


BREAKING ADVANCES


- 1781** Highlights from Recent Cancer Literature

REVIEWS

- 1783** **The Host Microbiome Regulates and Maintains Human Health: A Primer and Perspective for Non-Microbiologists**
Sunil Thomas, Jacques Izard, Emily Walsh, Kristen Batich, Pakawat Chongsathidkiet, Gerard Clarke, David A. Sela, Alexander J. Muller, James M. Mullin, Korin Albert, John P. Gilligan, Katherine DiGiulio, Rima Dilbarova, Walker Alexander, and George C. Prendergast

- 1813** **Behind the Scenes: Endo/Exocytosis in the Acquisition of Metastatic Traits**
 Letizia Lanzetti and Pier Paolo Di Fiore

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1818** **Effective Combination Therapies for B-cell Lymphoma Predicted by a Virtual Disease Model**
 Wei Du, Rebecca Goldstein, Yanwen Jiang, Omar Aly, Leandro Cerchiatti, Ari Melnick, and Olivier Elemento
Précis: A kinetic modeling-based computational approach identifies effective combination therapy in B-cell lymphoma

- 1831** **Combined PET Imaging of the Inflammatory Tumor Microenvironment Identifies Margins of Unique Radiotracer Uptake**
Bastian Zinnhardt, Hayet Pigeon, Benoit Thézé, Thomas Viel, Lydia Wachsmuth, Inga B. Fricke, Sonja Schelhaas, Lisa Honold, Katrin Schwegmann, Stefan Wagner, Andreas Faust, Cornelius Faber, Michael T. Kuhlmann, Sven Hermann, Michael Schäfers, Alexandra Winkeler, and Andreas H. Jacobs
Précis: These findings provide a novel method to improve clinical management of patients with gliomas by providing essential information about the tumor microenvironment, thus opening new avenues for the assessment of personalized immunotherapies.


- 1842** **Lapatinib Resistance in Breast Cancer Cells Is Accompanied by Phosphorylation-Mediated Reprogramming of Glycolysis**
Benjamin Ruprecht, Esther A. Zaal, Jana Zecha, Wei Wu, Celia R. Berkers, Bernhard Kuster, and Simone Lemeer
Précis: This study of the EGFR/HER2 inhibitor lapatinib shows how posttranslational modifications can trigger drug resistance in cancer.

- 1854** **Cellular Model of Colon Cancer Progression Reveals Signatures of mRNAs, miRNA, lncRNAs, and Epigenetic Modifications Associated with Metastasis**
Matjaz Rokavec, David Horst, and Heiko Hermeking
Précis: These findings identify numerous novel metastasis-associated changes in mRNA/miRNA/lncRNA expression and epigenetic alterations in colon cancers that offer a wellspring of candidate prognostic markers and therapeutic targets.

MICROENVIRONMENT AND IMMUNOLOGY

- 1868** **PanIN Neuroendocrine Cells Promote Tumorigenesis via Neuronal Cross-talk**
Smrita Sinha, Ya-Yuan Fu, Adrien Grimont, Maren Ketcham, Kelly Lafaro, Joseph A. Saglimbeni, Gokce Askan, Jennifer M. Bailey, Jerry P. Melchor, Yi Zhong, Min Geol Joo, Olivera Grbovic-Huezo, In-Hong Yang, Olca Basturk, Lindsey Baker, Young Park, Robert C. Kurtz, David Tuveson, Steven D. Leach, and Pankaj J. Pasricha
Précis: Nerves in certain tumors provide a physical route for invasive migration, but this study suggests they can also enable oncogenic signals that drive malignant progression.

- 1880** **LIGHT Elevation Enhances Immune Eradication of Colon Cancer Metastases**
Guilin Qiao, Jianzhong Qin, Nicholas Kunda, Jed F. Calata, Dolores L. Mahmud, Peter Gann, Yang-Xin Fu, Steven A. Rosenberg, Bellur S. Prabhakar, and Ajay V. Maker
Précis: Increasing expression of the immunostimulatory cytokine LIGHT in the tumor microenvironment improves T-cell activation and infiltration in colon tumors and liver metastases.

- 1892** **Differential PI3K δ Signaling in CD4⁺ T-cell Subsets Enables Selective Targeting of T Regulatory Cells to Enhance Cancer Immunotherapy**
 Shamim Ahmad, Rasha Abu-Eid, Rajeev Shrimali, Mason Webb, Vivek Verma, Atbin Doroodchi, Zuzana Berrong, Raed Samara, Paulo C. Rodriguez, Mikayel Mkrtychyan, and Samir N. Khleif
Précis: These findings offer a mechanistic rationale to employ specific inhibitors of the PI3K δ isoform to selectively target T regulatory cells and improve cancer immunotherapy.


- 1905** **Extracellular Matrix Receptor Expression in Subtypes of Lung Adenocarcinoma Potentiates Outgrowth of Micrometastases**
 Laura E. Stevens, William K.C. Cheung, Sally J. Adua, Anna Arnal-Estapé, Minghui Zhao, Zongzhi Liu, Kelly Brewer, Roy S. Herbst, and Don X. Nguyen
Précis: These findings reveal an important mechanism by which disseminated cancer cells program an inflammatory extracellular matrix to persist and to enable brain metastasis.

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- 1918** CD40 Signaling Drives Potent Cellular Immune Responses in Heterologous Cancer Vaccinations
Supot Nimanong, Dmitriy Ostroumov, Jessica Wingerath, Sarah Knocke, Norman Woller, Engin Gürlevik, Christine S. Falk, Michael P. Manns, Florian Kühnel, and Thomas C. Wirth

Précis: These findings show how antitumor T-cell responses after vaccination can be empowered by a secondary peptide vaccination that includes coadministration of CD40 and TLR3 agonists, which strengthen the magnitude of dendritic cell responses.

- 1927** Evolution of Cancer Stem-like Cells in Endocrine-Resistant Metastatic Breast Cancers Is Mediated by Stromal Microvesicles



Pasquale Sansone, Marjan Berishaj, Vinagolu K. Rajasekhar, Claudio Ceccarelli, Qing Chang, Antonio Strillacci, Claudia Savini, Lauren Shapiro, Robert L. Bowman, Chiara Mastroleo, Sabrina De Carolis, Laura Daly, Alberto Benito-Martin, Fabiana Perna, Nicola Fabbri, John H. Healey, Enzo Spisni, Monica Cricca, David Lyden, Massimiliano Bonafé, and Jacqueline Bromberg

Précis: These striking results show how horizontal transfer of noncoding RNA from host stromal cells to cancer cells is sufficient to promote the formation of therapy-resistant cancer stem-like cells

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 1942** Role of Megakaryocytes in Breast Cancer Metastasis to Bone
Walter Jackson III, Donna M. Sosnoski, Sara E. Ohanessian, Paige Chandler, Adam Mobley, Kacey D. Meisel, and Andrea M. Mastro

Précis: Megakaryocytes, the cells that produce platelets, may suppress breast cancer metastasis despite the fact that thromboembolisms are a leading cause of death in cancer patients.

- 1955** The STAT3-miRNA-92-Wnt Signaling Pathway Regulates Spheroid Formation and Malignant Progression in Ovarian Cancer

Min-Wei Chen, Shu-Ting Yang, Ming-Hsien Chien, Kuo-Tai Hua, Chin-Jui Wu, S.M. Hsiao, Hao Lin, Michael Hsiao, Jen-Liang Su, and Lin-Hung Wei

Précis: These findings define a STAT3-miR-92a-DKK1 pathway in the generation of cancer stem-like cells in ovarian tumors, with potential therapeutic applications in blocking their progression.

- 1968** Sodium Channel Subunit SCNN1B Suppresses Gastric Cancer Growth and Metastasis via GRP78 Degradation

Yun Qian, Chi Chun Wong, Jiaying Xu, Huarong Chen, Yanquan Zhang, Wei Kang, Hua Wang, Li Zhang, Weilin Li, Eagle S.H. Chu, Minnie Y.Y. Go, Philip W.Y. Chiu, Enders K.W. Ng, Francis K.L. Chan, Joseph J.Y. Sung, Jianmin Si, and Jun Yu

Précis: This study defines a novel tumor suppressor gene in gastric cancer that functions in the unfolded protein response, an important stress response that limits cancer cell growth, with clinical implications as a survival biomarker in patients.

- 1983** Distinct Interactions of EBP1 Isoforms with FBXW7 Elicits Different Functions in Cancer
Yuli Wang, Pengju Zhang, Yunshan Wang, Panpan Zhan, Chunyan Liu, Jian-Hua Mao, and Guangwei Wei

Précis: These results establish differential interactions between the SCF-type ubiquitin ligase FBXW7 and functionally distinct isoforms of the ErbB3-binding adaptor protein EBP1, providing insights into their roles in cancer.

- 1997** eIF5A-PEAK1 Signaling Regulates YAP1/TAZ Protein Expression and Pancreatic Cancer Cell Growth

Jan Strnad, Sunkyu Choi, Ken Fujimura, Huawei Wang, Wei Zhang, Meghan Wyse, Tracy Wright, Emilie Gross, Carlos Peinado, Hyun Woo Park, Jack Bui, Jonathan Kelber, Michael Bouvet, Kun-Liang Guan, and Richard L. Klemke

Précis: The focal adhesion kinase PEAK1 drives aggressive pancreatic cancer cell behaviors by activating a stem cell-like transcription factor program

- 2008** miRNA-520f Reverses Epithelial-to-Mesenchymal Transition by Targeting ADAM9 and TGFBR2
Jasmijn G.M. van Kampen, Onno van Hooij, Cornelius F. Jansen, Frank P. Smit, Paula I. van Noort, Iman Schultz, Roel Q.J. Schaapveld, Jack A. Schalken, and Gerald W. Verhaegh

Précis: A little studied microRNA is found to inhibit tumor cell invasion and metastasis, possibly offering a general therapeutic target for the treatment of advanced cancer.

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THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 2018** **Radiation Resistance in KRAS-Mutated Lung Cancer Is Enabled by Stem-like Properties Mediated by an Osteopontin–EGFR Pathway**
Meng Wang, Jing Han, Lynnette Marcar, Josh Black, Qi Liu, Xiangyong Li, Kshithija Nagulapalli, Lecia V. Sequist, Raymond H. Mak, Cyril H. Benes, Theodore S. Hong, Kristin Gurtner, Mechthild Krause, Michael Baumann, Jing X. Kang, Johnathan R. Whetstone, and Henning Willers
Précis: In elucidating mechanisms that link the stem-like phenotype of KRAS-mutated lung cancer cells to radiation resistance, this study identifies potential therapeutic targets to overcome this resistance.
- 2029** **Ex Vivo Explant Cultures of Non–Small Cell Lung Carcinoma Enable Evaluation of Primary Tumor Responses to Anticancer Therapy**
 Ellie Karekla, Wen-Jing Liao, Barry Sharp, John Pugh, Helen Reid, John Le Quesne, David Moore, Catrin Pritchard, Marion MacFarlane, and James Howard Pringle
Précis: This study describes a novel clinically validated ex vivo explant platform to predict tumor responses to anticancer drug treatments.
- 2040** **Armed Oncolytic Adenovirus–Expressing PD-L1 Mini-Body Enhances Antitumor Effects of Chimeric Antigen Receptor T Cells in Solid Tumors**
Kiyonori Tanoue, Amanda Rosewell Shaw, Norihiro Watanabe, Caroline Porter, Bhakti Rana, Stephen Gottschalk, Malcolm Brenner, and Masataka Suzuki
Précis: Degradation of a fundamental mechanism of immune escape can enhance the antitumor activity of CAR T cells in eradicating malignant cells in preclinical models.
- 2052** **Oncolytic Adenoviral Delivery of an EGFR-Targeting T-cell Engager Improves Antitumor Efficacy**
Carlos Alberto Fajardo, Sonia Guedan, Luis Alfonso Rojas, Rafael Moreno, Marcel Arias-Badia, Jana de Sostoa, Carl H. June, and Ramon Alemany
Précis: Immunotherapy with oncolytic adenovirus is improved by arming the virus with a BiTE antibody that binds T cells as well as tumor cells, thereby helping productively target infiltrating T cells in tumors and improving the efficacy of oncolytic viral therapies.
- 2064** **HSPA5 Regulates Ferroptotic Cell Death in Cancer Cells**
Shan Zhu, QiuHong Zhang, Xiaofan Sun, Herbert J. Zeh III, Michael T. Lotze, Rui Kang, and Daolin Tang
Précis: These findings suggest a therapeutic strategy to combat pancreatic cancer by targeting the HSPA5-GPX4 pathway of ferroptosis, a form of regulated cell death driven by oxidative injuries, which promote lipid peroxidation.
- 2078** **Amplification of EGFR Wild-Type Alleles in Non–Small Cell Lung Cancer Cells Confers Acquired Resistance to Mutation-Selective EGFR Tyrosine Kinase Inhibitors**
Shigenari Nukaga, Hiroyuki Yasuda, Katsuya Tsuchihara, Junko Hamamoto, Keita Masuzawa, Ichiro Kawada, Katsuhiko Naoki, Shingo Matsumoto, Sachiyo Mimaki, Shinnosuke Ikemura, Koichi Goto, Tomoko Betsuyaku, and Kenzo Soejima
Précis: This study introduces a novel concept in acquired resistance, namely, the role of wild-type allele-mediated resistance in response to mutation-selective inhibitors in cancer treatment.
- 2090** **E3 Ubiquitin Ligase UBR5 Drives the Growth and Metastasis of Triple-Negative Breast Cancer**
Liqiu Liao, Mei Song, Xin Li, Lili Tang, Tuo Zhang, Lixing Zhang, Yihang Pan, Lotfi Chouchane, and Xiaojing Ma
Précis: This potentially seminal report defines a targetable ubiquitin ligase as a pivotal modifier of metastasis and immune response in aggressive breast and ovarian cancers that fail conventional therapy, with immediate implications for developing it as a broad-based drug target.
- 2102** **OCTN1 Is a High-Affinity Carrier of Nucleoside Analogues**
Christina D. Drenberg, Alice A. Gibson, Stanley B. Pounds, Lei Shi, Dena P. Rhinehart, Lie Li, Shuiying Hu, Guoqing Du, Anne T. Nies, Matthias Schwab, Navjotsingh Pabla, William Blum, Tanja A. Gruber, Sharyn D. Baker, and Alex Sparreboom
Précis: Reduced expression of a high-affinity carrier of nucleoside analogues correlates with poor event-free survival in patients receiving treatment with nucleoside analogs, with implications for treatment strategies in cancer patients receiving these drugs.
- 2112** **Biomarker-Based PET Imaging of Diffuse Intrinsic Pontine Glioma in Mouse Models**
Susanne Kossatz, Brandon Carney, Melanie Schweitzer, Giuseppe Carlucci, Vesselin Z. Miloshev, Uday B. Maachani, Prajwal Rajappa, Kayvan R. Keshari, David Pisapia, Wolfgang A. Weber, Mark M. Souweidane, and Thomas Reiner
Précis: A noninvasive tactic to quantify tumor burden in a deadly pediatric brainstem tumor offers a rapid treatment monitoring option that may help improve management of this cancer.

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TUMOR AND STEM CELL BIOLOGY

2124 Distinct Levels of Radioresistance in Lgr5⁺ Colonic Epithelial Stem Cells versus Lgr5⁺ Small Intestinal Stem Cells

Guoqiang Hua, Chu Wang, Yan Pan, Zhaoshi Zeng, Sang Gyu Lee, Maria Laura Martin, Adriana Haimovitz-Friedman, Zvi Fuks, Philip B. Paty, and Richard Kolesnick

Précis: In the intestine, Lgr5⁺ colonic epithelial stem cells are found to be much more radioresistant than Lgr5⁺ crypt base columnar stem cells, a difference based on a mechanism termed checkpoint adaptation that might generally dictate tissue radiosensitivity.

2134 Cancer Stem Cells Regulate Cancer-Associated Fibroblasts via Activation of Hedgehog Signaling in Mammary Gland Tumors

Giovanni Valenti, Hazel M. Quinn, Guus J.J.E. Heynen, Linxiang Lan, Jane D. Holland, Regina Vogel, Annika Wulf-Goldenberg, and Walter Birchmeier

Précis: Hedgehog inhibitors in clinical trials may be useful to attack many types of cancers by blocking vital cross-talk between cancer stem cells and stromal fibroblasts needed to support tumor viability, as illustrated in this study of breast cancer.

2148 Prominent Oncogenic Roles of EVI1 in Breast Carcinoma

Hui Wang, Thorsten Schaefer, Martina Konantz, Martin Braun, Zsuzsanna Varga, Anna M. Paczulla, Selina Reich, Francis Jacob, Sven Perner, Holger Moch, Tanja N. Fehm, Lothar Kanz, Klaus Schulze-Osthoff, and Claudia Lengerke

Précis: An oncogene associated previously with myeloid leukemia development is discovered to have an important prognostic impact in aggressive triple-negative breast cancers, with possible implications for understanding its pathophysiology.

2161 Cyp24a1 Attenuation Limits Progression of Braf^{V600E}-Induced Papillary Thyroid Cancer Cells and Sensitizes Them to BRAF^{V600E} Inhibitor PLX4720

Minjing Zou, Essa Y. Baitei, Huda A. BinEssa, Futwan A. Al-Mohanna, Ranjit S. Parhar, René St-Arnaud, Shioko Kimura, Catrin Pritchard, Ali S. Alzahrani, Abdullah M. Assiri, Brian F. Meyer, and Yufei Shi

Précis: This study establishes that the vitamin D metabolizing enzyme Cyp24a1 functions as an oncogene to promote malignant progression and resistance to BRAF inhibitor treatment, offering a mechanistic rationale for targeting Cyp24a1 to improve cancer treatment.

CORRECTIONS

2173 Correction: SENP1 deSUMOylates and Regulates Pin1 Protein Activity and Cellular Function

2174 Correction: Mutational Landscape of Pediatric Acute Lymphoblastic Leukemia

2175 Correction: EGFL6 Regulates the Asymmetric Division, Maintenance, and Metastasis of ALDH⁺ Ovarian Cancer Cells

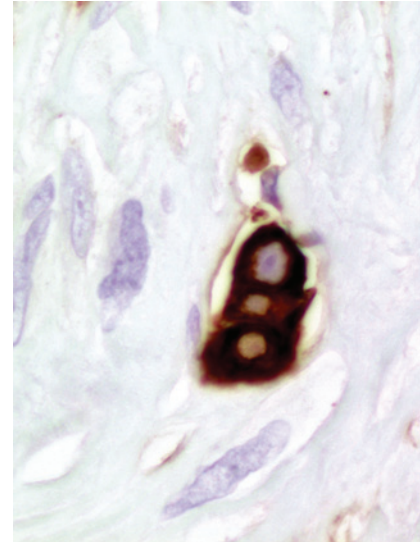
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ABOUT THE COVER

Stromal-derived exosomes promote the evolution of hormonal therapy-resistant cancer stem-like cells (CSC). In tumor-stroma niches of breast cancer, IL6 from cancer-associated fibroblasts (CAF) increases the biogenesis of miRNAs high exosomes, facilitating the transfer of genetic material from the stroma to tumor cells and the conversion of non-CSCs into CSCs. Using immunohistochemical analysis for pan-cytokeratin, we detected the presence of single breast cancer cell clusters surrounded by noncancer cells in human breast cancer xenografts from the coinjection of IL6 high CAFs with ER⁺ breast cancer cells. For details, see article by Sansone and colleagues on page 1927.



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