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Cancer Research

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Michael Jäger, Alexandra Schoberth, Peter Ruf, Juergen Hess, Michael Hennig, Barbara Schmalfeldt, Pauline Wimberger, Michael Ströhlein, Bettina Theissen, Markus M. Heiss, and Horst Lindhofer

Précis: This study offers a mechanistic explanation for the robust clinical response observed in advanced cancer patients with malignant ascites who are treated with an important new type of immunotherapy for this deadly condition.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 33 | **A Novel Method of Transcriptional Response Analysis to Facilitate Drug Repositioning for Cancer Therapy**
Guangxu Jin, Changhe Fu, Hong Zhao, Kemi Cui, Jenny Chang, and Stephen T.C. Wong

Précis: By developing a systematic approach to characterize off-target effects of drugs, this study may help speed the repositioning of existing approved and generic drugs for alternate uses in cancer treatment, addressing a huge but largely ignored opportunity in cancer research with obvious benefits to health care cost management.

MICROENVIRONMENT AND IMMUNOLOGY

- 45 | **Defective NF- κ B Signaling in Metastatic Head and Neck Cancer Cells Leads to Enhanced Apoptosis by Double-Stranded RNA**
Naoki Umemura, Jianzhong Zhu, Yvonne K. Mburu, Adriana Forero, Paishiun N. Hsieh, Ravikumar Muthuswamy, Pawel Kalinski, Robert L. Ferris, and Saumendra N. Sarkar

Précis: This study reveals that metastatic cells have a specific sensitivity to a certain class of Toll-receptor ligands, suggesting ways to exploit these ligands to improve targeted tumor therapy.

- 56 | **ATM-Mediated DNA Damage Signals Mediate Immune Escape through Integrin- α v β 3-Dependent Mechanisms**

Masahisa Jinushi, Shigeki Chiba, Muhammad Baghdadi, Ichiro Kinoshita, Hirotohi Dosaka-Akita, Koyu Ito, Hironori Yoshiyama, Hideo Yagita, Toshimitsu Uede, and Akinori Takaoka

Précis: Constitutive DNA damage signals in cancer cells may promote immune escape by upregulating cell surface expression of integrin α v β 3, which may target dendritic cell functions needed for effective immune control.

66 **A Dynamic Inflammatory Cytokine Network in the Human Ovarian Cancer Microenvironment**

Hagen Kulbe, Probir Chakravarty, D. Andrew Leinster, Kellie A. Charles, Joseph Kwong, Richard G. Thompson, Jermaine I. Coward, Tiziana Schioppa, Stephen C. Robinson, William M. Gallagher, Laura Galletta on behalf of the Australian Ovarian Cancer Study Group, Michael A. Salako, John F. Smyth, Thorsten Hagemann, Donal J. Brennan, David D. Bowtell, and Frances R. Balkwill

Précis: Key pathways involved in cancer-associated inflammation and Notch signaling appear to contribute to an autocrine cell network in ovarian cancer, with implications for new therapeutic approaches.

76 **Activated STAT5 Promotes Long-Lived Cytotoxic CD8⁺ T Cells That Induce Regression of Autochthonous Melanoma**

Magali Grange, Michel Buferne, Grégory Verdeil, Lee Leserman, Anne-Marie Schmitt-Verhulst, and Nathalie Auphan-Anezin

Précis: Activation of the transcription factor STAT5 in cytolytic T cells improves their antitumor potency, including by improving recall responses suppressed by the tumor microenvironment, suggesting new strategies to improve the durability of adoptive T-cell immunotherapy.

MOLECULAR AND CELLULAR PATHOBIOLOGY

88 **GLI1 Inhibition Promotes Epithelial-to-Mesenchymal Transition in Pancreatic Cancer Cells**

Simon Joost, Luciana L. Almada, Verena Rohhalter, Philipp S. Holz, Anne M. Vrabel, Maite G. Fernandez-Barrena, Robert R. McWilliams, Michael Krause, Martin E. Fernandez-Zapico, and Matthias Lauth

Précis: Strategies to restore the signals mediated by a key effector transcription factor in the Hedgehog pathway may abolish the malignant character of pancreatic cancer cells by restoring their ability to undergo epithelial differentiation.

100 **Identification of Genes Upregulated in ALK-Positive and EGFR/KRAS/ALK-Negative Lung Adenocarcinomas**

Hirokazu Okayama, Takashi Kohno, Yuko Ishii, Yoko Shimada, Kouya Shiraishi, Reika Iwakawa, Koh Furuta, Koji Tsuta, Tatsuhiko Shibata, Seiichiro Yamamoto, Shun-ichi Watanabe, Hiromi Sakamoto, Kensuke Kumamoto, Seiichi Takenoshita, Noriko Gotoh, Hideaki Mizuno, Akinori Sarai, Shuichi Kawano, Rui Yamaguchi, Satoru Miyano, and Jun Yokota

Précis: Findings provide a molecular basis to stratify more or less aggressive subgroups of lung adenocarcinomas lacking EGFR, KRAS and ALK mutations, possibly helping identify patients who may gain the most benefit from adjuvant chemotherapy after surgical resection.

112 **Integrative Genomic Analyses of Sporadic Clear Cell Renal Cell Carcinoma Define Disease Subtypes and Potential New Therapeutic Targets**

Vijay R. Dondeti, Bradley Wubbenhorst, Priti Lal, John D. Gordan, Kurt D'Andrea, Edward F. Attiyeh, M. Celeste Simon, and Katherine L. Nathanson

Précis: This study defines 2 new extracellular oncoproteins elevated by common amplification of chromosome 5q in deadly kidney cancers, with potential implications for improving therapeutic management.

122 **CXCR4 Activation Defines a New Subgroup of Sonic Hedgehog-Driven Medulloblastoma**

Rajarshi Sengupta, Adrian Dubuc, Stacey Ward, Lihua Yang, Paul Northcott, B. Mark Woerner, Kirsten Kroll, Jingqin Luo, Michael D. Taylor, Robert J. Wechsler-Reya, and Joshua B. Rubin

Précis: In defining a molecular subgroup of deadly pediatric brain tumors, this study provides a rationale to clinically evaluate a new combination of 2 experimental targeted drugs that might dramatically improve treatment.

133 **Metastasis Suppressor NM23-H1 Promotes Repair of UV-Induced DNA Damage and Suppresses UV-Induced Melanomagenesis**

Stuart G. Jarrett, Marian Novak, Sandrine Dabernat, Jean-Yves Daniel, Isabel Mellon, Qingbei Zhang, Nathan Harris, Michael J. Ciesielski, Robert A. Fenstermaker, Diane Kovacic, Andrzej Slominski, and David M. Kaetzel

Précis: Identification of a DNA repair-promoting function defined for the metastasis suppressor NM23 may shed light on how it can suppress formation of UV-induced melanoma.

- 144 **Opposing Effects of Pigment Epithelium–Derived Factor on Breast Cancer Cell versus Neuronal Survival: Implication for Brain Metastasis and Metastasis-Induced Brain Damage**
Daniel P. Fitzgerald, Preeti Subramanian, Monika Deshpande, Christian Graves, Ira Gordon, Yongzhen Qian, Yeva Snitkovsky, David J. Liewehr, Seth M. Steinberg, José D. Paltán-Ortiz, Mary M. Herman, Kevin Camphausen, Diane Palmieri, S. Patricia Becerra, and Patricia S. Steeg
Précis: A cytokine previously linked to tumor angiogenesis is discovered to suppress metastasis to the brain, where it also helps preserve neuronal survival, thereby acting through 2 unrecognized mechanisms to blunt metastatic spread and its consequences in the brain.
- 154 **A Combined Array-Based Comparative Genomic Hybridization and Functional Library Screening Approach Identifies mir-30d As an Oncomir in Cancer**
Ning Li, Sippy Kaur, Joel Greshock, Heini Lassus, Xiaomin Zhong, Yanling Wang, Arto Leminen, Zhongjun Shao, Xiaowen Hu, Shun Liang, Dionyssios Katsaros, Qihong Huang, Ralf Bützow, Barbara L. Weber, George Coukos, and Lin Zhang
Précis: Identification of oncogenic microRNAs by the approach validated in this study may help complete characterization of this class of potentially important theranostic markers.
- 165 **Contrasting Behavior of the p18^{INK4c} and p16^{INK4a} Tumor Suppressors in Both Replicative and Oncogene-Induced Senescence**
Sladjana Gagrica, Sharon Brookes, Emma Anderton, Janice Rowe, and Gordon Peters
Précis: The closely related CDK inhibitors p16^{INK4a} and p18^{INK4c} are tumor suppressors that behave differently during replicative senescence and oncogene-induced senescence, suggesting that their inactivation in human cancer is driven by different selective pressures.
- 176 **Novel Transcriptional Targets of the SRY-HMG Box Transcription Factor SOX4 Link Its Expression to the Development of Small Cell Lung Cancer**
Sandra D. Castillo, Ander Matheu, Niccolo Mariani, Julian Carretero, Fernando Lopez-Rios, Robin Lovell-Badge, and Montse Sanchez-Cespedes
Précis: Small-cell lung cancer, a type of lung cancer with neuroendocrine characteristics, is found to be driven by a family of transcription factors involved in neuronal development that exert oncogenic effects in this setting.
- 187 **Autocrine CSF-1 and CSF-1 Receptor Coexpression Promotes Renal Cell Carcinoma Growth**
Julia Menke, Jörg Kriegsmann, Carl Christoph Schimanski, Melvin M. Schwartz, Andreas Schwarting, and Vicki R. Kelley
Précis: Strategies to target a supportive macrophage pathway in breast cancer might also be effective in more aggressive renal cancers that master the kidney microenvironment to directly adopt this autocrine loop.
- 201 **Use of Multifunctional Sigma-2 Receptor Ligand Conjugates to Trigger Cancer-Selective Cell Death Signaling**
Dirk Spitzer, Peter O. Simon, Jr, Hiroyuki Kashiwagi, Jinbin Xu, Chenbo Zeng, Suwanna Vangveravong, Dong Zhou, Katherine Chang, Jonathan E. McDunn, John R. Hornick, Peter Goedegebuure, Richard S. Hotchkiss, Robert H. Mach, and William G. Hawkins
Précis: Findings provide proof of principle for a modular drug platform using ligands to the sigma-2 receptor, which is highly expressed on many types of human cancer cells, as a target to selectively deliver proapoptotic drugs.
- 210 **Intermittent Administration of MEK Inhibitor GDC-0973 plus PI3K Inhibitor GDC-0941 Triggers Robust Apoptosis and Tumor Growth Inhibition**
Klaus P. Hoeflich, Mark Merchant, Christine Orr, Jocelyn Chan, Doug Den Otter, Leanne Berry, Ian Kasman, Hartmut Koeppen, Ken Rice, Nai-Ying Yang, Stefan Engst, Stuart Johnston, Lori S. Friedman, and Marcia Belvin
Précis: Continuous suppression of pathway signaling is apparently not required for the combinatorial efficacy of a MEK inhibitor plus a PI3K inhibitor, contrary to what might have been expected.
- 220 **Global Characterization of the SRC-1 Transcriptome Identifies ADAM22 as an ER-Independent Mediator of Endocrine-Resistant Breast Cancer**
Damian McCartan, Jarlath C. Bolger, Ailis Fagan, Christopher Byrne, Yuan Hao, Li Qin, Marie McIlroy, Jianming Xu, Arnold D. Hill, Peadar Ó Gaora, and Leonie S. Young
Précis: Findings suggest new insights into how breast tumors switch from hormone-sensitive to hormone-resistant states, also revealing a novel prognostic and therapeutic target that may improve treatment of hormone-resistant tumors.

230 **HMGB1 Promotes Drug Resistance in Osteosarcoma**
Jun Huang, Jiangdong Ni, Ke Liu, Yan Yu, Min Xie, Rui Kang, Philip Vernon, Lizhi Cao, and Daolin Tang

Précis: A protein implicated in chromatin binding and immune signaling contributes to chemotherapeutic resistance in osteosarcoma, revealing a novel therapeutic target for an often chemoresistant disease.

239 **Dual Inhibition of the PI3K/mTOR Pathway Increases Tumor Radiosensitivity by Normalizing Tumor Vasculature**

Emmanouil Fokas, Jae Hong Im, Sally Hill, Sabira Yameen, Michael Stratford, John Beech, Wolfgang Hackl, Sauveur-Michel Maira, Eric J. Bernhard, W. Gillies McKenna, and Ruth J. Muschel

Précis: This study offers a preclinical rationale for the clinical evaluation of dual inhibitors of the PI3K and mTOR pathways which can normalize the blood vasculature of solid tumors to enhance their radiosensitivity, with potentially broad implications to treat all types of solid tumors.

249 **Expression and Function of Survivin in Canine Osteosarcoma**

Jenette K. Shoeneman, E.J. Ehrhart III, Jens C. Eickhoff, J.B. Charles, Barbara E. Powers, and Douglas H. Thamm

Précis: This study demonstrates the potential translational utility of canine osteosarcoma for the investigation of survivin-directed therapeutics.

260 **Norathyriol Suppresses Skin Cancers Induced by Solar Ultraviolet Radiation by Targeting ERK Kinases**

Jixia Li, Margarita Malakhova, Madhusoodanan Mottamal, Kanamata Reddy, Igor Kurinov, Andria Carper, Alyssa Langfald, Naomi Oi, Myoung Ok Kim, Feng Zhu, Carlos P. Sosa, Keyuan Zhou, Ann M. Bode, and Zigang Dong

Précis: A natural product found in mango fruit that was discovered by a screen of the Chinese Medicine Library is shown to be an effective new chemopreventive agent for UV-induced skin cancer.

271 **Genetically Modified T cells Targeting Interleukin-11 Receptor α -Chain Kill Human Osteosarcoma Cells and Induce the Regression of Established Osteosarcoma Lung Metastases**

Gangxiang Huang, Ling Yu, Laurence J.N. Cooper, Mario Hollomon, Helen Huls, and Eugenie S. Kleinerman

Précis: T cells expressing chimeric antigen receptors (CAR cells) show enormous promise for cancer treatment, as illustrated here in treating lung metastases for deadly bone cancers.

282 **Radiosensitization of Human Pancreatic Cancer Cells by MLN4924, an Investigational NEDD8-Activating Enzyme Inhibitor**

Dongping Wei, Hua Li, Jie Yu, Jonathan T. Sebolt, Lili Zhao, Theodore S. Lawrence, Peter G. Smith, Meredith A. Morgan, and Yi Sun

Précis: A small-molecule inhibitor of an E3 ubiquitin ligase known to be broadly significant in cancer pathophysiology is found to be an effective radiosensitizer, prompting clinical attention to pivot ongoing phase I trials of this inhibitor toward radiosensitization studies where its activity may be particularly beneficial.

294 **Pim Kinase Inhibitors Sensitize Prostate Cancer Cells to Apoptosis Triggered by Bcl-2 Family Inhibitor ABT-737**

Jin H. Song and Andrew S. Kraft

Précis: A combinatorial drug strategy involving inhibition of the Pim protein kinase to enhance cancer cell death may be broadly active in many types of human cancer, especially in chemoresistant tumors overexpressing Bcl-2 family proteins that are of high clinical urgency.

304 **Intracellular ATP Levels Are a Pivotal Determinant of Chemoresistance in Colon Cancer Cells**

Yunfei Zhou, Federico Tozzi, Jinyu Chen, Fan Fan, Ling Xia, Jinrong Wang, Guang Gao, Aijun Zhang, Xuefeng Xia, Heather Brasher, William Widger, Lee M. Ellis, and Zhang Weihua

Précis: This study suggests that simply reducing ATP production in cancer cells may be sufficient to subvert chemoresistance, still the central challenge in clinical management of many advanced cancers.

TUMOR AND STEM CELL BIOLOGY

315 **EZH2 Mediates Epigenetic Silencing of Neuroblastoma Suppressor Genes CASZ1, CLU, RUNX3, and NGFR**

Chunxi Wang, Zhihui Liu, Chan-Wook Woo, Zhijie Li, Lifeng Wang, Jun S. Wei, Victor E. Marquez, Susan E. Bates, Qihuang Jin, Javed Khan, Kai Ge, and Carol J. Thiele

Précis: Dysregulation of a single targetable histone methyltransferase is found to be a core contributor to neuroblastoma phenotypes, highlighting a novel general approach to treat this common and deadly pediatric tumor.

325 **The White Adipose Tissue Used in Lipotransfer Procedures Is a Rich Reservoir of CD34⁺ Progenitors Able to Promote Cancer Progression**

Ines Martin-Padura, Giuliana Gregato, Paola Marighetti, Patrizia Mancuso, Angelica Calleri, Chiara Corsini, Giancarlo Pruneri, Michela Manzotti, Visnu Lohsiriwat, Mario Rietjens, Jean-Yves Petit, and Francesco Bertolini

Précis: This study suggests that there might be risks involved in autologous transfer of white adipose tissue, a surgical procedure employed in certain breast cancer patients, due to the large numbers of a stem cell population that has strongly prometastatic properties in that tissue.

335 **Curcumin Analogue CDF Inhibits Pancreatic Tumor Growth by Switching on Suppressor microRNAs and Attenuating EZH2 Expression**

Bin Bao, Shadan Ali, Sanjeev Banerjee, Zhiwei Wang, Farah Logna, Asfar S. Azmi, Dejuan Kong, Aamir Ahmad, Yiwei Li, Subhash Padhye, and Fazlul H. Sarkar

Précis: A synthetic derivative of curcumin, the chief bioactive component of the spice turmeric used for thousands of years in Indian Ayurvedic medicine, is found to de-repress expression of microRNAs that inhibit a master epigenetic driver of cancer cell proliferation and invasion.

346 **Mesenchymal Stromal Cell Mutations and Wound Healing Contribute to the Etiology of Desmoid Tumors**

Adelaide M. Carothers, Hira Rizvi, Rian M. Hasson, Yvonne I. Heit, Jennifer S. Davids, Monica M. Bertagnolli, and Nancy L. Cho

Précis: Findings implicate mesenchymal stromal cells in the etiology of desmoid tumors, often associated with familial colon cancer syndromes, and they suggest novel strategies for systemic treatment of this disease.

356 **Metabolomic NMR Fingerprinting to Identify and Predict Survival of Patients with Metastatic Colorectal Cancer**

Ivano Bertini, Stefano Cacciatore, Benny V. Jensen, Jakob V. Schou, Julia S. Johansen, Mogens Kruhøffer, Claudio Luchinat, Dorte L. Nielsen, and Paola Turano

Précis: The metabolomic signature derived from patients with metastatic colorectal cancer predicts overall survival and provides insight into potential new biomarkers that can be used to predict disease progression and personalize treatment.

365 **ERK1/2 Regulation of CD44 Modulates Oral Cancer Aggressiveness**

Nancy P. Judd, Ashley E. Winkler, Oihana Murillo-Sauca, Joshua J. Brotman, Jonathan H. Law, James S. Lewis, Jr, Gavin P. Dunn, Jack D. Bui, John B. Sunwoo, and Ravindra Uppaluri

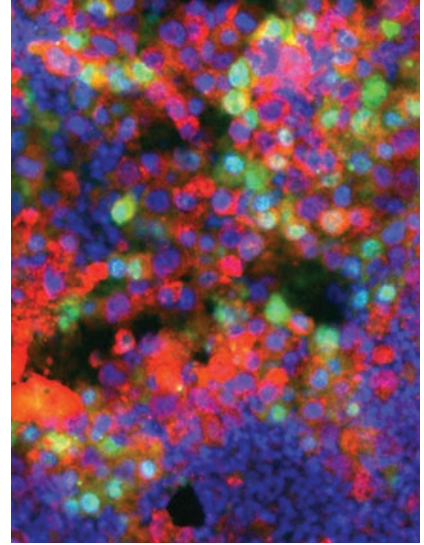
Précis: A pivotal regulator of stem cell function is a crucial downstream effector in the ERK1/2 pathway that mediates the growth of oral squamous carcinomas, which are rising rapidly in incidence in developed countries.

CORRECTION

375 **Correction: LY303511 Enhances TRAIL Sensitivity of SHEP-1 Neuroblastoma Cells via Hydrogen Peroxide-Mediated Mitogen-Activated Protein Kinase Activation and Up-regulation of Death Receptors**

ABOUT THE COVER

Brain metastases of breast and other cancers are increasing in incidence and limiting the gains made by systemic therapy. Here, brain-tropic human metastatic breast cancer cells overexpressing pigment epithelium-derived factor rapidly became apoptotic when implanted into a mouse brain. Red, human mitochondria (tumor cells); green, cleaved caspase-3 stain (apoptosis); blue, DAPI. For details, see the article by Fitzgerald and colleagues on page 144 of this issue.



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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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