Cancer Treated with Interleukin-1 Receptor Blockade: Implications for Treating Cytokine Release Syndrome of Checkpoint Inhibitors
Charles Anthony Dinarello
See related article by Wu et al., p. 5243

MOLECULAR CELL BIOLOGY

- 5203** BMX-Mediated Regulation of Multiple Tyrosine Kinases Contributes to Castration Resistance in Prostate Cancer
Sen Chen, Changmeng Cai, Adam G. Sowalsky, Huihui Ye, Fen Ma, Xin Yuan, Nicholas I. Simon, Nathanael S. Gray, and Steven P. Balk
Significance: The tyrosine kinase BMX is negatively regulated by androgen and contributes to castration-resistant prostate cancer by enhancing the phosphorylation and activation of multiple receptor tyrosine kinases following ADT.
- 5216** ZNF677 Suppresses Akt Phosphorylation and Tumorigenesis in Thyroid Cancer
Yujun Li, Qi Yang, Haixia Guan, Bingyin Shi, Meiju Ji, and Peng Hou
Significance: These findings report a tumor suppressive role of the zinc-finger protein ZNF677 in primary papillary thyroid cancer through inhibition of Akt phosphorylation.

TUMOR BIOLOGY AND IMMUNOLOGY

- 5229** Matrix Stiffening and EGFR Cooperate to Promote the Collective Invasion of Cancer Cells
Eloise M. Grasset, Thomas Bertero, Alexandre Bozec, Jonas Friard, Isabelle Bourget, Sabrina Pisano, Margaux Lecacheur, Majdi Maiel, Caroline Bailleux, Alexander Emelyanov, Marius Ilie, Paul Hofman, Guerrino Meneguzzi, Christophe Duranton, Dmitry V. Bulavin, and Cedric Gaggioli



Significance: This work demonstrates that calcium channels blockers verapamil and diltiazem inhibit mechano-sensitization of EGF-dependent cancer cell collective invasion, introducing potential clinical strategies against stromal-dependent collective invasion.

- 5243** IL1 Receptor Antagonist Controls Transcriptional Signature of Inflammation in Patients with Metastatic Breast Cancer



Te-Chia Wu, Kangling Xu, Jan Martinek, Robyn R. Young, Romain Banchereau, Joshy George, Jacob Turner, Kyung In Kim, Sandra Zurawski, Xuan Wang, Derek Blankenship, Hannah M. Brookes, Florentina Marches, Gerlinde Obermoser, Elizabeth Lavecchio, Maren K. Levin, Sookyoung Bae, Cheng-Han Chung, Jennifer L. Smith, Alma-Martina Cepika, Kyp L. Oxley, George J. Snipes, Jacques Banchereau, Virginia Pascual, Joyce O'Shaughnessy, and A. Karolina Palucka

See related commentary by Dinarello, p. 5200

Significance: IL1 β orchestrates tumor-promoting inflammation in breast cancer and can be targeted in patients using an IL1 receptor antagonist.

- 5259** miRNA-30 Family Members Inhibit Breast Cancer Invasion, Osteomimicry, and Bone Destruction by Directly Targeting Multiple Bone Metastasis-Associated Genes
Martine Croset, Francesco Pantano, Casina W.S. Kan, Edith Bonnelye, Françoise Descotes, Catherine Alix-Panabières, Charles-Henri Lecellier, Richard Bachelier, Nathalie Allioli, Saw-See Hong, Kai Bartkowiak, Klaus Pantel, and Philippe Clézardin

Significance: These findings suggest miR-30 family members may serve as an effective means to therapeutically attenuate metastasis in triple-negative breast cancer.

- 5274** FBXO22 Possesses Both Protumorigenic and Antimetastatic Roles in Breast Cancer Progression
Rui Sun, Hong-Yan Xie, Jin-Xian Qian, Yan-Ni Huang, Fan Yang, Fang-Lin Zhang, Zhi-Min Shao, and Da-Qiang Li
Significance: These findings highlight the paradoxical roles of FBXO22 in breast cancer, as it promotes breast tumor cell proliferation but prevents EMT and metastasis.

Table of Contents

- 5287** **Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma**
 Yoav Binenbaum, Eran Fridman, Zvi Yaari, Neta Milman, Avi Schroeder, Gil Ben David, Tomer Shlomi, and Ziv Gil
Significance: Harnessing macrophage-derived exosomes as conveyers of antagomiRs augments the effect of chemotherapy against cancer, opening new therapeutic options against malignancies where resistance to nucleotide analogs remains an obstacle to overcome.

- 5300** **Modulating Bone Marrow Hematopoietic Lineage Potential to Prevent Bone Metastasis in Breast Cancer**
 Jessalyn M. Ubellacker, Ninib Baryawno, Nicolas Severe, Molly J. DeCristo, Jaclyn Sceneay, John N. Hutchinson, Marie-Therese Haider, Catherine S. Rhee, Yuanbo Qin, Walter M. Gregory, Ana C. Garrido-Castro, Ingunn Holen, Janet E. Brown, Robert E. Coleman, David T. Scadden, and Sandra S. McAllister
Significance: Bone marrow myeloid/osteoclast progenitor cell lineage potential has a profound impact on breast cancer bone metastasis and can be modulated by G-CSF and bone-targeting agents.

- 5315** **Activation of NKT Cells in an Anti-PD-1-Resistant Tumor Model Enhances Antitumor Immunity by Reinvigorating Exhausted CD8 T Cells**
 Eun-Ah Bae, Hyungseok Seo, Byung-Seok Kim, Jeongwon Choi, Insu Jeon, Kwang-Soo Shin, Choong-Hyun Koh, Boyeong Song, Il-Kyu Kim, Byung Soh Min, Yoon Dae Han, Sang Joon Shin, and Chang-Yuil Kang
Significance: These findings provide mechanistic insights into the application of NKT cell stimulation as a potent adjuvant for immunotherapy against advanced cancer.

- 5327** **Mucosal HPV E6/E7 Peptide Vaccination in Combination with Immune Checkpoint Modulation Induces Regression of HPV⁺ Oral Cancers**
 Stephanie Dorta-Estremera, Renee L. Chin, Gloria Sierra, Courtney Nicholas, Ananta V. Yanamandra, Sita M.K. Nookala, Guojun Yang, Shail Singh, Michael A. Curran, and K. Jagannadha Sastry
Significance: Combinations of vaccine and checkpoint modulation are effective and safe treatment options for HPV⁺ oral cancers.

- 5340** **Targeting CCR8 Induces Protective Antitumor Immunity and Enhances Vaccine-Induced Responses in Colon Cancer**
 Daniel O. Villarreal, Andrew L'Huillier, Susan Armington, Cristina Mottershead, Elena V. Filippova, Brandon D. Coder, Robert G. Petit, and Michael F. Princiotta
Significance: Inhibition of CCR8 represents a promising new cancer immunotherapy strategy that modulates tumor-resident regulatory T cells to enhance antitumor immunity and prolong patient survival.

TRANSLATIONAL SCIENCE

- 5349** **Targeting USP7 Identifies a Metastasis-Competent State within Bone Marrow-Resident Melanoma CTCs**

 Monika Vishnoi, Debasish Boral, Haowen Liu, Marc L. Sprouse, Wei Yin, Debalina Goswami-Sewell, Michael T. Tetzlaff, Michael A. Davies, Isabella C. Clitza Oliva, and Dario Marchetti
Significance: These findings provide insights into mechanism of melanoma recurrence and propose a novel approach to inhibit systematic metastatic disease by targeting bone marrow-resident tumor cells through pharmacological inhibition of USP7.

- 5363** **Spliceosome Mutations Induce R Loop-Associated Sensitivity to ATR Inhibition in Myelodysplastic Syndromes**
 Hai Dang Nguyen, Wan Yee Leong, Weiling Li, Pavankumar N.G. Reddy, Jack D. Sullivan, Matthew J. Walter, Lee Zou, and Timothy A. Graubert
Significance: This study provides preclinical evidence that patients with MDS or other myeloid malignancies driven by spliceosome mutations may benefit from ATR inhibition to exploit the R loop-associated vulnerability induced by perturbations in splicing.

- 5375** **Mouse Homolog of the Human TP53 R337H Mutation Reveals Its Role in Tumorigenesis**
 Ji-Hoon Park, Jie Li, Matthew F. Starost, Chengyu Liu, Jie Zhuang, Jichun Chen, Maria I. Achatz, Ju-Gyeong Kang, Ping-yuan Wang, Sharon A. Savage, and Paul M. Hwang
Significance: A germline mutation in the oligomerization domain of p53 decreases its transactivation potential and renders mice susceptible to carcinogen-induced liver tumorigenesis.

Table of Contents

- 5384** **mTOR Inhibition via Displacement of Phosphatidic Acid Induces Enhanced Cytotoxicity Specifically in Cancer Cells**
 Tra-Ly Nguyen, Marie-Julie Nokin, Maxim Egorov, Mercedes Tomé, Clément Bodineau, Carmelo Di Primo, Lætitia Minder, Joanna Wdzieczak-Bakala, Maria Concepcion Garcia-Alvarez, Jérôme Bignon, Odile Thoison, Bernard Delpech, Georgiana Surpateanu, Yves-Michel Frapart, Fabienne Peyrot, Kahina Abbas, Silvia Terés, Serge Evrard, Abdel-Majid Khatib, Pierre Soubeyran, Bogdan I. Iorga, Raúl V. Durán, and Pascal Collin
Significance: ICSN3250 defines a new class of mTORC1 inhibitors that displaces phosphatidic acid at the FRB domain of mTOR, inducing cell death specifically in cancer cells but not in noncancer cells.

- 5398** **Phase Ib Results of the Rational Combination of Selumetinib and Cyclosporin A in Advanced Solid Tumors with an Expansion Cohort in Metastatic Colorectal Cancer**
 Anuradha Krishnamurthy, Arvind Dasari, Anne M. Noonan, Janice M. Mehnert, Albert C. Lockhart, Stephen Leong, Anna Capasso, Mark N. Stein, Hanna K. Sanoff, James J. Lee, Aaron Hansen, Usha Malhotra, Sarah Rippke, Daniel L. Gustafson, Todd M. Pitts, Kim Ellison, S. Lindsey Davis, Wells A. Messersmith, S. Gail Eckhardt, and Christopher H. Lieu
Significance: These findings translate preclinical studies combining selumetinib and cyclosporin into a phase I first-in-human clinical trial of such a combination in patients with advanced solid malignancies.

- 5408** **Metabolic Imaging Detects Low Levels of Glycolytic Activity That Vary with Levels of c-Myc Expression in Patient-Derived Xenograft Models of Glioblastoma**
 Richard Mair, Alan J. Wright, Susana Ros, De-en Hu, Tom Booth, Felix Kreis, Jyotsna Rao, Colin Watts, and Kevin M. Brindle
Significance: Metabolic imaging with hyperpolarized [$1\text{-}^{13}\text{C}$]pyruvate detects low levels of c-Myc-driven glycolysis in patient-derived glioblastoma models, which, when translated to the clinic, could be used to detect occult disease, determine disease prognosis, and target radiotherapy.

- 5419** **A Transcriptome-Wide Association Study Among 97,898 Women to Identify Candidate Susceptibility Genes for Epithelial Ovarian Cancer Risk**
 Yingchang Lu, Alicia Beeghly-Fadiel, Lang Wu, Xingyi Guo, Bingshan Li, Joellen M. Schildkraut, Hae Kyung Im, Yian A. Chen, Jennifer B. Permuth, Brett M. Reid, Jamie K. Teer, Kirsten B. Moysich, Irene L. Andrulis, Hoda Anton-Culver, Banu K. Arun, Elisa V. Bandera, Rosa B. Barkardottir, Daniel R. Barnes, Javier Benitez, Line Bjorge, James Brenton, Ralf Butzow, Trinidad Caldes, Maria A. Caligo, Ian Campbell,

Jenny Chang-Claude, Kathleen B.M. Claes, Fergus J. Couch, Daniel W. Cramer, Mary B. Daly, Anna deFazio, Joe Dennis, Orland Diez, Susan M. Domchek, Thilo Dörk, Douglas F. Easton, Diana M. Eccles, Peter A. Fasching, Renée T. Fortner, George Fountzilas, Eitan Friedman, Patricia A. Ganz, Judy Garber, Graham G. Giles, Andrew K. Godwin, David E. Goldgar, Marc T. Goodman, Mark H. Greene, Jacek Gronwald, Ute Hamann, Florian Heitz, Michelle A.T. Hildebrandt, Claus K. Høgdall, Antoinette Hollestelle, Peter J. Hulick, David G. Huntsman, Evgeny N. Imyaninov, Claudine Isaacs, Anna Jakubowska, Paul James, Beth Y. Karlan, Linda E. Kelemen, Lambertus A. Kiemeny, Susanne K. Kjaer, Ava Kwong, Nhu D. Le, Goska Leslie, Fabienne Lesueur, Douglas A. Levine, Amalia Mattiello, Taymaa May, Lesley McGuffog, Iain A. McNeish, Melissa A. Merritt, Francesmary Modugno, Marco Montagna, Susan L. Neuhausen, Heli Nevanlinna, Finn C. Nielsen, Liene Nikitina-Zake, Robert L. Nussbaum, Kenneth Offit, Edith Olah, Olufunmilayo I. Olopade, Sara H. Olson, Håkan Olsson, Ana Osorio, Sue K. Park, Michael T. Parsons, Petra H.M. Peeters, Tanja Pejovic, Paolo Peterlongo, Catherine M. Phelan, Miquel Angel Pujana, Susan J. Ramus, Gad Rennert, Harvey Risch, Gustavo C. Rodriguez, Cristina Rodríguez-Antona, Isabelle Romieu, Matti A. Rookus, Mary Anne Rossing, Iwona K. Rzepecka, Dale P. Sandler, Rita K. Schmutzler, Veronica W. Setiawan, Priyanka Sharma, Weiva Sieh, Jacques Simard, Christian F. Singer, Honglin Song, Melissa C. Southey, Amanda B. Spurdle, Rebecca Sutphen, Anthony J. Swerdlow, Manuel R. Teixeira, Soo H. Teo, Mads Thomassen, Marc Tischkowitz, Amanda E. Toland, Antonia Trichopoulou, Nadine Tung, Shelley S. Tworoger, Elizabeth J. van Rensburg, Adriaan Vanderstichele, Ana Vega, Digna Velez Edwards, Penelope M. Webb, Jeffrey N. Weitzel, Nicolas Wentzensen, Emily White, Alicja Wolk, Anna H. Wu, Drakoulis Yannoukakos, Kristin K. Zorn, Simon A. Gayther, Antonis C. Antoniou, Andrew Berchuck, Ellen L. Goode, Georgia Chenevix-Trench, Thomas A. Sellers, Paul D.P. Pharoah, Wei Zheng, and Jirong Long

Significance: Transcriptomic analysis of a large cohort confirms earlier GWAS loci and reveals FZD4 as a novel locus associated with EOC risk.

CONVERGENCE AND TECHNOLOGIES

- 5431** **A Targeted Quantitative Proteomic Approach Assesses the Reprogramming of Small GTPases during Melanoma Metastasis**
 Ming Huang, Tianyu F. Qi, Lin Li, Gao Zhang, and Yinsheng Wang
Significance: A novel quantitative proteomic method leads to the discovery of RAB38 as a new driver of metastasis in melanoma.

Table of Contents

5446 Network Propagation Predicts Drug Synergy in Cancers

Hongyang Li, Tingyang Li, Daniel Quang, and Yuanfang Guan

Significance: This study presents a novel network propagation-based method that predicts anticancer drug synergy to the accuracy of experimental replicates, which establishes a state-of-the-field method as benchmarked by the pharmacogenomics research community involving models generated by 160 teams.

POPULATION AND PREVENTION SCIENCE

5458 Neonatal Inflammatory Markers Are Associated with Childhood B-cell Precursor Acute Lymphoblastic Leukemia

Signe Holst Sjøgaard, Klaus Rostgaard, Kristin Skogstrand, Joseph Leo Wiemels, Kjeld Schmiegelow, and Henrik Hjalgrim

Significance: Children who develop acute lymphoblastic leukemia are immunologically distinct at birth and could potentially react abnormally to infections in early childhood.

CORRECTION

5464 Correction: Carbonyl Reductase 1 Offers a Novel Therapeutic Target to Enhance Leukemia Treatment by Arsenic Trioxide

EDITOR'S NOTE

5465 Editor's Note: *In vitro* and *In vivo* Molecular Evidence for Better Therapeutic Efficacy of ABT-627 and Taxotere Combination in Prostate Cancer

RETRACTIONS

5466 Retraction: Gemcitabine Sensitivity Can Be Induced in Pancreatic Cancer Cells through Modulation of miR-200 and miR-21 Expression by Curcumin or Its Analogue CDF

5467 Retraction: 3,3'-Diindolylmethane Enhances Chemosensitivity of Multiple Chemotherapeutic Agents in Pancreatic Cancer

5468 Retraction: Antitumor Activity of Gemcitabine and Oxaliplatin Is Augmented by Thymoquinone in Pancreatic Cancer

5469 Retraction: Down-regulation of Platelet-Derived Growth Factor-D Inhibits Cell Growth and Angiogenesis through Inactivation of Notch-1 and Nuclear Factor- κ B Signaling

5470 Retraction: Down-regulation of Forkhead Box M1 Transcription Factor Leads to the Inhibition of Invasion and Angiogenesis of Pancreatic Cancer Cells

5471 Retraction: Inhibition of Angiogenesis and Invasion by 3,3'-Diindolylmethane Is Mediated by the Nuclear Factor- κ B Downstream Target Genes *MMP-9* and *uPA* that Regulated Bioavailability of Vascular Endothelial Growth Factor in Prostate Cancer

5472 Retraction: Potentiation of the Effect of Erlotinib by Genistein in Pancreatic Cancer: The Role of Akt and Nuclear Factor- κ B

5473 Retraction: Down-regulation of Androgen Receptor by 3,3'-Diindolylmethane Contributes to Inhibition of Cell Proliferation and Induction of Apoptosis in Both Hormone-Sensitive LNCaP and Insensitive C4-2B Prostate Cancer Cells

5474 Retraction: Epidermal Growth Factor Receptor-Related Protein Inhibits Cell Growth and Invasion in Pancreatic Cancer

5475 Retraction: Antitumor and Antimetastatic Activities of Docetaxel Are Enhanced by Genistein through Regulation of Osteoprotegerin/Receptor Activator of Nuclear Factor- κ B (RANK)/RANK Ligand/MMP-9 Signaling in Prostate Cancer

5476 Retraction: Down-regulation of Notch-1 Inhibits Invasion by Inactivation of Nuclear Factor- κ B, Vascular Endothelial Growth Factor, and Matrix Metalloproteinase-9 in Pancreatic Cancer Cells

5477 Retraction: Antitumor Activity of Epidermal Growth Factor Receptor-Related Protein Is Mediated by Inactivation of ErbB Receptors and Nuclear Factor- κ B in Pancreatic Cancer

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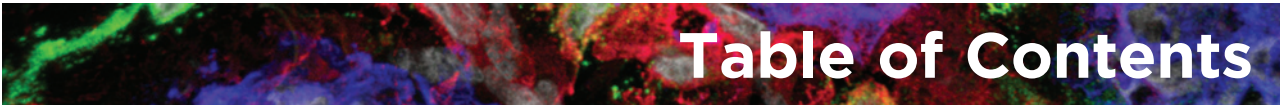


Table of Contents

ABOUT THE COVER

Human breast cancer tissue stained by immunofluorescence illustrates the interplay between secreted and surface-bound TGF β (red) expressed by cancer cells (blue), which primes tumor-infiltrating myeloid cells to produce IL1 β (green). This in turn will lead to chronic inflammation associated with breast cancer progression. Gray, nuclei. For details, see article by Wu and colleagues on page 5243.

