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Cancer Research

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- 5320 | **Mammary Tumor Formation and Metastasis Evoked by a HER2 Splice Variant**
Abdullah Alajati, Nina Sausgruber, Nicola Aceto, Stephan Duss, Sophie Sarret, Hans Voshol, Debora Bonenfant, and Mohamed Bentires-Alj
- Précis:* Mechanistic studies of an uncharacterized splice variant of the HER2 growth receptor, an oncogenic driver in a large number of aggressive breast cancers, may help explain wide variations in patient outcomes to HER2-targeting therapy.

CLINICAL STUDIES

- 5328 | **EPR Oxygen Images Predict Tumor Control by a 50% Tumor Control Radiation Dose**
Martyna Elas, Jessica M. Magwood, Brandi Butler, Chanel Li, Rona Wardak, Rebekah DeVries, Eugene D. Barth, Boris Epel, Samuel Rubinstein, Charles A. Pelizzari, Ralph R. Weichselbaum, and Howard J. Halpern
- Précis:* New imaging methods for tumor oxygenation based on electron paramagnetic resonance open a basis to deliver higher radiation doses to hypoxic tumor regions as a way to improve outcomes after radiotherapy.

MICROENVIRONMENT AND IMMUNOLOGY

- 5336 | **Stromally Derived Lysyl Oxidase Promotes Metastasis of Transforming Growth Factor- β -Deficient Mouse Mammary Carcinomas**
Michael W. Pickup, Hanane Laklai, Irene Acerbi, Philip Owens, Agnieszka E. Gorska, Anna Chytil, Mary Aakre, Valerie M. Weaver, and Harold L. Moses
- Précis:* These findings suggest that microenvironmental changes triggered by oncogenically transformed epithelial cells can offer important therapeutic targets to inhibit metastasis.

- 5347 | **Mesenchymal CD44 Expression Contributes to the Acquisition of an Activated Fibroblast Phenotype via TWIST Activation in the Tumor Microenvironment**
Erika L. Spaeth, Adam M. Labaff, Bryan P. Toole, Ann Klopp, Michael Andreoff, and Frank C. Marini
- Précis:* The cancer stem-like cell marker CD44 has a functional role not only in cancer cells but also in mesenchymal stem cells, which are a significant source of cancer-associated fibroblasts and other core components of the supportive tumor stroma.

- 5360 | **Fusion-Derived Epithelial Cancer Cells Express Hematopoietic Markers and Contribute to Stem Cell and Migratory Phenotype in Ovarian Carcinoma**
Mallika Ramakrishnan, Sandeep R. Mathur, and Asok Mukhopadhyay
- Précis:* Fusion of hematopoietic cells with cancer cells provides a novel mechanism for targeting metastasis of solid tumors.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5371 | **Candidate Tumor Suppressor and pVHL Partner Jade-1 Binds and Inhibits AKT in Renal Cell Carcinoma**
Liling Zeng, Ming Bai, Amit K. Mittal, Wassim El-Jouni, Jing Zhou, David M. Cohen, Mina I. Zhou, and Herbert T. Cohen
- Précis:* These findings identify an important new candidate biomarker in renal cell carcinoma that functions in tumor suppression as a key negative modifier of AKT signaling, with potentially broader implications in human cancer.

- 5381 **Notch1-Induced Brain Tumor Models the Sonic Hedgehog Subgroup of Human Medulloblastoma**
Sivaraman Natarajan, Yaochen Li, Emily E. Miller, David J. Shih, Michael D. Taylor, Timothy M. Stearns, Roderick T. Bronson, Susan L. Ackerman, Jeong K. Yoon, and Kyuson Yun
Précis: This study is the first to clearly demonstrate the oncogenic potential of activated Notch1 and in doing so establishes a novel mouse model of medulloblastoma.
- 5391 **Survivin-3B Potentiates Immune Escape in Cancer but Also Inhibits the Toxicity of Cancer Chemotherapy**
Frédérique Végran, Romain Mary, Anne Gibeaud, Céline Mirjole, Bertrand Collin, Alexandra Oudot, Céline Charon-Barra, Laurent Arnould, Sarab Lizard-Nacol, and Romain Boidot
Précis: Cancer-specific alternate splicing that occurs in the cell death inhibitor survivin generates a potent mediator of resistance against immune-mediated or chemotherapeutic killing.
- 5402 **miR-205 Targets PTEN and PHLPP2 to Augment AKT Signaling and Drive Malignant Phenotypes in Non-Small Cell Lung Cancer**
Junchao Cai, Lishan Fang, Yongbo Huang, Rong Li, Jie Yuan, Yi Yang, Xun Zhu, Baixue Chen, Jueheng Wu, and Mengfeng Li
Précis: These results reveal how AKT becomes activated in lung adenocarcinoma, identifying a pivotal role for an oncomir of emerging importance in the development and progression of this widespread disease.
- 5416 **FOXL1, a Novel Candidate Tumor Suppressor, Inhibits Tumor Aggressiveness and Predicts Outcome in Human Pancreatic Cancer**
Geng Zhang, Peijun He, Jochen Gaedcke, B. Michael Ghadimi, Thomas Ried, Harris G. Yfantis, Dong H. Lee, Nader Hanna, H. Richard Alexander, and S. Perwez Hussain
Précis: FOX transcription factors continue to emerge as central determinants of cancer pathophysiology and patient outcomes in many deadly human solid tumors, illustrated in this study of FOXL1 in pancreatic cancer.
- 5426 **PTK6 Activation at the Membrane Regulates Epithelial-Mesenchymal Transition in Prostate Cancer**
Yu Zheng, Zebin Wang, Wenjun Bie, Patrick M. Brauer, Bethany E. Perez White, Jing Li, Veronique Nogueira, Pradip Raychaudhuri, Nissim Hay, Debra A. Tonetti, Virgilia Macias, André Kajdacsy-Balla, and Angela L. Tyner
Précis: Membrane relocalization and activation of the nonreceptor tyrosine kinase PTK6 serves as a novel marker for prostate cancer staging and prognosis, also offering potential therapeutic implications for treatment of prostate cancer.
- 5438 **Myoferlin Is a Key Regulator of EGFR Activity in Breast Cancer**
Andrei Turtoi, Arnaud Blomme, Akeila Bellahcène, Christine Gilles, Vincent Hennequière, Paul Peixoto, Elettra Bianchi, Agnès Noel, Edwin De Pauw, Eric Lifrange, Philippe Delvenne, and Vincent Castronovo
Précis: Given the therapeutic significance of EGFR targeting, this study's findings highlight a rational candidate function to target for future drug development.
- 5449 **HOXB13 Mediates Tamoxifen Resistance and Invasiveness in Human Breast Cancer by Suppressing ER α and Inducing IL-6 Expression**
Nilay Shah, Kideok Jin, Leigh-Ann Cruz, Sunju Park, Helen Sadik, Soonweng Cho, Chirayu Pankaj Goswami, Harikrishna Nakshatri, Rajnish Gupta, Howard Y. Chang, Zhe Zhang, Ashley Cimino-Mathews, Leslie Cope, Christopher Umbricht, and Saraswati Sukumar
Précis: These results establish a function for the homeodomain transcription factor HOXB13 in the emergence of tamoxifen resistance in breast cancer through direct blockade of ER α and upregulation of the IL-6 pathway.
- 5459 **Inhibition of AMPK and Krebs Cycle Gene Expression Drives Metabolic Remodeling of Pten-Deficient Preneoplastic Thyroid Cells**
Valeria G. Antico Arciuch, Marika A. Russo, Kristy S. Kang, and Antonio Di Cristofano
Précis: This study describes a novel mechanism of glycolytic upregulation that is distinct from the Warburg effect and mediated by PI3K-dependent inactivation of the core metabolic kinase AMPK, with potentially great impact on understanding a central metabolic question in cancer.

PREVENTION AND EPIDEMIOLOGY

5473 | **Chemopreventive Activity of Plant Flavonoid Isorhamnetin in Colorectal Cancer Is Mediated by Oncogenic Src and β -Catenin**

Shakir M. Saud, Matthew R. Young, Yava L. Jones-Hall, Lilia Ileva, Moses O. Evbuomwan, Jennifer Wise, Nancy H. Colburn, Young S. Kim, and Gerd Bobe

Précis: This study advances mechanistic understanding for the anticancer properties of a natural flavonol that can prevent tumorigenesis, reverse EMT, and block metastasis with limited toxicity in various types of cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5485 | **Novel Small-Molecule Inhibitors of Bcl-XL to Treat Lung Cancer**

Dongkyoo Park, Andrew T. Magis, Rui Li, Taofeek K. Owonikoko, Gabriel L. Sica, Shi-Yong Sun, Suresh S. Ramalingam, Fadlo R. Khuri, Walter J. Curran, and Xingming Deng

Précis: The new class of Bcl-XL inhibitors identified in this report exhibits distinct specificities and strong potency against lung cancer and acquired radioresistance in this setting.

5497 | **Werner Syndrome Helicase Has a Critical Role in DNA Damage Responses in the Absence of a Functional Fanconi Anemia Pathway**

Monika Aggarwal, Taraswi Banerjee, Joshua A. Sommers, Chiara Iannascoli, Pietro Pichierri, Robert H. Shoemaker, and Robert M. Brosh, Jr.

Précis: These findings advance our understanding of cellular resistance to a DNA crosslinking agent used to combat cancer, implicating the WRN helicase as a target for inhibition in cells defective in the Fanconi anemia pathway of DNA repair targeted by certain chemotherapy strategies.

5508 | **A Synthetic Lethality–Based Strategy to Treat Cancers Harboring a Genetic Deficiency in the Chromatin Remodeling Factor BRG1**

Takahiro Oike, Hideaki Ogiwara, Yuichi Tominaga, Kentaro Ito, Osamu Ando, Koji Tsuta, Tatsuji Mizukami, Yoko Shimada, Hisanori Isomura, Mayumi Komachi, Koh Furuta, Shun-Ichi Watanabe, Takashi Nakano, Jun Yokota, and Takashi Kohno

Précis: These results offer a rationale for an epigenetic-based treatment of many lung cancers and other common cancers lacking known therapeutic gene mutations, providing a broad catchment strategy for treatment.

5519 | **AC1MMYR2, an Inhibitor of Dicer-Mediated Biogenesis of Oncomir miR-21, Reverses Epithelial–Mesenchymal Transition and Suppresses Tumor Growth and Progression**

Zhendong Shi, Junxia Zhang, Xiaomin Qian, Lei Han, Kailiang Zhang, Luyue Chen, Jilong Liu, Yu Ren, Ming Yang, Anling Zhang, Peiyu Pu, and Chunsheng Kang

Précis: This study offers a novel, high-throughput method to screen for small-molecule inhibitors of microRNA maturation and presents an inhibitor of oncomir miR-21 maturation as a candidate antitumor drug.

5532 | **KEAP1-Dependent Synthetic Lethality Induced by AKT and TXNRD1 Inhibitors in Lung Cancer**

Bingbing Dai, Suk-Young Yoo, Geoffrey Bartholomeusz, Ryan A. Graham, Mourad Majidi, Shaoyu Yan, Jieru Meng, Lin Ji, Kevin Coombes, John D. Minna, Bingliang Fang, and Jack A. Roth

Précis: This study shows how the Nrf2 cellular antioxidant system of great current interest can be harnessed with Akt inhibitors to attack lung cancer more effectively.

TUMOR AND STEM CELL BIOLOGY

5544 | **SOX2 Expression Associates with Stem Cell State in Human Ovarian Carcinoma**

Petra M. Bareiss, Anna Paczulla, Hui Wang, Rebekka Schairer, Stefan Wiehr, Ursula Kohlhofer, Oliver C. Rothfuss, Anna Fischer, Sven Perner, Annette Staebler, Diethelm Wallwiener, Falko Fend, Tanja Fehm, Bernd Pichler, Lothar Kanz, Leticia Quintanilla-Martinez, Klaus Schulze-Osthoff, Frank Essmann, and Claudia Lengerke

Précis: The embryonic protein SOX2, which serves as a cancer stem cell marker in a variety of cancers, is shown here to induce the tumor-initiating capacity of serous ovarian carcinoma cells.

5556 | **Hbo1 Is a Cyclin E/CDK2 Substrate That Enriches Breast Cancer Stem-like Cells**

MyLinh T. Duong, Said Akli, Sira Macalou, Anna Biernacka, Bisrat G. Debeb, Min Yi, Kelly K. Hunt, and Khandan Keyomarsi

Précis: The increased oncogenic potency of cyclin E proteolytic cleavage products, which accumulate in some breast cancers, relates to their ability to promote EMT and cancer stem-like properties, the mechanistic aspects of which have immediate therapeutic implications.

5569

MUC1 Is a Potential Target for the Treatment of Acute Myeloid Leukemia Stem Cells

Dina Stroopinsky, Jacalyn Rosenblatt, Keisuke Ito, Heidi Mills, Li Yin, Hasan Rajabi, Baldev Vasir, Turner Kufe, Katarina Luptakova, Jon Arnason, Caterina Nardella, James D. Levine, Robin M. Joyce, Ilene Galinsky, Yoram Reiter, Richard M. Stone, Pier Paolo Pandolfi, Donald Kufe, and David Avigan

Précis: A mucin gene widely upregulated in solid cancers and studied as an immunotherapeutic target is reported here to serve as a leukemia stem cell marker, broadening interest in its potential uses to better define or eradicate malignancy.

5580

CIGALT1 Enhances Proliferation of Hepatocellular Carcinoma Cells via Modulating MET Glycosylation and Dimerization

Yao-Ming Wu, Chiung-Hui Liu, Miao-Juei Huang, Hong-Shiee Lai, Po-Huang Lee, Rey-Heng Hu, and Min-Chuan Huang

Précis: These findings offer evidence in support of an O-glycosyl transferase as an appealing therapeutic target to develop for treatment of liver cancer.

5591

Distinct FAK Activities Determine Progenitor and Mammary Stem Cell Characteristics

Ming Luo, Xiaofeng Zhao, Song Chen, Suling Liu, Max S. Wicha, and Jun-Lin Guan

Précis: These findings define distinct kinase-dependent and kinase-independent activities of the FAK kinase that permit therapeutic strategies to address cancer heterogeneity more effectively, a major challenge for molecular targeted therapeutics generally.

CORRECTIONS

5603

Correction: Cancer Angiogenesis Induced by Kaposi's Sarcoma-Associated Herpesvirus Is Mediated by EZH2

5606

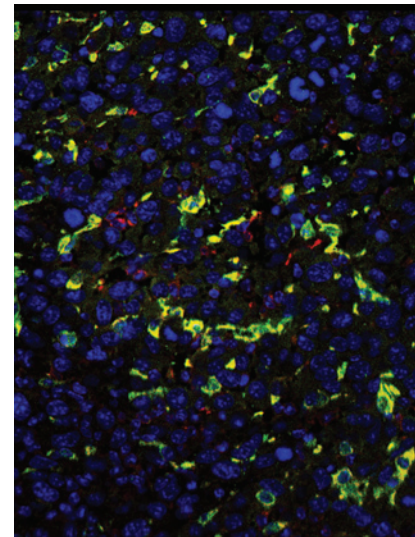
Correction: Emil Frei III, MD: In Memoriam (1924–2013)

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ABOUT THE COVER

The tumor microenvironment contains numerous cellular elements, such as cancer-associated fibroblasts (CAF) and activated myofibroblasts that participate in fibrovascular, vascular, and chemo/cytokine support of tumors. Using bone marrow transplant recipient mice harboring CD44 knockout (KO) mesenchymal stem cells (MSC), the precursor population for CAFs and myofibroblasts, Spaeth and colleagues observed the inability of engrafted CD44-KO stromal cells to provide tumor support, to generate vascular support, and importantly, to transition from the benign MSC phenotype to the tumor-supportive aggressive myofibroblast phenotype. The spectrally unmixed image displays smooth muscle actin + CAFs and myofibroblasts (red) from bone marrow derived CD44-KO (green) MSC in the tumor microenvironment. For details, see article by Spaeth and colleagues on page 5347.



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