**BREAKING ADVANCES**

1 Highlights from Recent Cancer Literature

**REVIEWS**

3 Integrin: Critical Path to Antiangiogenic Therapy Resistance and Beyond
Arman Jahangiri, Manish K. Aghi, and W. Shawn Carbonell

8 Inflammation Amplifier, a New Paradigm in Cancer Biology
Toru Atsumi, Rajeev Singh, Lavannya Sabharwal, Hidenori Bando, Jie Meng, Yasunobu Arima, Moe Yamada, Masaya Harada, Jing-Jing Jiang, Daisuke Kamimura, Hideki Ogura, Toshio Hirano, and Masaaki Murakami

**PRIORITY REPORTS**

15 A Genetic Mouse Model of Invasive Endometrial Cancer Driven by Concurrent Loss of Pten and Lkb1 Is Highly Responsive to mTOR Inhibition
Hailing Cheng, Pixiu Liu, Fan Zhang, Erbo Xu, Lynn Symonds, Carolyn E. Oldson, Roderick T. Bronson, Sauveur-Michel Maira, Emmanuelle Di Tomaso, Jane Li, Andrea P. Myers, Lewis C. Cantley, Jane Li, Andrea P. Myers, Lewis C. Cantley, Gordon B. Mills, and Jean J. Zhao

24 Tumor Hypoxia Does Not Drive Differentiation of Tumor-Associated Macrophages but Rather Fine-Tunes the M2-like Macrophage Population
Dannya Laoui, Eva Van Overmeire, Giusy Di Conza, Chiara Aldeni, Jiri Keirse, Yannick Morias, Kavash Movahedi, Isabelle Houbrechken, Elio Schouppe, Yvon Elkrin, Oussama Karroum, Bénédicte Jordan, Peter Carmellet, Conny Gysemans, Patrick De Baetselier, Massimiliano Mazzone, and Jo A. Van Ginderachter

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

31 Targeting PARP-1 Allosteric Regulation Offers Therapeutic Potential against Cancer
Jamin D. Steffen, Renee M. Tholey, Marie-France Langelier, Jamie L. Planck, Matthew J. Schiewer, Shruti Lal, Nikolai A. Bidzukewicz, Charles J. Yeo, Karen E. Knudsen, Jonathan R. Brody, and John M. Pascal

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

38 The NADH Oxidase ENOX1, a Critical Mediator of Endothelial Cell Radiosensitization, Is Crucial for Vascular Development
Amudhan Venkateswaran, Konjeti R. Sekhar, Daniel S. Levi, David B. Melville, Travis A. Clark, Witold M. Byhski, Alexandra J. Walsh, Melissa C. Skala, Peter A. Crooks, Ela W. Knapik, and Michael L. Freeman

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

44 A Macrophage-Specific Fluorescent Probe for Intraoperative Lymph Node Staging
Jung Sun Yoo, Sung-Chan Lee, Zhi Yen Jow, Pamela Yun Xiang Koh, and Young-Tae Chang

56 A Preclinical Assay for Chemosensitivity in Multiple Myeloma
Zayar P. Khin, Maria L.C. Ribeiro, Timothy Jacobson, Lori Hazlehurst, Lia Perez, Rachid Baz, Kenneth Shain, and Ariosto S. Silva

Précis: This study establishes a new strategy to selectively inhibit the DNA repair enzyme PARP-1, a clinically validated target for cancer treatment.

Précis: ENOX1 may offer an appealing new antiangiogenic target for cancer therapy based on its role in influencing sensitivity to radiotherapy and DNA-damaging cytotoxic agents.

Précis: These findings suggest insights into the basis for development of an aggressive form of endometrial cancer that is driven by deregulated mTOR signaling.

Précis: These findings illustrate an intraoperative platform technology to improve lymph node staging, providing fluorescent guidance during cancer surgery that might reduce complications such as lymphedema.

Précis: This study challenges the notion that TAMs are a primary beneficiary of hypoxia in the tumor microenvironment, shifting attention to M2 macrophages to explain how the poorly organized vasculature of tumors promotes malignant progression.
Doxorubicin Eliminates Myeloid-Derived Suppressor Cells and Enhances the Efficacy of Adoptive T-Cell Transfer in Breast Cancer
Darya Alizadeh, Malika Trad, Neale T. Hanke, Claire B. Larmonier, Nona Janikashvili, Bernard Bonnotte, Emmanuel Katsanis, and Nicolas Larmonier

Precis: This study shows how a traditional cytotoxic cancer drug can be used to reverse myeloid immunosuppression in the tumor microenvironment and to enhance the efficacy of adoptively transferred T cells that attack tumors, creating a highly effective immunochemotherapy regimen.
MOLECULAR AND CELLULAR PATHOBIOLOGY

162 MAPK Kinase 3 Is a Tumor Suppressor with Reduced Copy Number in Breast Cancer
Adam J. MacNeil, Shun-Chang Jiao, Lori A. McEachern, Yong Jun Yang, Amanda Dennis, Haiming Yu, Zhaolin Xu, Jean S. Marshall, and Tong-Jun Lin

Précis: These findings reveal the functional significance of a MAPK kinase as a tumor suppressor in breast cancer, improving understanding of the dynamic role of the MAPK pathway in tumor progression.

173 Integrin-Free Tetraspanin CD151 Can Inhibit Tumor Cell Motility upon Clustering and Is a Clinical Indicator of Prostate Cancer Progression
Trenis D. Palmer, Carlos H. Martínez, Catalina Vasquez, Katie E. Helron, Celestial Jones-Paris, Shanna A. Arnold, Susanne M. Chan, Venu Chalasani, Jose A. Gomez-Lemus, Andrew K. Williams, Joseph L. Chin, Giovanna A. Giannico, Tatiana Ketova, John D. Lewis, and Andries Zijlstra

Précis: A common component of cell surface scaffolds that organize cell motility and physiology is altered during oncogenesis in a manner that confers cancer cells with aggressive qualities, causing poor outcomes.

188 HTLV-1 bZIP Factor Suppresses Apoptosis by Attenuating the Function of FoxO3a and Altering Its Localization
Azusa Tanaka-Nakanishi, Jun-ichirou Yasunaga, Ken Takai, and Masao Matsuoka

Précis: These findings reveal mechanistic insights into the molecular pathogenicity of the cancer-causing human virus HTLV-1 by defining the antiapoptotic effects of one of its key gene products.

201 Casein Kinase 1c Promotes Cell Proliferation by Regulating mRNA Translation
Sejeong Shin, Laura Wolgamott, Philippe P. Roux, and Sang-Oh Yoon

Précis: These findings suggest a rationale for a generalized strategy to treat human cancers by blocking a pivotal kinase-regulated step in mRNA translation.

212 Bcl2 Induces DNA Replication Stress by Inhibiting Ribonucleotide Reductase
Maohua Xie, Yun Yen, Taofeek K. Owonikoko, Suresh S. Ramalingam, Padlo R. Khuri, Walter J. Curran, Paul W. Doetsch, and Xingming Deng

Précis: These findings uncover a novel link between Bcl2 function and the progress of DNA replication, with potential implications on how to apply Bcl2 inhibitors in the clinic for cancer treatment.

PREVENTION AND EPIDEMIOLOGY

235 Childhood Height and Body Mass Index Were Associated with Risk of Adult Thyroid Cancer in a Large Cohort Study
Cari M. Kitahara, Michael Gamborg, Amy Berrington de Gonzalez, Thorkild I.A. Sørensen, and Jennifer L. Baker

Précis: Findings from this large study suggest that early-life exposures affecting childhood height and weight may increase the risk of thyroid cancer later in life.

243 6-C-(E-phenylethenyl)-Naringenin Suppresses Colorectal Cancer Growth by Inhibiting Cyclooxygenase-1
Haitao Li, Feng Zhu, Hanyong Chen, Ka Wing Cheng, Tatyana Zykov, Naomi Oi, Ronald A. Lubet, Ann M. Bode, Mingfu Wang, and Zigang Dong

Précis: COX-1 plays a critical role in human colorectal carcinogenesis and a rationale is presented here to target its activity as a strategy to prevent colorectal cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

253 MET and AXL Inhibitor NPS-1034 Exerts Efficacy against Lung Cancer Cells Resistant to EGFR Kinase Inhibitors Because of MET or AXL Activation
Jin Kyung Rho, Yun Jung Choi, Seon Ye Kim, Tae Won Kim, Eun Kyung Choi, Seon-Joo Yoon, Bu Man Park, Eunhye Park, Jong Hwan Bae, Chang-Min Choi, and Jae Cheol Lee

Précis: A new drug that targets two tyrosine kinase receptors that drive invasive growth and drug resistance may be particularly useful for treatment of acquired resistance to EGFR inhibitors.
A Reevaluation of CD22 Expression in Human Lung Cancer

Précis: These findings challenge a previous study reporting widespread overexpression of the cell surface protein CD22 in lung cancers, for which it had been suggested as a new target for immunotherapy.

USP22 Regulates Oncogenic Signaling Pathways to Drive Lethal Cancer Progression

Précis: These findings define a deubiquitinating enzyme as an important positive modifier of tumor progression, providing a strong rationale for it as an appealing therapeutic target to treat advanced cancers.

Genome-wide Profiling of Genetic Synthetic Lethality Identities CDK12 as a Novel Determinant of PARP1/2 Inhibitor Sensitivity
Ilirjana Bajrami, Jessica R. Frankum, Asha Konde, Rowan E. Miller, Farah L. Rehman, Rachel Brough, James Campbell, David Sims, Rumana Rafiq, Sean Hooper, Lina Chen, Ivanka Kozarewa, Ioannis Assiotis, Kerry Fenwick, Rachael Natrajan, Christopher J. Lord, and Alan Ashworth

Précis: These important findings suggest much greater utility for cancer treatment with PARP inhibitors than appreciated previously and also reveal a clinically relevant biomarker that is likely to be important for predicting PARP inhibitor responses.

SIRT1 and AMPK Mediate Hypoxia-Induced Resistance of Non–Small Cell Lung Cancers to Cisplatin and Doxorubicin
Dong Hoon Shin, Yong-Joon Choi, and Jong-Wan Park

Précis: This study provides a preclinical proof-of-concept to target the SIRT1–AMPK pathway as a strategy to overcome hypoxia-induced chemoresistance in lung cancer, with potentially broader implications for solid tumors generally.

ERK1/2 Blockade Prevents Epithelial–Mesenchymal Transition in Lung Cancer Cells and Promotes Their Sensitivity to EGFR Inhibition
Janine M. Buonato and Matthew J. Lazzara

Précis: Combining targeted inhibitors of MEK or ERK with EGFR inhibitors not only restrains the epithelial–mesenchymal transition in lung cancer cells associated with drug resistance but also overcomes the resistance to EGFR-targeted therapy, suggesting immediate applications in the clinic, where this issue is both timely and important.

ΔNp63 Promotes Pediatric Neuroblastoma and Osteosarcoma by Regulating Tumor Angiogenesis
Hemant K. Bid, Ryan D. Roberts, Maren Cam, Anthony Audino, Raushan T. Kurmasheva, Jiayuh Lin, Peter J. Houghton, and Hakan Cam

Précis: These findings reveal a key support to tumor angiogenesis in two aggressive childhood cancers, with implications for understanding progression and potential treatments.

Cancer Usurps Skeletal Muscle as an Energy Repository
Yi Luo, Junya Yoneda, Hitoshi Ohmori, Takamitsu Sasaki, Kazutaka Shimbo, Sachio Eto, Yumiko Kato, Hiroshi Miyano, Tsuyoshi Kobayashi, Tomonori Sasahira, Yoshitomo Chihara, and Hiroki Kuniyasu

Précis: This important study shows how budding tumors recruit muscle to supply glutamine to cancer cells as an energy source through the release of HMGB1, a pro-inflammatory autophagy-inducing molecule that influences muscle physiology.

Neuregulin Autocrine Signaling Promotes Self-Renewal of Breast Tumor-Initiating Cells by Triggering HER2/HER3 Activation
Cleo Yi-Fang Lee, Yuan Lin, Scott V. Bratman, Wei Guo Feng, Angera H. Ku, Ferenc A. Scheeren, Jesse M. Engreitz, Susanna Varma, Robert B. West, and Maximilian Diehn

Précis: This important work shows why HER2-targeting therapies might benefit a considerably larger number of breast cancer patients than they currently reach.

Tumor Suppressor NF2/Merlin Is a Microtubule Stabilizer
Zlatko Smole, Claudio R. Thoma, Kathryn T. Applegate, Maria Duda, Katrin L. Gutbrodt, Gaudenz Danuser, and Wilhelm Krek

Précis: NF2 regulates the dynamic instability of microtubules, a function shared with the tumor suppressor VHL that also helps block aberrant microtubule-mediated processes needed for tumorigenesis.
### 363 14-3-3ζ Orchestrates Mammary Tumor Onset and Progression via miR-221–Mediated Cell Proliferation

Sumaiyah K. Rehman, Shau-Hsuan Li, Shannon L. Wyszomierski, Qingfei Wang, Ping Li, Ötgur Sahin, Yi Xiao, Siyuan Zhang, Yan Xiong, Jun Yang, Hai Wang, Hua Guo, Jitao D. Zhang, Daniel Medina, William J. Muller, and Dihua Yu

**Précis:** This study establishes a powerful oncogenic function for a factor with a broad-acting modifier role in signaling that is commonly overexpressed in breast cancer cells, with potential implications for etiology, diagnosis, and prognosis.

### 374 Activation of the FGFR–STAT3 Pathway in Breast Cancer Cells Induces a Hyaluronan-Rich Microenvironment That Licenses Tumor Formation


**Précis:** Aberrant growth factor receptor signaling in tumor cells leads to profound changes in their microenvironment that can promote therapeutic resistance and posttreatment relapses.

### 387 Proteogenomic Analysis Reveals Unanticipated Adaptations of Colorectal Tumor Cells to Deficiencies in DNA Mismatch Repair

Patrick J. Halvey, Xiaojing Wang, Jing Wang, Ajaz A. Bhat, Punita Dhawan, Ming Li, Bing Zhang, Daniel C. Liebler, and Robbert J.C. Slebos

**Précis:** Global proteomic profiling reveals adaptations to mutations in DNA mismatch repair that occur in certain colon cancers that were not previously appreciated, providing a broader basis to mechanistically interpret phenotypes seen in colon cancer patients.

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### ABOUT THE COVER

Changes in intratumoral macrophages in response to CSF-1R inhibitor, PLX3397. C57BL/6 mice with established SM1-OVA murine melanoma tumors received OT-1 ACT without the small molecule inhibitor, PLX3397. Tissue immunofluorescence microscopy was performed to detect macrophages by anti-F4/80-FITC staining (green) and nuclei stained with DAPI (blue). SM1-OVA tumors in the OT-1 ACT group were infiltrated with more intratumoral macrophages compared with other groups treated with PLX3397. For details, see article by Mok and colleagues on page 153.