


BREAKING ADVANCES

- 219** Highlights from Recent Cancer Literature


REVIEWS

- 221** The RAS–Effector Interaction as a Drug Target
Adam B. Keeton, E. Alan Salter, and Gary A. Piazza
- 227** Mutated Chromatin Regulatory Factors as Tumor Drivers in Cancer
 Carl Koschmann, Felipe J. Nunez, Flor Mendez, Jacqueline A. Brosnan-Cashman, Alan K. Meeker, Pedro R. Lowenstein, and Maria G. Castro

MEETING REPORT

- 234** A Conference of New Ideas in Cancer—Challenging Dogmas
Varsha Gandhi and Rakesh Jalali

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 238** Quantitative Fluorescence Microscopy Measures Vascular Pore Size in Primary and Metastatic Brain Tumors
 Rajendar K. Mittapalli, Chris E. Adkins, Kaci. A. Bohn, Afroz S. Mohammad, Julie A. Lockman, and Paul R. Lockman
Précis: In vivo fluorescent imaging calculates chemotherapeutic permeability into tumors in the brain and details a new hypothesis on how monoclonal antibodies work in brain metastases of breast cancer.
- 247** Label-Free Raman Spectroscopy Detects Stromal Adaptations in Premetastatic Lungs Primed by Breast Cancer
Santosh Kumar Paidi, Asif Rizwan, Chao Zheng, Menglin Cheng, Kristine Glunde, and Ishan Barman
Précis: This imaging study elucidates stromal adaptations in premetastatic lung sites, enabling an objective recognition of tumor metastatic potential.

- 257** A Novel Platinum(II)–Based Bifunctional ADC Linker Benchmarked Using ⁸⁹Zr-Desferal and Auristatin F–Conjugated Trastuzumab
Niels J. Sijbrandi, Eugen Merkul, Joey A. Muns, Dennis C.J. Waalboer, Kevin Adamzek, Marije Bolijn, Veronica Montserrat, Govert W. Somsen, Rob Haselberg, Paul J.G.M. Steverink, Hendrik-Jan Houthoff, and Guus A.M.S. van Dongen
Précis: This study illustrates the potential of a robust conjugation platform for the preparation of antibody–drug conjugates that have potent anticancer properties.

MICROENVIRONMENT AND IMMUNOLOGY


- 268** Lysyl Oxidase Is a Strong Determinant of Tumor Cell Colonization in Bone
Caroline Reynaud, Laura Ferreras, Paola Di Mauro, Casina Kan, Martine Croset, Edith Bonnelye, Floriane Pez, Clémence Thomas, Géraldine Aimond, Antoine E. Karnoub, Marie Brevet, and Philippe Clézardin
Précis: These findings reveal a targetable mechanism that could be exploited to block metastasis of colorectal cancer to bone, an essentially untreatable form of the disease.
- 279** Macrophage-Secreted TNF α and TGF β 1 Influence Migration Speed and Persistence of Cancer Cells in 3D Tissue Culture via Independent Pathways
Ran Li, Jess D. Hebert, Tara A. Lee, Hao Xing, Alexandra Boussommier-Calleja, Richard O. Hynes, Douglas A. Lauffenburger, and Roger D. Kamm
Précis: These findings identify independent cooperating pathways through which macrophages control the speed and persistence of cancer cell migration in 3D tissue microenvironments.
- 291** Basophils Promote Tumor Rejection via Chemotaxis and Infiltration of CD8⁺ T Cells
Ibrahim M. Sektioglu, Rafael Carretero, Nadja Bulbuc, Tobias Bald, Thomas Tüting, Alexander Y. Rudensky, and Günter J. Hämmerling
Précis: These findings elucidate a novel contribution of basophils to tumor rejection that can be exploited to enhance the efficacy of cancer immunotherapy.
- 303** MIF-Induced Stromal PKC β /IL8 Is Essential in Human Acute Myeloid Leukemia
 Amina M. Abdul-Aziz, Manar S. Shafat, Tarang K. Mehta, Federica Di Palma, Matthew J. Lawes, Stuart A. Rushworth, and Kristian M. Bowles
Précis: In identifying the bidirectional MIF/IL8 survival mechanism between AML cells and bone marrow–derived mesenchymal stromal cells, this study provides a rationale to therapeutically target this protumoral feedback loop.

Table of Contents

312 PolyI:C and CpG Synergize with Anti-ErbB2 mAb for Treatment of Breast Tumors Resistant to Immune Checkpoint Inhibitors

Roxanne Charlebois, Bertrand Allard, David Allard, Laurence Buisseret, Martin Turcotte, Sandra Pommey, Pavel Chrobak, and John Stagg

Précis: Immune stimulating polyI:C and CpG oligodeoxynucleotides that have been used safely in clinical trials are found to powerfully enhance the therapeutic efficacy of HER2 monoclonal antibody drugs.

MOLECULAR AND CELLULAR PATHOBIOLOGY

320 IKBKE Is Required during KRAS-Induced Pancreatic Tumorigenesis

Mihir Rajurkar, Kyvan Dang, Maite G. Fernandez-Barrena, Xiangfan Liu, Martin E. Fernandez-Zapico, Brian C. Lewis, and Junhao Mao

Précis: These findings offer preclinical proof of concept for combined inhibition of two key growth and survival signaling pathways as a therapeutic strategy to kill pancreatic cancer cells.

330 KLF6 Suppresses Metastasis of Clear Cell Renal Cell Carcinoma via Transcriptional Repression of E2F1



Yu Gao, Hongzhao Li, Xin Ma, Yang Fan, Dong Ni, Yu Zhang, Qingbo Huang, Kan Liu, Xintao Li, Lei Wang, Liangyou Gu, Yuanxin Yao, Qing Ai, Qingshan Du, Erlin Song, and Xu Zhang

Précis: A key mediator of metastasis in clear cell renal cell carcinoma acts via a novel regulatory axis, suggesting a general strategy to improve management of this disease.

343 Molecular Chaperone HSP90 Is Necessary to Prevent Cellular Senescence via Lysosomal Degradation of p14ARF

Su Yeon Han, Aram Ko, Haruhisa Kitano, Chel Hun Choi, Min-Sik Lee, Jinho Seo, Junya Fukuoka, Soo-Youl Kim, Stephen M. Hewitt, Joon-Yong Chung, and Jaewhan Song

Précis: In elucidating how the tumor suppressor p14ARF is degraded, this study has implications for prognosis and treatment of p14ARF-expressing lung cancers.

355 Vitamin D3 Prevents Calcium-Induced Progression of Early-Stage Prostate Tumors by Counteracting TRPC6 and Calcium Sensing Receptor Upregulation

Sophie Bernichtein, Natascha Pigat, Nicolas Barry Delongchamps, Florence Boutillon, Virginie Verkarre, Philippe Camparo, Edouard Reyes-Gomez, Arnaud Méjean, Stéphane M. Oudard, Eve M. Lepicard, Mélanie Viltard, Jean-Claude Souberbielle, Gérard Friedlander, Thierry Capiod, and Vincent Goffin

Précis: Opposing effects of calcium and vitamin D in prostate cancer progression provide a paradigm to evaluate calcium intake and to consider vitamin D supplementation in patients on active surveillance for low-risk prostate cancer.

366 ZIC5 Drives Melanoma Aggressiveness by PDGFD-Mediated Activation of FAK and STAT3



Reiko Satow, Tomomi Nakamura, Chiaki Kato, Miku Endo, Mana Tamura, Ryosuke Batori, Shiori Tomura, Yumi Murayama, and Kiyoko Fukami

Précis: An siRNA-based screen of neural crest cells from which melanocytes are derived identifies candidate targets to attack melanoma and to overcome drug resistance in this disease.

378 Androgen-Dependent Repression of ERR γ Reprograms Metabolism in Prostate Cancer

Étienne Audet-Walsh, Tracey Yee, Shawn McGuiRK, Mathieu Vernier, Carlo Ouellet, Julie St-Pierre, and Vincent Giguère

Précis: Metabolic insights into how the androgen receptor affects the estrogen-related receptor ERR γ in prostate cancer suggests new routes for its therapeutic management.

390 Mutational Landscape of Pediatric Acute Lymphoblastic Leukemia

Ling-Wen Ding, Qiao-Yang Sun, Kar-Tong Tan, Wenwen Chien, Anand Mayakonda Thippeswamy, Allen Eng Juh Yeoh, Norihiko Kawamata, Yasunobu Nagata, Jin-Fen Xiao, Xin-Yi Loh, De-Chen Lin, Manoj Garg, Yan-Yi Jiang, Liang Xu, Su-Lin Lim, Li-Zhen Liu, Vikas Madan, Masashi Sanada, Lucia Torres Fernández, Hema Preethi, Michael Lill, Hagop M. Kantarjian, Steven M. Kornblau, Satoru Miyano, Der-Cherng Liang, Seishi Ogawa, Lee-Yung Shih, Henry Yang, and H. Phillip Koeffler

Précis: By providing a detailed mutational portrait of pediatric acute lymphocytic leukemias, this study suggests how to target drug-resistant tumors and develop less toxic targeted therapies.

Table of Contents

- 401** **Menin and Daxx Interact to Suppress Neuroendocrine Tumors through Epigenetic Control of the Membrane Metallo-Endopeptidase**
Zijie Feng, Lei Wang, Yanmei Sun, Zongzhe Jiang, John Domsic, Chiying An, Bowen Xing, Jingjing Tian, Xiuheng Liu, David C. Metz, Xiaolu Yang, Ronen Marmorstein, Xiaosong Ma, and Xianxin Hua
Précis: This study suggesting new insights into tumor suppressor interplay in epigenetic regulation of neuroendocrine tumors may impact decisions about their therapy.
- 412** **Polycomb-Mediated Disruption of an Androgen Receptor Feedback Loop Drives Castration-Resistant Prostate Cancer**
 Ka-wing Fong, Jonathan C. Zhao, Jung Kim, Shangze Li, Yeqing A. Yang, Bing Song, Laure Rittie, Ming Hu, Ximing Yang, Bernard Perbal, and Jindan Yu
Précis: These provocative results identify an intracellular function of a matricellular protein in directing cytosolic regulation of androgen receptor signaling and prostate cancer progression.
- 423** **Integrative Comparison of mRNA Expression Patterns in Breast Cancers from Caucasian and Asian Americans with Implications for Precision Medicine**
Yanxia Shi, Albert Steppi, Ye Cao, Jianan Wang, Max M. He, Liren Li, and Jinfeng Zhang
Précis: Genetic associations identified in this study may enable a more focused study of genotypic differences that can explain the disparity in BRCA incidence and mortality rates between Asian and Caucasian patient populations in the U.S.
- 434** **Plk4 Promotes Cancer Invasion and Metastasis through Arp2/3 Complex Regulation of the Actin Cytoskeleton**
Karineh Kazazian, Christopher Go, Hannah Wu, Olga Brashavitskaya, Roland Xu, James W. Dennis, Anne-Claude Gingras, and Carol J. Swallow
Précis: These findings reveal a novel role for Plk4 in promoting cancer invasion and metastasis through regulation of Arp2/3-mediated actin cytoskeletal rearrangement, thus validating Plk4 as a viable therapeutic target in cancer treatment.
- 448** **Chemopreventive Effects of ROS Targeting in a Murine Model of BRCA1-Deficient Breast Cancer**
Mo Li, Qian Chen, and Xiaochun Yu
Précis: This potentially seminal study suggests an answer to the long-standing question of why germline BRCA1 mutations cause tissue-specific tumors, with immediate implications for evaluating suitable antioxidant modalities as a strategy to mitigate the risks of familial breast cancer increased by BRCA1 mutation.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY


- 459** **Quantification of Pathway Cross-talk Reveals Novel Synergistic Drug Combinations for Breast Cancer**
 Samira Jaeger, Ana Igea, Rodrigo Arroyo, Victor Alcalde, Begoña Canovas, Modesto Orozco, Angel R. Nebreda, and Patrick Aloy
Précis: This study uses a computational approach to discover synergistic combinations between targeted drugs to treat breast cancer, with the capability of providing broad-spectrum utility across several cancer types.
- 470** **Transcriptional Selectivity of Epigenetic Therapy in Cancer**
Takahiro Sato, Matteo Cesaroni, Woonbok Chung, Shoghag Panjarian, Anthony Tran, Jozef Madzo, Yasuyuki Okamoto, Hanghang Zhang, Xiaowei Chen, Jaroslav Jelinek, and Jean-Pierre J. Issa
Précis: In providing a comprehensive analysis of the specificity of epigenetic therapy in cancer, this study shows how combined targeting of DNA and histone methylation may offer an improved efficacy of this type of therapy for cancer treatment.
- 482** **EpCAM Inhibition Sensitizes Chemoresistant Leukemia to Immune Surveillance**
Xiaohu Zheng, Xiaolei Fan, Binqing Fu, Meijuan Zheng, Aimei Zhang, Kai Zhong, Jialai Yan, Rui Sun, Zhigang Tian, and Haiming Wei
Précis: This study shows how yet another cancer cell-targeting strategy actually mediates its efficacy by modulating the immune system, a growing theme in targeted drug development.
- 494** **Aurora A and NF- κ B Survival Pathway Drive Chemoresistance in Acute Myeloid Leukemia via the TRAF-Interacting Protein TIFA**
 Tong-You Wade Wei, Pei-Yu Wu, Ting-Jung Wu, Hsin-An Hou, Wen-Chien Chou, Chieh-Lin Jerry Teng, Chih-Ru Lin, Jo-Mei Maureen Chen, Ting-Yang Lin, Hsiang-Chun Su, Chia-Chi Flora Huang, Chang-Tze Ricky Yu, Shih-Lan Hsu, Hwei-Fang Tien, and Ming-Daw Tsai
Précis: These findings show how a survival signaling pathway mediated by a key mitotic regulator can be targeted to enhance the chemosensitivity of deadly leukemias.

Table of Contents

509 **Genomic Profiling of a Large Set of Diverse Pediatric Cancers Identifies Known and Novel Mutations across Tumor Spectra**



Juliann Chmielecki, Mark Bailey, Jie He, Julia Elvin, Jo-Anne Vergilio, Shakti Ramkissoon, James Suh, Garrett M. Frampton, James X. Sun, Samantha Morley, Daniel Spritz, Siraj Ali, Laurie Gay, Rachel L. Erlich, Jeffrey S. Ross, Joana Buxhaku, Hilary Davies, Vinny Faso, Alexis Germain, Blair Glanville, Vincent A. Miller, Philip J. Stephens, Katherine A. Janeway, John M. Maris, Soheil Meshinchi, Trevor J. Pugh, Jack F. Shern, and Doron Lipson

Précis: Analysis of an aggregate genomic dataset for pediatric tumors may illuminate novel therapeutic targets, validate oncogenic mechanisms, guide treatment decisions, and design appropriate clinical trials for children with cancer.

520 **Biphasic Rapamycin Effects in Lymphoma and Carcinoma Treatment**

Yang Liu, Srilakshmi Pandeswara, Vinh Dao, Álvaro Padrón, Justin M. Drerup, Shunhua Lao, Aijie Liu, Vincent Hurez, and Tyler J. Curiel

Précis: These findings show how novel low-dose administration of mTOR inhibitors can effectively cooperate with, rather than antagonize immunotherapy, resuscitating interest in mTOR-targeting therapies, which have otherwise been mainly disappointing in clinical trials.

532 **Circadian Clock Gene *Bmal1* Inhibits Tumorigenesis and Increases Paclitaxel Sensitivity in Tongue Squamous Cell Carcinoma**

Qingming Tang, Bo Cheng, Mengru Xie, Yatao Chen, Jiajia Zhao, Xin Zhou, and Lili Chen

Précis: By identifying a novel tumor suppressor gene that sensitizes cancer cells to paclitaxel, this study may have implications for timed chronotherapy of head and neck cancer, where this drug is used.

545 **Breast Cancer Resistance to Antiestrogens Is Enhanced by Increased ER Degradation and ERBB2 Expression**

Tomohiro Shibata, Kosuke Watari, Hiroto Izumi, Akihiko Kawahara, Satoshi Hattori, Chihiro Fukumitsu, Yuichi Murakami, Ryuji Takahashi, Uhi Toh, Ken-ichi Ito, Shigehiro Ohdo, Maki Tanaka, Masayoshi Kage, Michihiko Kuwano, and Mayumi Ono

Précis: These findings unravel a novel mechanism of resistance to antiestrogen drugs in ER⁺ breast cancer cells, with potential prognostic and therapeutic implications.

557 **A Novel Spectroscopically Determined Pharmacodynamic Biomarker for Skin Toxicity in Cancer Patients Treated with Targeted Agents**

Antoine Azan, Peter J. Caspers, Tom C. Bakker Schut, Séverine Roy, Céline Boutros, Christine Mateus, Emilie Routier, Benjamin Besse, David Planchard, Atmane Seck, Nyam Kamsu Kom, Gorana Tomasic, Senada Koljenović, Vincent Noordhoek Hegt, Matthieu Texier, Emilie Lanoy, Alexander M.M. Eggermont, Angelo Paci, Caroline Robert, Gerwin J. Puppels, and Lluís M. Mir

Précis: This study describes a noninvasive imaging technique to rapidly assess skin toxicity caused by diverse cancer treatments, addressing a common type of side effect experienced by patients receiving cancer therapy.

566 **Systematic Drug Screening Identifies Tractable Targeted Combination Therapies in Triple-Negative Breast Cancer**

Vikram B. Wali, Casey G. Langdon, Matthew A. Held, James T. Platt, Gauri A. Patwardhan, Anton Safonov, Bilge Aktas, Lajos Pusztai, David F. Stern, and Christos Hatzis

Précis: Through a guided screen of FDA-approved and investigational drugs, this study suggests new treatments for aggressive triple-negative breast cancers that can be immediately translated to clinical trials.

TUMOR AND STEM CELL BIOLOGY

579 **SPINK6 Promotes Metastasis of Nasopharyngeal Carcinoma via Binding and Activation of Epithelial Growth Factor Receptor**

Li-Sheng Zheng, Jun-Ping Yang, Yun Cao, Li-Xia Peng, Rui Sun, Ping Xie, Meng-Yao Wang, Dong-Fang Meng, Dong-Hua Luo, Xiong Zou, Ming-Yuan Chen, Hai-Qiang Mai, Ling Guo, Xiang Guo, Jian-Yong Shao, Bi-Jun Huang, Wei Zhang, and Chao-Nan Qian

Précis: These findings identify a novel EGFR ligand and candidate prognostic marker for metastasis in nasopharyngeal carcinoma.



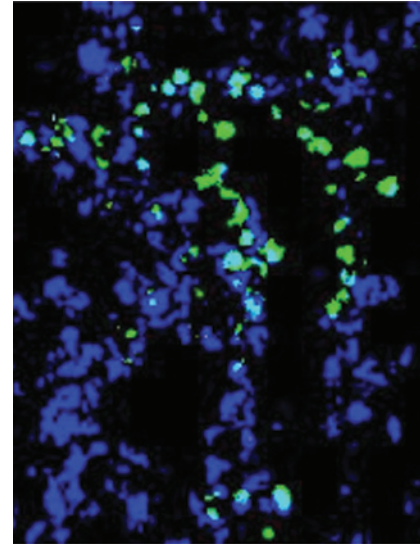
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Table of Contents

ABOUT THE COVER

Epithelial cell adhesion molecule (EpCAM) is frequently overexpressed in patients with myeloid leukemia, but not in normal donors. Therefore, EpCAM has the potential to serve as an effective therapeutic target in leukemia. In a myeloid leukemia xenograft model, the mice were treated with anti-EpCAM antibody or IgG for 3 weeks. Immunofluorescence staining for intratumor apoptotic leukemia cells (TUNEL positive, green) was increased in tumors treated with anti-EpCAM antibody. Nuclei were stained with DAPI (blue). For details, see article by Zheng and colleagues on page 482.



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