

BREAKING ADVANCES

- 6761** Highlights from Recent Cancer Literature


CANCER RESEARCH 75TH ANNIVERSARY COMMENTARIES

- 6763** Commentary on "Apoptosis, p53, and Tumor Cell Sensitivity to Anticancer Agents"
Elsa R. Flores
- 6765** Combine and Conquer: Double CTLA-4 and PD-1 Blockade Combined with Whole Tumor Antigen Vaccine Cooperate to Eradicate Tumors
Krisztian Homicsko, Jaikumar Duraiswamy, Marie-Agnès Doucey, and George Coukos

PERSPECTIVE

- 6768** Conflicting Signals for Cancer Treatment
Pierre Sjobert and Alain Trautmann


MEETING REPORT

- 6774** Systems Approaches to Cancer Biology
 Tenley C. Archer, Elana J. Fertig, Sara J.C. Gosline, Marc Hafner, Shannon K. Hughes, Brian A. Joughin, Aaron S. Meyer, Stephen R. Piccolo, and Ayesha N. Shajahan-Haq

PRIORITY REPORT

- 6778** Inflammation Triggers Zeb1-Dependent Escape from Tumor Latency
Jasmine M. De Cock, Tsukasa Shibue, Anushka Dongre, Zuzana Keckesova, Ferenc Reinhardt, and Robert A. Weinberg
- Précis:* This study provides mechanistic insight into the awakening of dormant disseminated tumor cells by an inflamed tissue, highlighting Zeb1 as a key mediator in this process.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6785** Signal-Oriented Pathway Analyses Reveal a Signaling Complex as a Synthetic Lethal Target for p53 Mutations
 Songjian Lu, Chunhui Cai, Gonghong Yan, Zhuan Zhou, Yong Wan, Vicky Chen, Lujia Chen, Gregory F. Cooper, Lina M. Obeid, Yusuf A. Hannun, Adrian V. Lee, and Xinghua Lu
- Précis:* This report presents a computational model capable of defining signaling pathways that can elicit synthetic lethality with oncogenic mutations, as illustrated by definition of a complex that cooperates with p53 mutation to kill cancer cells.

- 6795** Cancer Detection in Human Tissue Samples Using a Fiber-Tip pH Probe
Erik P. Schartner, Matthew R. Henderson, Malcolm Purdey, Deepak Dhattrak, Tanya M. Monro, P. Grantley Gill, and David F. Callen
- Précis:* An optical fiber probe can rapidly differentiate between healthy and cancerous tissue in human samples, with near-term implications for use during tumor resections by surgeons.

MICROENVIRONMENT AND IMMUNOLOGY


- 6802** Modulation of Immune Checkpoints and Graft-versus-Leukemia in Allogeneic Transplants by Antagonizing Vasoactive Intestinal Peptide Signaling
 Jian-Ming Li, Christopher T. Petersen, Jing-Xia Li, Reema Panjwani, Daniel J. Chandra, Cynthia R. Giver, Bruce R. Blazar, and Edmund K. Waller
- Précis:* Inhibiting signaling from the vasoactive intestinal polypeptide receptor offers a novel approach to activate antigen-specific T cells with potent anticancer properties.
- 6816** The Biodistribution and Immune Suppressive Effects of Breast Cancer-Derived Exosomes
Shu Wen Wen, Jaclyn Sceneay, Luize Goncalves Lima, Christina S.F. Wong, Melanie Becker, Sophie Krumeich, Richard J. Lobb, Vanessa Castillo, Ke Ni Wong, Sarah Ellis, Belinda S. Parker, and Andreas Möller
- Précis:* This study shows how breast cancer-derived exosomes accumulate in premetastatic organs, impact immune cell character and activity, and promote metastatic spread.

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6828 Tie2 Expression on Macrophages Is Required for Blood Vessel Reconstruction and Tumor Relapse after Chemotherapy



Lin Chen, Jie Li, Fei Wang, Chengliang Dai, Fan Wu, Xiaoman Liu, Taotao Li, Rainer Glauben, Yi Zhang, Guangjun Nie, Yulong He, and Zhihai Qin

Précis: These findings illuminate how tumor-associated macrophages license a tissue microenvironment for tumor regrowth after chemotherapy.

6839 Regeneration of CD8 $\alpha\beta$ T Cells from T-cell-Derived iPSC Imparts Potent Tumor Antigen-Specific Cytotoxicity



Takuya Maeda, Seiji Nagano, Hiroshi Ichise, Keisuke Kataoka, Daisuke Yamada, Seishi Ogawa, Haruhiko Koseki, Toshio Kitawaki, Norimitsu Kadowaki, Akifumi Takaori-Kondo, Kyoko Masuda, and Hiroshi Kawamoto

Précis: This report shows how to generate leukemia-killing cytotoxic T lymphocytes from T-cell-derived induced pluripotent stem cells, addressing a gap in applications of adoptive T-cell immunotherapy.

6851 Chemoresistance in Pancreatic Cancer Is Driven by Stroma-Derived Insulin-Like Growth Factors



Lucy Ireland, Almudena Santos, Muhammad S. Ahmed, Carolyn Rainer, Sebastian R. Nielsen, Valeria Quaranta, Ulrike Weyer-Czernilofsky, Danielle D. Engle, Pedro A. Perez-Mancera, Sarah E. Coupland, Azzam Taktak, Thomas Bogenrieder, David A. Tuveson, Fiona Campbell, Michael C. Schmid, and Ainhua Mielgo

Précis: Tumor-associated macrophages and fibroblasts contribute to chemoresistance by secreting IGF1 and IGF2 in the pancreatic tumor microenvironment.

6864 Adoptive Transfer of Tumor-Specific Th2 Cells Eradicates Tumors by Triggering an In Situ Inflammatory Immune Response



Kristina Berg Lorvik, Clara Hammarström, Marte Fauskanger, Ole Audun Werner Haabeth, Michael Zangani, Guttorm Haraldsen, Bjarne Bogen, and Alexandre Corthay

Précis: This study reveals the unexpected potential of tumor-specific Th2 cells for cancer immunotherapy by adoptive cell transfer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6877 Transcription Factor ZBP-89 Drives a Feedforward Loop of β -Catenin Expression in Colorectal Cancer

Bryan E. Essien, Sinju Sundaresan, Ramon Ocadiz-Ruiz, Aaron Chavis, Amy C. Tsao, Arthur J. Tessier, Michael M. Hayes, Amanda Photenhauer, Milena Saqui-Salces, Anthony J. Kang, Yatrik M. Shah, Balazs Györfy, and Juanita L. Merchant

Précis: Common germline mutations that occur in colorectal cancer contribute to a novel mechanism for sustaining cellular proliferation.

6888 Cdk5 Directly Targets Nuclear p21^{CIP1} and Promotes Cancer Cell Growth

Pao-Hsuan Huang, Mei-Chih Chen, Yu-Ting Peng, Wei-Hsiang Kao, Chih-Hsiang Chang, Yun-Chi Wang, Chih-Ho Lai, Jer-Tsong Hsieh, Jo-Hsin Wang, Yueh-Tsung Lee, Eugene Lin, Chia-Herng Yue, Hsin-Yi Wang, Shuen-Chi You, and Ho Lin

Précis: These findings suggest that highly expressed Cdk5 promotes cancer growth by directly and rapidly releasing p21^{CIP1}-dependent cell-cycle inhibition, leading to subsequent Cdk2 activation and cell proliferation.

6901 Cell Adhesion Molecule CD166 Drives Malignant Progression and Osteolytic Disease in Multiple Myeloma

Linlin Xu, Khalid S. Mohammad, Hao Wu, Colin Crean, Bradley Poteat, Yinghua Cheng, Angelo A. Cardoso, Christophe Machal, Helmut Hanenberg, Rafat Abonour, Melissa A. Kacena, John Chirgwin, Attaya Suvannasankha, and Edward F. Srour

Précis: These results show how multiple myeloma cells are seeded into the bone marrow, a key step in progression to incurable disease, rationalizing further study of the mechanism as a therapeutic direction.

6911 mTORC2 Signaling Drives the Development and Progression of Pancreatic Cancer



David R. Driscoll, Saadia A. Karim, Makoto Sano, David M. Gay, Wright Jacob, Jun Yu, Yusuke Mizukami, Aarthi Gopinathan, Duncan I. Jodrell, T.R. Jeffry Evans, Nabeel Bardeesy, Michael N. Hall, Brian J. Quattrochi, David S. Klimstra, Simon T. Barry, Owen J. Sansom, Brian C. Lewis, and Jennifer P. Morton

Précis: These findings offer a preclinical rationale to investigate the inhibition of mTORC2 signaling in pancreatic cancer as a candidate therapeutic strategy.

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- 6924** Destabilization of Fatty Acid Synthase by Acetylation Inhibits *De Novo* Lipogenesis and Tumor Cell Growth
Huai-Peng Lin, Zhou-Li Cheng, Ruo-Yu He, Lei Song, Meng-Xin Tian, Li-Sha Zhou, Beezly S. Groh, Wei-Ren Liu, Min-Biao Ji, Chen Ding, Ying-Hong Shi, Kun-Liang Guan, Dan Ye, and Yue Xiong
Précis: These findings reveal a regulatory mechanism for fatty acid synthase, the study of which may have implications for anticancer therapy.
- 6937** E2A-PBX1 Remodels Oncogenic Signaling Networks in B-cell Precursor Acute Lymphoid Leukemia
Jesús Duque-Afonso, Chiou-Hong Lin, Kyuho Han, Michael C. Wei, Jue Feng, Jason H. Kurzer, Corina Schneidawind, Stephen Hon-Kit Wong, Michael C. Bassik, and Michael L. Cleary
Précis: These findings show how the oncogenic fusion protein E2A-PBX1 perturbs signaling pathways upstream of PLC γ 2 and renders leukemias amenable to targeted therapeutic inhibition.
- THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**
- 6950** High-Order Drug Combinations Are Required to Effectively Kill Colorectal Cancer Cells
Thomas Horn, Stéphane Ferretti, Nicolas Ebel, Angela Tam, Samuel Ho, Fred Harbinski, Ali Farsidjani, Matthew Zubrowski, William R. Sellers, Robert Schlegel, Dale Porter, Erick Morris, Jens Wuertner, Sébastien Jeay, Joel Greshock, Ensar Halilovic, Levi A. Garraway, Giordano Caponigro, and Joseph Lehár
Précis: For the promise of personalized therapy to be realized, it will be important to define themes in combination drug treatments (polypharmacology) that can be most widely leveraged to achieve remission of aggressive cancers, as addressed by this study.
- 6964** Tumor-Intrinsic PD-L1 Signals Regulate Cell Growth, Pathogenesis, and Autophagy in Ovarian Cancer and Melanoma
Curtis A. Clark, Harshita B. Gupta, Gangadhara Sareddy, Srilakshmi Pandeswara, Shunhua Lao, Bin Yuan, Justin M. Drerup, Alvaro Padron, José Conejo-García, Kruthi Murthy, Yang Liu, Mary Jo Turk, Kathrin Thedieck, Vincent Hurez, Rong Li, Ratna Vadlamudi, and Tyler J. Curiel
Précis: These findings reveal a new function for PD-L1 beyond its immunoregulatory role in cancer pathogenesis, with implications for nonimmune effects of PD-L1 antibodies as checkpoint immunotherapy and broader uses of PD-L1 as a biomarker of therapeutic responses.
- 6975** TLR Adaptor Protein MYD88 Mediates Sensitivity to HDAC Inhibitors via a Cytokine-Dependent Mechanism
Maria New, Semira Sheikh, Mina Bekheet, Heidi Olzscha, Marie-Laetitia Thezenas, Matthew A. Care, Susan Fotheringham, Reuben M. Tooze, Benedikt Kessler, and Nicholas B. La Thangue
Précis: These important findings offer an explanation for the selective sensitivity of certain cancers to HDAC inhibitor-based therapies, providing knowledge that could potentially expand their use.
- 6988** Efficacy of Cotargeting Angiopoietin-2 and the VEGF Pathway in the Adjuvant Postsurgical Setting for Early Breast, Colorectal, and Renal Cancers
Florence T.H. Wu, Shan Man, Ping Xu, Annabelle Chow, Marta Paez-Ribes, Christina R. Lee, Steven R. Pirie-Shepherd, Urban Emmenegger, and Robert S. Kerbel
Précis: This study provides a preclinical rationale for improving the efficacy of VEGF/VEGFR2 pathway-targeting antiangiogenic therapies to treat early-stage metastatic disease.
- 7001** PP2A Inhibitor PME-1 Drives Kinase Inhibitor Resistance in Glioma Cells
Amanpreet Kaur, Oxana V. Denisova, Xi Qiao, Mikael Jumppanen, Emilia Peuhu, Shafiq U. Ahmed, Olayinka Raheem, Hannu Haapasalo, John Eriksson, Anthony J. Chalmers, Pirjo Laakkonen, and Jukka Westermark
Précis: A novel mechanism elucidates the resistance of glioma cells to kinase inhibitor therapies and may help develop novel glioblastoma therapy strategies.
- 7012** Genetic Polymorphisms in the Long Noncoding RNA MIR2052HG Offer a Pharmacogenomic Basis for the Response of Breast Cancer Patients to Aromatase Inhibitor Therapy
 James N. Ingle, Fang Xie, Matthew J. Ellis, Paul E. Goss, Lois E. Shepherd, Judith-Anne W. Chapman, Bingshu E. Chen, Michiaki Kubo, Yoichi Furukawa, Yukihide Momozawa, Vered Stearns, Kathleen I. Pritchard, Poulami Barman, Erin E. Carlson, Matthew P. Goetz, Richard M. Weinshilboum, Krishna R. Kalari, and Liewei Wang
Précis: These findings suggest a host biomarker that predicts a basis for individual differences in the efficacy of aromatase inhibitors used widely in the treatment of breast cancer.

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7024 TRPA1 Mediates Aromatase Inhibitor–Evoked Pain by the Aromatase Substrate Androstenedione

Francesco De Logu, Raquel Tonello, Serena Materazzi, Romina Nassini, Camilla Fusi, Elisabetta Coppi, Simone Li Puma, Ilaria M. Marone, Laura R. Sadofsky, Alyn H. Morice, Tommaso Susini, Alessandro Terreni, Gloriano Moneti, Mariarosaria Di Tommaso, Pierangelo Geppetti, and Silvia Benemei

Précis: Involvement of a pain-transducing receptor in the ability of an aromatase inhibitor to generate musculoskeletal side effects in breast cancer patients receiving these drugs identifies a new direction to treat these side effects.

7049 Oncogenic Functions of Gli1 in Pancreatic Adenocarcinoma Are Supported by Its PRMT1-Mediated Methylation

Yan Wang, Jung-Mao Hsu, Ya'an Kang, Yongkun Wei, Pei-Chih Lee, Shing-Jyh Chang, Yi-Hsin Hsu, Jennifer L. Hsu, Hung-Ling Wang, Wei-Chao Chang, Chia-Wei Li, Hsin-Wei Liao, Shih-Shin Chang, Weiya Xia, How-Wen Ko, Chao-Kai Chou, Jason B. Fleming, Huamin Wang, Rosa F. Hwang, Yue Chen, Jun Qin, and Mien-Chie Hung

Précis: This study offers key mechanistic insights into the posttranslational regulation of the noncanonical Hedgehog pathway in pancreatic ductal adenocarcinoma.

7059 NRBP2 Overexpression Increases the Chemosensitivity of Hepatocellular Carcinoma Cells via Akt Signaling

Lixing Zhang, Chao Ge, Fangyu Zhao, Yang Zhang, Xin Wang, Ming Yao, and Jinjun Li

Précis: These findings reveal a mechanism of sensitivity to the drugs cisplatin and perifosine, which are used to treat liver cancer.

TUMOR AND STEM CELL BIOLOGY

7036 Epigenetic Switch between SOX2 and SOX9 Regulates Cancer Cell Plasticity

Sheng-Chieh Lin, Yu-Ting Chou, Shih Sheng Jiang, Junn-Liang Chang, Chih-Hung Chung, Yu-Rung Kao, I-Shou Chang, and Cheng-Wen Wu

Précis: These findings identify two nodal epigenetic regulators of self-renewal and cell differentiation that generate significant cellular heterogeneity in tumors, thereby broadening pathophysiology and limiting prospects for targeted therapy.

CORRECTION

7072 Correction: Jak1–STAT3 Signals Are Essential Effectors of the USP6/TRE17 Oncogene in Tumorigenesis

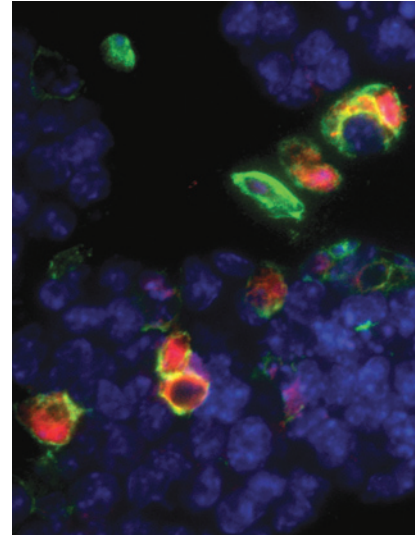
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ABOUT THE COVER

Adoptive cell transfer (ACT) of tumor-specific Th2 cells is a highly efficient immunotherapy protocol against cancer in mice. Immunofluorescence microscopy revealed that Th2 ACT induced expression of arginase (red) by tumor-infiltrating macrophages (green). Cell nuclei are stained blue. Arginase was shown to be critical for cancer eradication by Th2 cells. For details, see article by Lorvik and colleagues on page 6864.



Cancer Research

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