

BREAKING ADVANCES

- 3129** Highlights from Recent Cancer Literature

REVIEWS

- 3131** Nature and Nurture: What Determines Tumor Metabolic Phenotypes?
Jared R. Mayers and Matthew G. Vander Heiden
- 3135** FOXM1 in Cancer: Interactions and Vulnerabilities
Andrei L. Gartel

PERSPECTIVE

- 3140** Human Subjects Protection and Cancer Surveillance Research: Revised Regulations, Expanded Opportunities
Robert H. McLaughlin, Scarlett Lin Gomez, Dennis Deapen, and Marta Induni

PRIORITY REPORTS

- 3144** Interaction between Tumor Cell Surface Receptor RAGE and Proteinase 3 Mediates Prostate Cancer Metastasis to Bone
Mikhail G. Kolonin, Anna Sergeeva, Daniela I. Staquicini, Tracey L. Smith, Christy A. Tarleton, Jeffrey J. Mollidrem, Richard L. Sidman, Serena Marchiò, Renata Pasqualini, and Wadih Arap
Précis: Binding of a prostate cancer cell receptor to a proteinase expressed by myeloid cells in the bone microenvironment drives the most common type of metastasis during prostate cancer progression, with immediate implications for molecular prognosis and intervention.
- 3151** Merkel Cell Polyomavirus Small T Antigen Initiates Merkel Cell Carcinoma-like Tumor Development in Mice
Monique E. Verhaegen, Doris Mangelberger, Paul W. Harms, Markus Eberl, Dawn M. Wilbert, Julia Meireles, Christopher K. Bichakjian, Thomas L. Saunders, Sunny Y. Wong, and Andrzej A. Dlugosz
Précis: Analysis of nine different mouse models support the concept that Merkel cell polyomavirus small T antigen, via its FBXW7-interacting domain, is the primary oncogenic driver initiating virus-associated Merkel cell carcinoma development.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3158** Increased T-cell Infiltration Elicited by *Erk5* Deletion in a *Pten*-Deficient Mouse Model of Prostate Carcinogenesis
Carolyn J. Loveridge, Ernest J. Mui, Rachana Patel, Ee Hong Tan, Imran Ahmad, Michelle Welsh, Julie Galbraith, Ann Hedley, Colin Nixon, Karen Blyth, Owen Sansom, and Hing Y. Leung
Précis: These results offer a preclinical proof of concept for *ERK5* as a target to enhance T-cell infiltrates in prostate cancer, with possible implications for leveraging immune therapy in this disease.
- 3169** Plk1 Phosphorylation of Mre11 Antagonizes the DNA Damage Response
Zhiguo Li, Jie Li, Yifan Kong, Shan Yan, Nihal Ahmad, and Xiaoqi Liu
Précis: This study provides a mechanistic rationale to study the administration of PARP inhibitors in cancer patients whose tumors express high levels of the mitotic kinase Plk1.
- 3181** TWIST1-WDR5-Hottip Regulates *Hoxa9* Chromatin to Facilitate Prostate Cancer Metastasis
Reem Malek, Rajendra P. Gajula, Russell D. Williams, Belinda Nghiem, Brian W. Simons, Katriana Nugent, Hailun Wang, Kekoa Tapparra, Ghali Lemtiri-Chlieh, Arum R. Yoon, Lawrence True, Steven S. An, Theodore L. DeWeese, Ashley E. Ross, Edward M. Schaeffer, Kenneth J. Pienta, Paula J. Hurley, Colm Morrissey, and Phuoc T. Tran
Précis: A TWIST1-induced histone methylation event at the *Hoxa9* promoter reactivates its expression during prostate cancer metastasis, offering a candidate therapeutic target.
- 3194** tRF/miR-1280 Suppresses Stem Cell-like Cells and Metastasis in Colorectal Cancer
Bingqing Huang, Huipeng Yang, Xixi Cheng, Dan Wang, Shuyu Fu, Wencui Shen, Qi Zhang, Lijuan Zhang, Zhenyi Xue, Yan Li, Yurong Da, Qing Yang, Zesong Li, Li Liu, Liang Qiao, Ying Kong, Zhi Yao, Peng Zhao, Min Li, and Rongxin Zhang
Précis: This provocative study shows that functional miRNA can be derived from tRNA fragments, acting here to mediate a tumor suppressor signaling cascade in human colorectal cancer.

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3207 Assessing Prostate Cancer Aggressiveness with Hyperpolarized Dual-Agent 3D Dynamic Imaging of Metabolism and Perfusion

Hsin-Yu Chen, Peder E.Z. Larson, Robert A. Bok, Cornelius von Morze, Renuka Sriram, Romelyn Delos Santos, Justin Delos Santos, Jeremy W. Gordon, Naeim Bahrami, Marcus Ferrone, John Kurhanewicz, and Daniel B. Vigneron

Précis: Prostate cancer grade can be differentiated using a new noninvasive MRI-based method reading tumor metabolism and perfusion.

3217 Pyruvate Kinase Inhibits Proliferation during Postnatal Cerebellar Neurogenesis and Suppresses Medulloblastoma Formation

Katherine Tech, Andrey P. Tikunov, Hamza Farooq, A. Sorana Morrissy, Jessica Meidinger, Taylor Fish, Sarah C. Green, Hedi Liu, Yisu Li, Andrew J. Mungall, Richard A. Moore, Yussanne Ma, Steven J.M. Jones, Marco A. Marra, Matthew G. Vander Heiden, Michael D. Taylor, Jeffrey M. Macdonald, and Timothy R. Gershon

Précis: These findings show that the growth-supporting effects of glycolysis can be dissociated from lactate production, such that efforts to disrupt glycolytic metabolism in cancer cells should target reactions upstream of pyruvate kinase.

3255 p62/SQSTM1 Cooperates with Hyperactive mTORC1 to Regulate Glutathione Production, Maintain Mitochondrial Integrity, and Promote Tumorigenesis

Hilaire C. Lam, Christian V. Baglini, Alicia Llorente Lope, Andrey A. Parkhitko, Heng-Jia Liu, Nicola Alesi, Izabela A. Malinowska, Darius Ebrahimi-Fakhari, Afshin Saffari, Jane J. Yu, Ana Pereira, Damir Khabibullin, Barbara Ogorek, Julie Nijmeh, Taylor Kavanagh, Adam Handen, Stephen Y. Chan, John M. Asara, William M. Oldham, Maria T. Diaz-Meco, Jorge Moscat, Mustafa Sahin, Carmen Priolo, and Elizabeth P. Henske

Précis: These findings define a key pathway in sustaining glutathione biosynthesis to maintain mitochondrial integrity, a particularly important feature for mTORC1-driven tumorigenesis.

3268 IL4 Primes the Dynamics of Breast Cancer Progression via DUSP4 Inhibition

Miriam Gaggianesi, Alice Turdo, Aurora Chinnici, Elisa Lipari, Tiziana Apuzzo, Antonina Benfante, Isabella Sperduti, Simone Di Franco, Serena Meraviglia, Elena Lo Presti, Francesco Dieli, Valentina Caputo, Gabriella Militello, Salvatore Vieni, Giorgio Stassi, and Matilde Todaro

Précis: This study defines a positive modifier of metastatic spread in the breast tumor microenvironment, whose inhibition derepresses immunity and may improve therapeutic management.

TUMOR AND STEM CELL BIOLOGY

3231 Activation of NOTCH Signaling by Tenascin-C Promotes Growth of Human Brain Tumor-Initiating Cells

Susobhan Sarkar, Reza Mirzaei, Franz J. Zemp, Wu Wei, Donna L. Senger, Stephen M. Robbins, and V. Wee Yong

Précis: These results identify a novel NOTCH signaling pathway in glioma stem cells as a candidate for therapeutic interventions to improve the prognosis of patients with malignant glioma.

3244 Micellar Delivery of miR-34a Modulator Rubone and Paclitaxel in Resistant Prostate Cancer

Di Wen, Yang Peng, Feng Lin, Rakesh K. Singh, and Ram I. Mahato

Précis: A polymeric nanomedicine that upregulates tumor suppressor miR-34a in prostate cancer cells may offer an effective method to attack chemoresistant metastatic prostate cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3280 Extracellular Matrix/Integrin Signaling Promotes Resistance to Combined Inhibition of HER2 and PI3K in HER2⁺ Breast Cancer

Ariella B. Hanker, Mónica Valeria Estrada, Giampaolo Bianchini, Preston D. Moore, Junfei Zhao, Feixiong Cheng, James P. Koch, Luca Gianni, Darren R. Tyson, Violeta Sánchez, Brent N. Rexer, Melinda E. Sanders, Zhongming Zhao, Thomas P. Stricker, and Carlos L. Arteaga

Précis: Collagens and other components of the tumor microenvironment contribute to therapeutic resistance of HER2 and PI3K inhibitor combinations currently being tested clinically in HER2⁺ breast cancer.

3293 Multifunctional Telodendrimer Nanocarriers Restore Synergy of Bortezomib and Doxorubicin in Ovarian Cancer Treatment

Lili Wang, Changying Shi, Forrest A. Wright, Dandan Guo, Xu Wang, Dongliang Wang, Richard J.H. Wojcikiewicz, and Juntao Luo

Précis: Drug synergy in solid tumor treatments can be optimized by novel nanocarriers that can coordinately enhance drug pharmacokinetics and biodistribution of codelivered drugs.



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3306 Oncogenic Role of SND1 in Development and Progression of Hepatocellular Carcinoma

Nidhi Jariwala, Devaraja Rajasekaran, Rachel G. Mendoza, Xue-Ning Shen, Ayesha Siddiq, Maaged A. Akiel, Chadia L. Robertson, Mark A. Subler, Jolene J. Windle, Paul B. Fisher, Arun J. Sanyal, and Devanand Sarkar

Précis: A small-molecule inhibitor of the liver cancer oncogene SND1 shows preclinical efficacy by abrogating tumor-initiating cell formation, suggesting its development as a novel therapy.

MICROENVIRONMENT AND IMMUNOLOGY

3317 Immune Gene Expression Is Associated with Genomic Aberrations in Breast Cancer

Anton Safonov, Tingting Jiang, Giampaolo Bianchini, Balázs Györfy, Thomas Karn, Christos Hatzis, and Lajos Pusztai

Précis: Analysis of 1025 breast cancers revealed that higher expression of immune-associated genes associates with lower clonal heterogeneity in all breast cancer subtypes, suggesting immune escape is enabled by genomic diversification.

INTEGRATED SYSTEMS AND TECHNOLOGIES

3325 Personalized Management of Pancreatic Ductal Adenocarcinoma Patients through Computational Modeling

Kimiyo N. Yamamoto, Shinichi Yachida, Akira Nakamura, Atsushi Niida, Minoru Oshima, Subhajyoti De, Lauren M. Rosati, Joseph M. Herman, Christine A. Jacobuzio-Donahue, and Hiroshi Haeno

Précis: A new mathematical model identifies pancreatic cancer patients with a lower propensity to develop metastatic disease and shows this subpopulation benefits from locally intensive therapies such as surgery and radiation therapy.

3336 An Ex Vivo Platform for the Prediction of Clinical Response in Multiple Myeloma

Ariosto Silva, Maria C. Silva, Praneeth Sudalagunta, Allison Distler, Timothy Jacobson, Aunshka Collins, Tuan Nguyen, Jinming Song, Dung-Tsa Chen, Lu Chen, Christopher Cubitt, Rachid Baz, Lia Perez, Dmitri Rebatchouk, William Dalton, James Greene, Robert Gatenby, Robert Gillies, Eduardo Sontag, Mark B. Meads, and Kenneth H. Shain

Précis: These findings describe a novel tool to quickly predict the clinical response to a large number of drugs used to treat multiple myeloma using fresh bone marrow aspirates, a digital image analysis algorithm, mathematical models, and pharmacokinetic data.

3352 Western Diet Deregulates Bile Acid Homeostasis, Cell Proliferation, and Tumorigenesis in Colon

Denis Dermadi, Satu Valo, Saara Ollila, Rabah Soliymani, Nina Sipari, Marjaana Pussila, Laura Sarantaus, Jere Linden, Marc Baumann, and Minna Nyström

Précis: These findings establish a comprehensive deep proteomics resource for the colon cancer community and observes changes in normal mucosa caused by Western-style diet preceding colon cancer development.

3364 Drug Resistance Mechanisms in Colorectal Cancer Dissected with Cell Type-Specific Dynamic Logic Models



Federica Eduati, Victoria Doldàn-Martelli, Bertram Klinger, Thomas Cokelaer, Anja Sieber, Fiona Kogera, Mathurin Dorel, Mathew J. Garnett, Nils Blüthgen, and Julio Saez-Rodriguez

Précis: Dynamic logic models of signaling pathways based on perturbation data provide biomarkers of efficacy for drugs for which no genomic marker exist and suggest strategies to overcome drug resistance.

LETTER TO THE EDITOR

3376 TLR-3/9 Agonists Synergize with Anti-ErbB2 mAb—Letter

Anna H. Turaj, Lekh N. Dahal, Stephen A. Beers, Mark S. Cragg, and Sean H. Lim

CORRECTION

3379 Correction: TALEN-Mediated Inactivation of PD-1 in Tumor-Reactive Lymphocytes Promotes Intratumoral T-cell Persistence and Rejection of Established Tumors



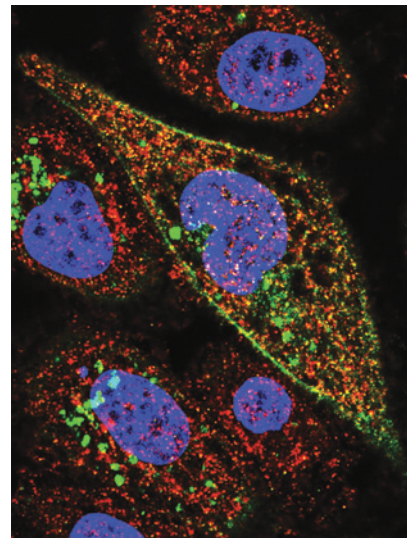
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ABOUT THE COVER

Human prostate cancer selectively metastasizes to the bone with mechanisms that are partially unknown. RAGE is a receptor overexpressed by prostate cancer cells whose expression correlates with the capacity of colonizing the bone marrow microenvironment. Proteinase 3 (PR3) is a serine protease produced and released by myeloid cells, and has been identified as a RAGE-interacting protein. Using high resolution confocal microscopy, it was found that soluble PR3 (red) accumulates at the surface of prostate cancer cells overexpressing RAGE (green). This result supports further evidence of heterotypic cell-cell interactions between prostate cancer cells expressing RAGE and hematopoietic cells expressing PR3. For more details, see article by Kolonin and colleagues on page 3144.



Cancer Research

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