

BREAKING ADVANCES

- 4305** Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 4307** We Are Standing on the Shoulders of Giants
Anton Berns
- 4309** Commentary on "KRAS Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer"
Laura E. Benjamin

REVIEW

- 4311** Tumor-Induced NETosis as a Risk Factor for Metastasis and Organ Failure
Jessica Cedervall, Yanyu Zhang, and Anna-Karin Olsson

MEETING REPORT

- 4316** Meeting Report: The Role of the Mobilome in Cancer
Daniel Ardeljan, Martin S. Taylor, Kathleen H. Burns, Jef D. Boeke, Michael Graham Espey, Elisa C. Woodhouse, and Thomas Kevin Howcroft

INTEGRATED SYSTEMS AND TECHNOLOGIES


- 4320** Functional Flow Patterns and Static Blood Pooling in Tumors Revealed by Combined Contrast-Enhanced Ultrasound and Photoacoustic Imaging
Avinoam Bar-Zion, Melissa Yin, Dan Adam, and F. Stuart Foster
- Précis:* A new noninvasive imaging method can simultaneously provide information about tumors in viable regions, hemorrhagic regions (blood lakes), and necrotic areas, surpassing the capabilities of existing imaging methods.

MICROENVIRONMENT AND IMMUNOLOGY

- 4332** Expansion of a BDCA1⁺CD14⁺ Myeloid Cell Population in Melanoma Patients May Attenuate the Efficacy of Dendritic Cell Vaccines
Ghaith Bakdash, Sonja I. Buschow, Mark A.J. Gorris, Altuna Halilovic, Stanleyson V. Hato, Annette E. Sköld, Gerty Schreibelt, Simone P. Sittig, Ruurd Torensma, Tjitske Duiveman-de Boer, Christoph Schröder, Evelien L. Smits, Carl G. Figdor, and I. Jolanda M. de Vries
- Précis:* This study identifies a novel immunosuppressive cell population, which accumulates in melanoma patients, the targeting of which may improve immunotherapeutic responses.
- 4347** Melanoma Lesions Independently Acquire T-cell Resistance during Metastatic Latency
Fang Zhao, Antje Sucker, Susanne Horn, Christina Heeke, Nicola Bielefeld, Barbara Schrörs, Anne Bicker, Monika Lindemann, Alexander Roesch, Gustav Gaudernack, Mathias Stiller, Jürgen C. Becker, Volker Lennerz, Thomas Wölfel, Dirk Schadendorf, Klaus Griewank, and Annette Paschen
- Précis:* These clinical findings show how melanoma recurrences after long-term latency evolve toward T-cell resistance by independent genetic events, as a means for immune escape and immunotherapeutic resistance.
- 4359** Incipient Melanoma Brain Metastases Instigate Astrogliosis and Neuroinflammation
Hila Schwartz, Eran Blacher, Malak Amer, Nir Livneh, Lilach Abramovitz, Anat Klein, Dikla Ben-Shushan, Shelly Soffer, Raquel Blazquez, Alonso Barrantes-Freer, Meike Müller, Karin Müller-Decker, Reuven Stein, Galia Tsarfay, Ronit Satchi-Fainaro, Viktor Umansky, Tobias Pukrop, and Neta Erez
- Précis:* Studying spontaneous melanoma brain metastasis in a clinically relevant setting is the key to developing therapeutic approaches that may prevent brain metastatic relapse.
- 4372** Adenosine 2B Receptor Expression on Cancer Cells Promotes Metastasis
Deepak Mittal, Debottam Sinha, Deborah Barkauskas, Arabella Young, Murugan Kalimutho, Kimberley Stannard, Franco Caramia, Benjamin Haibe-Kains, John Stagg, Kum Kum Khanna, Sherene Loi, and Mark J. Smyth
- Précis:* Expression patterns of A2B adenosine receptor that can mediate immunosuppressive effects in cancer appear to be most critical in tumor cells, but not host cells, in conveying metastatic capability and poor prognosis.

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MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4383** **MSH2 Dysregulation Is Triggered by Proinflammatory Cytokine Stimulation and Is Associated with Liver Cancer Development**
Yuji Eso, Atsushi Takai, Tomonori Matsumoto, Tadashi Inuzuka, Takahiro Horie, Koh Ono, Shinji Uemoto, Kyeryoung Lee, Winfried Edelmann, Tsutomu Chiba, and Hiroyuki Marusawa
Précis: These findings provide insight into how inflammation potentiates susceptibility to genetic alterations, leading to cancer by dysregulating the DNA mismatch repair system.
- 4394** **Nucleolin Promotes Heat Shock–Associated Translation of VEGF-D to Promote Tumor Lymphangiogenesis**
Florent Morfoisse, Florence Tatin, Fransky Hantelys, Aurelien Adoue, Anne-Catherine Helfer, Stephanie Cassant-Sourdy, Françoise Pujol, Anne Gomez-Brouchet, Laetitia Ligat, Frederic Lopez, Stephane Pyronnet, Jose Courty, Julie Guillermet-Guibert, Stefano Marzi, Robert J. Schneider, Anne-Catherine Prats, and Barbara H. Garmy-Susini
Précis: These findings identify a ribosome maturation factor located normally in the nucleolus as a key regulator of lymphangiogenesis during tumor development, an important step in facilitating tumor cell extravasation and metastasis.
- 4406** **PTK6 Inhibition Suppresses Metastases of Triple-Negative Breast Cancer via SNAIL-Dependent E-Cadherin Regulation**
 Koichi Ito, Sun Hee Park, Anupma Nayak, Jessica H. Byerly, and Hanna Y. Irie
Précis: This important paper identifies a readily tractable therapeutic target to address high-risk triple-negative breast cancer patients, providing a powerful preclinical rationale to drive clinical translation in this setting.
- 4418** **IKBKE Is a Substrate of EGFR and a Therapeutic Target in Non–Small Cell Lung Cancer with Activating Mutations of EGFR**
Sridevi Challa, Jian-Ping Guo, Xiaowen Ding, Cheng-Xiong Xu, Yajuan Li, Donghwa Kim, Matthew A. Smith, Douglas W. Cress, Domenico Coppola, Eric B. Haura, and Jin Q. Cheng
Précis: These findings offer a mechanistic rationale to target the NF- κ B/AKT regulatory kinase IKBKE as a strategy to eradicate lung cancer cells that acquire resistance to EGFR inhibitors, including those with the common EGFR T790M secondary mutation.

- 4430** **PHGDH Expression Is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance, and Lung Metastasis**
Debangshu Samanta, Youngrok Park, Shaida A. Andrabi, Laura M. Shelton, Daniele M. Gilkes, and Gregg L. Semenza
Précis: These findings highlight roles for an enzyme involved in L-serine synthesis in tumorigenesis, metastasis, and chemotherapeutic sensitivity, with implications for understanding how hypoxia promotes the development of lethal cancers.
- 4443** **HOXC10 Expression Supports the Development of Chemotherapy Resistance by Fine Tuning DNA Repair in Breast Cancer Cells**
Helen Sadik, Preethi Korangath, Nguyen K. Nguyen, Balazs Gyorffy, Rakesh Kumar, Mohammad Hedayati, Wei Wen Teo, Sunju Park, Hardik Panday, Teresa Gonzalez Munoz, Otilia Menyhart, Nilay Shah, Raj K. Pandita, Jenny C. Chang, Theodore DeWeese, Howard Y. Chang, Tej K. Pandita, and Saraswati Sukumar
Précis: HOXC10 overexpression limits cytotoxic responses to chemotherapy in breast cancer cells by promoting DNA repair and checkpoint recovery, mainly through its interaction with the cell-cycle kinase CDK7.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 4457** **Ivermectin Induces Cytostatic Autophagy by Blocking the PAK1/Akt Axis in Breast Cancer**
Qianhui Dou, Hai-Ning Chen, Kui Wang, Kefei Yuan, Yunlong Lei, Kai Li, Jiang Lan, Yan Chen, Zhao Huang, Na Xie, Lu Zhang, Rong Xiang, Edouard C. Nice, Yuquan Wei, and Canhua Huang
Précis: These provocative preclinical results suggest a mechanistic rationale to immediately clinically evaluate the antiparasitic drug ivermectin as a treatment for breast cancer.
- 4470** **Eradication of Acute Myeloid Leukemia with FLT3 Ligand–Targeted miR-150 Nanoparticles**
Xi Jiang, Jason Bugno, Chao Hu, Yang Yang, Tobias Herold, Jun Qi, Ping Chen, Sandeep Gurbuxani, Stephen Arnovitz, Jennifer Strong, Kyle Ferchen, Bryan Ulrich, Hengyou Weng, Yungui Wang, Hao Huang, Shenglai Li, Mary Beth Neilly, Richard A. Larson, Michelle M. Le Beau, Stefan K. Bohlander, Jie Jin, Zejuan Li, James E. Bradner, Seungpyo Hong, and Jianjun Chen
Précis: Most acute myeloid leukemias harbor mutant forms of the tyrosine kinase receptor FLT3, which, as exploited by the targeted nanoparticle strategy used in this preclinical study to drive terminal differentiation, is able to achieve excellent anticancer efficacy without evident side effects.



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4481 Genetic Disruption of the Multifunctional CD98/LAT1 Complex Demonstrates the Key Role of Essential Amino Acid Transport in the Control of mTORC1 and Tumor Growth



Yann Cormerais, Sandy Giuliano, Renaud LeFloch, Benoît Front, Jerome Durivault, Eric Tambutté, Pierre-André Massard, Laura Rodriguez de la Ballina, Hitoshi Endou, Michael F. Wempe, Manuel Palacin, Scott K. Parks, and Jacques Pouyssegur

Précis: These findings offer a preclinical proof of concept, which validates the essential amino acid transporter LAT1 widely overexpressed in aggressive tumors as a promising anticancer target for drug development.

4493 Preclinical Efficacy of Bevacizumab with CRLX101, an Investigational Nanoparticle–Drug Conjugate, in Treatment of Metastatic Triple-Negative Breast Cancer

Elizabeth Pham, Melissa Yin, Christian G. Peters, Christina R. Lee, Donna Brown, Ping Xu, Shan Man, Lata Jayaraman, Ellen Rohde, Annabelle Chow, Douglas Lazarus, Scott Eliasof, F. Stuart Foster, and Robert S. Kerbel

Précis: These findings offer preclinical proof of concept for a unique combination therapy with potent efficacy against an especially aggressive subtype of breast cancer.

4504 Molecular Landscape of Acquired Resistance to Targeted Therapy Combinations in BRAF-Mutant Colorectal Cancer

Daniele Oddo, Erin M. Sennott, Ludovic Barault, Emanuele Valtorta, Sabrina Arena, Andrea Cassingena, Genny Filiciotto, Giulia Marzolla, Elena Elez, Robin M.J.M. van Geel, Alice Bartolini, Giovanni Crisafulli, Valentina Boscaro, Jason T. Godfrey, Michela Buscarino, Carlotta Cancelliere, Michael Linnebacher, Giorgio Corti, Mauro Truini, Giulia Siravegna, Julieta Grasselli, Margherita Gallicchio, René Bernards, Jan H.M. Schellens, Josep Tabernero, Jeffrey A. Engelman, Andrea Sartore-Bianchi, Alberto Bardelli, Salvatore Siena, Ryan B. Corcoran, and Federica Di Nicolantonio

Précis: These seminal findings reveal that mechanisms of acquired resistance in BRAF mutant colorectal cancer all converge on reactivating MAPK signaling, which can be overcome by drug combinations that include an ERK inhibitor.

4516 A Radiotracer Strategy to Quantify PARP-1 Expression *In Vivo* Provides a Biomarker That Can Enable Patient Selection for PARP Inhibitor Therapy

Mehran Makvandi, Kuiying Xu, Brian P. Lieberman, Redmond-Craig Anderson, Samuel Sander Effron, Harrison D. Winters, Chenbo Zeng, Elizabeth S. McDonald, Daniel A. Pryma, Roger A. Greenberg, and Robert H. Mach

Précis: These results validate a novel technology with the potential to serve as a companion diagnostic for identifying cancer patients most likely to respond therapeutically to a PARP inhibitor, addressing a need for a response biomarker.

4525 Proteasome Addiction Defined in Ewing Sarcoma Is Effectively Targeted by a Novel Class of 19S Proteasome Inhibitors

Neerav Shukla, Romel Somwar, Roger S. Smith, Sri Ambati, Stanley Munoz, Melinda Merchant, Padraig D'Arcy, Xin Wang, Rachel Kobos, Christophe Antczak, Bhavneet Bhinder, David Shum, Constantin Radu, Guangbin Yang, Barry S. Taylor, Charlotte K.Y. Ng, Britta Weigelt, Inna Khodos, Elisa de Stanchina, Jorge S. Reis-Filho, Ouathek Ouerfelli, Stig Linder, Hakim Djaballah, and Marc Ladanyi

Précis: This study used high-throughput chemical and functional screens to identify a novel class of deubiquitinase inhibitors with significant efficacy in preclinical models of an often fatal type of sarcoma.

TUMOR AND STEM CELL BIOLOGY

4535 EF Hand Protein IBA2 Promotes Cell Proliferation in Breast Cancers via Transcriptional Control of Cyclin D1

Ying Zhang, Shuling Wang, and Lingsong Li

Précis: This study addresses a gap in knowledge about EF hand domain-containing proteins, which have been linked to cancer but for which functional contributions have been obscure.

4546 DNMT1 Inhibition Reprograms Pancreatic Cancer Stem Cells via Upregulation of the miR-17-92 Cluster



Sladjana Zagorac, Sonia Alcalá, Gustavo Fernandez Bayon, Tony Bou Kheir, Matthieu Schoenhals, Anna González-Neira, Mario Fernandez Fraga, Alexandra Aicher, Christopher Heeschen, and Bruno Sainz, Jr.

Précis: These proof-of-concept findings rationalize the clinical exploration of DNA methylation inhibitors as a means to target cancer stem-like functions and to improve clinical outcomes.

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4559 AIMP2 Controls Intestinal Stem Cell Compartments and Tumorigenesis by Modulating Wnt/ β -Catenin Signaling

Min Kyu Yum, Jong-Seol Kang, Al-Eum Lee, Young-Woo Jo, Ji-Yun Seo, Hyun-A Kim, Yoon-Young Kim, Jinwoo Seong, Eun Byul Lee, Ji-Hoon Kim, Jung Min Han, Sunghoon Kim, and Young-Yun Kong

Précis: This study identifies a novel important negative regulator of intestinal Wnt/ β -catenin signaling that keeps crypt stem cell pools in check to prevent tumorigenesis.

4569 Decreased Mitochondrial Mutagenesis during Transformation of Human Breast Stem Cells into Tumorigenic Cells

Eun Hyun Ahn, Seung Hyuk Lee, Joon Yup Kim, Chia-Cheng Chang, and Lawrence A. Loeb

Précis: This study delineates changes in the human mitochondrial genome at progressive steps during the transformation of normal breast stem cells into tumorigenic cells, using a recently established ultra-accurate deep sequencing method termed Duplex DNA sequencing.

4579 Acute Sensitivity of Ph-like Acute Lymphoblastic Leukemia to the SMAC-Mimetic Birinapant

Jennifer Richmond, Alissa Robbins, Kathryn Evans, Dominik Beck, Raushan T. Kurmasheva, Catherine A. Billups, Hernan Carol, Sue Heatley, Rosemary Sutton, Glenn M. Marshall, Deborah White, John Pimanda, Peter J. Houghton, Malcolm A. Smith, and Richard B. Lock

Précis: These preclinical results offer a compelling rationale to position the use of a small-molecule mimetic of the proapoptotic protein SMAC as a treatment for a particular subtype of acute lymphoblastic leukemia.

CORRECTION

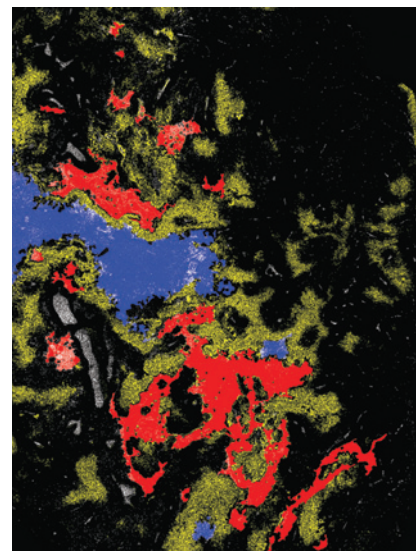
4592 Correction: ATF3 Suppresses Metastasis of Bladder Cancer by Regulating Gelsolin-Mediated Remodeling of the Actin Cytoskeleton

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ABOUT THE COVER

Composite histological image of a LS174T xenograft combining information from hematoxylin and eosin, CA9, and CD31 stains depicts the complexity of the tumor, showing blood lakes (red), small necrotic regions (blue), widespread hypoxic regions (yellow), and red blood cells (white). The composition of the tumor matches the perfusion and oxygen saturation patterns seen in dynamic contrast-enhanced ultrasound (DCEUS) and photoacoustic (PA) imaging scans, respectively. When used in combination, DCEUS and PA imaging have the potential to facilitate the discrimination between blood lakes and necrotic areas. For details, see article by Bar-Zion and colleagues on page 4320.



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