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, Carolyln 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
Dannys Laoui, Eva Van Overmeire, Gisay Di Conza, Chiara Aldeni, Jiri Keirse, Yannick Morias, Kiavash Movahedi, Isabelle Houbraeken, Elio Schouppe, Yvon Elkrim, Oussama Karroum, Bénédicte Jordan, Peter Carmeliet, Conny Gysemans, Patrick De Baetselier, Massimiliano Mazzon, and Jo A. Van Ginderachter

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 Yong-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

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. Schwierer, Shruti Lal, Nikolai A. Bildzikiewicz, Charles J. Yeo, Karen E. Knudsen, Jonathan R. Brody, and John M. Pascal

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

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

37 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.

36 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.

36 This study describes a system to test cancer cells from patients against a panel of drugs and to generate computational models with the potential to inform the best treatment for individual patents.
Table of Contents

MICROENVIRONMENT AND IMMUNOLOGY

68 Regulation of CD4\(^{+}\)NKG2D\(^{+}\) Th1 Cells in Patients with Metastatic Melanoma Treated with Sorafenib: Role of IL-15 and NKG2D Triggering


Précis: These important findings suggest that the multikinase inhibitor sorafenib acts as an immunotherapy to modulate T cells in the cancer patient, inducing a rare but clinically important subset of T cells that has been associated with prolonged survival in metastatic melanoma patients.

81 Mature Cytotoxic CD56\(^{bright}\)/CD16\(^{−}\) Natural Killer Cells Can Infiltrate Lymph Nodes Adjacent to Metastatic Melanoma

Meriem Messaouene, Giulia Fregni, Emmanuelle Fourmentiaux-Neves, Johan Chanal, Eve Maubec, Sarra Mazouz-Dorval, Benoit Coutaudud, Angélique Girod, Xavier Sastre-Garau, Sébastien Albert, Charles Guédon, Lydia Deschamps, Delphine Mitilian, Isabelle Cremer, Nicolas Jacquelot, Sylvie Russakiewicz, Laurence Zitvogel, Marie-Francoise Avril, and Anne Caïnard

Précis: Metastatic lymph nodes from melanoma patients contain a unique subset of natural killer cells endowed with high cytotoxic potential toward melanoma cells, the activation of which can be realized by exposure to IL-2 or IL-15.

93 T Lymphocytes Expressing a CD16 Signaling Receptor Exert Antibody-Dependent Cancer Cell Killing

Ko Kudo, Chihaya Imai, Paolo Lorenzini, Takahiro Kamiya, Koji Kono, Andrew M. Davidoff, Wee Joo Chng, and Dario Campana

Précis: This report describes a means to endow T lymphocytes with antibody-dependent cell cytotoxicity, offering a powerful strategy to improve antibody-based immunotherapies for human cancer.

104 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, Noni Janakshavili, Bernard Bonnotte, Emmanuel Katsanis, and Nicolas Larmonier

Précis: 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.

119 Cytokine-Induced Killer Cells Eradicate Bone and Soft-Tissue Sarcomas

Dario Sangiolo, Giulia Mesiano, Loretta Gammaitoni, Valeria Leuci, Maja Todorovic, Lidia Giraudo, Cristina Cammarata, Carmine Dell’Aglio, Lorenzo D’Ambrosio, Alberto Picacane, Ivana Sarotto, Sara Miano, Ivana Ferrero, Fabrizio Carnevale-Schianca, Ymera Pignochino, Francesco Sassi, Andrea Bertotti, Wanda Piaccibello, Franca Fagioli, Massimo Aglietta, and Giovanni Grignani

Précis: This report offers a preclinical proof-of-concept for a novel type of cellular immunotherapy to attack untreatable metastatic sarcomas, which continue to pose a major clinical challenge.

130 Transcriptional Profiling of Melanoma Sentinel Nodes Identify Patients with Poor Outcome and Reveal an Association of CD30\(^{+}\) T Lymphocytes with Progression

Viviana Vallacchi, Elisabetta Vergani, Chiara Camisaschi, Paola Debo, Antonello D. Cabras, Marialisa Sensi, Loris De Cocco, Niccolò Bassani, Federico Ambrogi, Antonino Carbone, Federica Crippa, Barbara Vergani, Paola Frati, Flavio Arienti, Roberto Patuzzo, Antonello Villa, Elia Biganozzi, Silvana Canevari, Mario Santinini, Chiara Castelli, Licia Rovoltini, and Monica Rodolfo

Précis: By deepening the evidence that sentinel lymph nodes help direct tumoral immunosuppression, this study identifies an immune activation marker associated with poor prognosis that might allow targeting by a drug recently approved by the FDA.

141 Effects of Notch Signaling on Regulation of Myeloid Cell Differentiation in Cancer

Pengyan Cheng, Vinit Kumar, Hao Liu, Je-In Youn, Mayer Fishman, Simon Sherman, and Dmitry Gabrilovich

Précis: These results suggest new insights into how abnormal myeloid cells accumulate in tumors, with possible implications for therapy of cancers driven by Notch.

153 Inhibition of CSF-1 Receptor Improves the Antitumor Efficacy of Adoptive Cell Transfer Immunotherapy

Stephen Mok, Richard C. Koya, Christopher Tsui, Jingying Xu, Lidia Robert, Lily Wu, Thomas G. Graeber, Brian L. West, Gideon Bollag, and Antoni Ribas

Précis: These findings suggest an important new use for inhibitors of a myeloid cell receptor that is responsible for recruiting immune-suppressive cells into tumors as a strategy to enhance adoptive T-cell immunotherapy.
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. Hebron, 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 1ε 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 González, 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 Zykovka, 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 Identifies 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, Iwanka 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. Kurnasheva, 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, Sachise 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, Weiqiao Feng, Angera H. Kuo, Ferenc A. Scheeren, Jesse M. Engreitz, Sushama 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.
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, Özgür Sahin, Yi Xiao, Siyuan Zhang, Yan Xiaoy, Jun Yang, Hai Wang, Hua Guo, Jiato 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.

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.

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.

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.