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- 8 **Inflammation Amplifier, a New Paradigm in Cancer Biology**
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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, Pixu Liu, Fan Zhang, Erbo Xu, Lynn Symonds,Carolynn E. Ohlson, Roderick T. Bronson, Sauveur-Michel Maira, Emmanuelle Di Tomaso, Jane Li, Andrea P. Myers, Lewis C. Cantley, Gordon B. Mills, and Jean J. Zhao
Précis: These findings suggest insights into the basis for development of an aggressive form of endometrial cancer that is driven by deregulated mTOR signaling.
- 24 **Tumor Hypoxia Does Not Drive Differentiation of Tumor-Associated Macrophages but Rather Fine-Tunes the M2-like Macrophage Population**
Damyia Laoui, Eva Van Overmeire, Giusy Di Conza, Chiara Aldeni, Jiri Keirsse, Yannick Morias, Kiavash Movahedi, Isabelle Houbracken, Elio Schouppe, Yvon Elkrim, Oussama Karroum, Bénédicte Jordan, Peter Carmeliet, Conny Gysemans, Patrick De Baetselier, Massimiliano Mazzone, and Jo A. Van Ginderachter
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.

- 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. Bildzukewicz, Charles J. Yeo, Karen E. Knudsen, Jonathan R. Brody, and John M. Pascal
Précis: This study establishes a new strategy to selectively inhibit the DNA repair enzyme PARP-1, a clinically validated target for cancer treatment.
- 38 **The NADH Oxidase ENOX1, a Critical Mediator of Endothelial Cell Radiosensitization, Is Crucial for Vascular Development**
Amudhan Venkateswaran, Konjeti R. Sekhar, Daniel S. Levic, David B. Melville, Travis A. Clark, Witold M. Rybski, Alexandra J. Walsh, Melissa C. Skala, Peter A. Crooks, Ela W. Knapik, and Michael L. Freeman
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.

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
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.
- 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 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 patients.

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MICROENVIRONMENT AND IMMUNOLOGY

68 Regulation of CD4⁺NKG2D⁺ Th1 Cells in Patients with Metastatic Melanoma Treated with Sorafenib: Role of IL-15R α and NKG2D Triggering

Ana I. Romero, Nathalie Chaput, Vichnou Poirier-Colame, Sylvie Rusakiewicz, Nicolas Jacquolot, Kariman Chaba, Erwan Mortier, Yannick Jacques, Sophie Caillat-Zucman, Caroline Flament, Anne Caignard, Meriem Messaoudene, Anne Aupérin, Philippe Vielh, Philippe Dessen, Camillo Porta, Christine Mateus, Maha Ayyoub, Danila Valmori, Alexander Eggermont, Caroline Robert, and Laurence Zitvogel

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 Messaoudene, Giulia Fregni, Emmanuelle Fourmentraux-Neves, Johan Chanal, Eve Maubec, Sarra Mazouz-Dorval, Benoit Couturaud, Angélique Girod, Xavier Sastre-Garau, Sébastien Albert, Charles Guédon, Lydia Deschamps, Delphine Mitilian, Isabelle Cremer, Nicolas Jacquolot, Sylvie Rusakiewicz, Laurence Zitvogel, Marie-Françoise Avril, and Anne Caignard

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, Nona Janikashvili, 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 Giraud, Cristina Cammarata, Carmine Dell'Aglio, Lorenzo D'Ambrosio, Alberto Pisacane, Ivana Sarotto, Sara Miano, Ivana Ferrero, Fabrizio Carnevale-Schianca, Ymera Pignochino, Francesco Sassi, Andrea Bertotti, Wanda Piacibello, 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 Deho, Antonello D. Cabras, Marialuisa Sensi, Loris De Cecco, Niccolò Bassani, Federico Ambrogi, Antonino Carbone, Federica Crippa, Barbara Vergani, Paola Frati, Flavio Arienti, Roberto Patuzzo, Antonello Villa, Elia Biganzoli, Silvana Canevari, Mario Santinami, Chiara Castelli, Licia Rivoltini, 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

Pingyan 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.

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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 1 ϵ 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, Fadlo 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.

- 224** **3'-UTR Poly(T/U) Tract Deletions and Altered Expression of *EWSR1* Are a Hallmark of Mismatch Repair–Deficient Cancers**
 Shivendra Kishore, Salvatore Piscuoglio, Michal B. Kovac, Annette Gylling, Friedel Wenzel, Francesca Trapani, Hans Joerg Altermatt, Valentina Mele, Giancarlo Marra, Päivi Peltomäki, Luigi Terracciano, Mihaela Zavolan, and Karl Heinimann
Précis: This study identifies a novel genetic locus that is fully informative and accurate in detecting mismatch-repair deficient cancers, with major implications for routine daily practice in the clinic.

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 Zykova, 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.

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263 A Reevaluation of CD22 Expression in Human Lung Cancer

Laurentiu M. Pop, Stephen Barman, Chunli Shao, Jonathan C. Poe, Guglielmo M. Venturi, John M. Shelton, Iliodora V. Pop, David E. Gerber, Luc Girard, Xiao-yun Liu, Carmen Behrens, Jaime Rodriguez-Canales, Hui Liu, Ignacio I. Wistuba, James A. Richardson, John D. Minna, Thomas F. Tedder, and Ellen S. Vitetta

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.

272 USP22 Regulates Oncogenic Signaling Pathways to Drive Lethal Cancer Progression

Randy S. Schrecengost, Jeffrey L. Dean, Jonathan F. Goodwin, Matthew J. Schiewer, Mark W. Urban, Timothy J. Stanek, Robyn T. Sussman, Jessica L. Hicks, Ruth C. Birbe, Rossitza A. Draganova-Tacheva, Tapio Visakorpi, Angelo M. DeMarzo, Steven B. McMahon, and Karen E. Knudsen

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.

287 Genome-wide Profiling of Genetic Synthetic Lethality Identifies CDK12 as a Novel Determinant of PARP1/2 Inhibitor Sensitivity

Ilijana 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.

298 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.

TUMOR AND STEM CELL BIOLOGY

309 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.

320 Δ Np63 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.

330 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.

341 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, Weiguo 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.

353 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.

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363 **14-3-3 ζ 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, Ozgur 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**

Laura R. Bohrer, Pavlina Chuntova, Lindsey K. Bade, Thomas C. Beadnell, Ronald P. Leon, Nicholas J. Brady, Yungil Ryu, Jodi E. Goldberg, Stephen C. Schmechel, Joseph S. Koopmeiners, James B. McCarthy, and Kathryn L. Schwertfeger

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

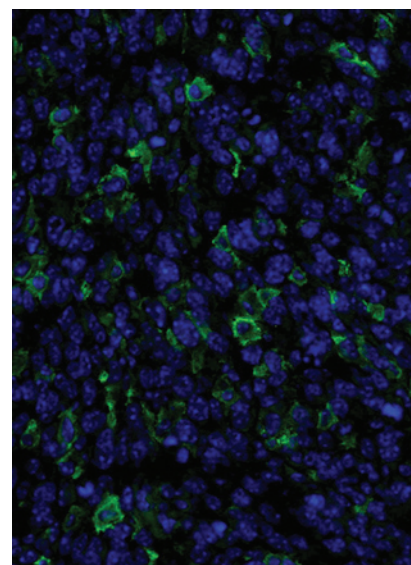
Précis: *Global proteomic profiling reveals adaptations to mutations in DNA mismatch repair that occur in certain colon cancers that were not previously appreciated, providing a broader basis to mechanistically interpret phenotypes seen in colon cancer patients.*

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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.



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