## Highlights from Recent Cancer Literature

1257

**Regulation of the Na\(^+\)/H\(^+\) Exchanger (NHE1) in Breast Cancer Metastasis**
Schammim R. Amith and Larry Fliegel

## Oncolytic Vaccinia Virus Disrupts Tumor-Associated Vasculature in Humans

1265

Caroline J. Breitbach, Rozanne Arulanandam, Naomi De Silva, Steve H. Thorne, Richard Patt, Manijeh Daneshmand, Anne Moon, Carolina Ilkow, James Burke, Tae-Ho Hwang, Jeong Heo, Mong Cho, Hannah Chen, Fernando A. Angarita, Christina Addison, J. Andrea McCart, John C. Bell, and David H. Kirn

**Précis:** While effective clinical applications of many oncolytic viruses have been frustrated, the use of oncolytic vaccinia to destroy established tumor vasculatures may offer a powerful outlet for this technology.

## Nitroreductase, a Near-Infrared Reporter Platform for In Vivo Time-Domain Optical Imaging of Metastatic Cancer

1276

Emmet McCormack, Elisabeth Silden, Richard M. West, Tina Pavlin, David R. Micklem, James B. Lorens, Bengt Erik Haug, Michael E. Cooper, and Bjorn Tore Gjertsen

**Précis:** Improvements to noninvasive imaging methods are important to assist the preclinical development of drugs that are active in clinically relevant orthotopic models of advanced metastatic cancer, where the core challenge for treatment remains.

## STC1 Expression By Cancer-Associated Fibroblasts Drives Metastasis of Colorectal Cancer

1287

Cristina Peña, Maria Virtudes Céspedes, Maja Bradic Lindh, Sara Kiflemariam, Artur Mezhevetsky, Per-Henrik Edqvist, Christina Haggjöf, Helgi Birgisson, Linda Bojmar, Karin Jirström, Per Sandström, Eleonor Olsson, Srinivas Veerla, Alberto Gallardo, Tobias Sjöblom, Andy C.-M. Chang, Roger R. Reddel, Ramón Mangués, Martin Augsten, and Arne Ostman

**Précis:** Findings reveal a mechanistic basis for understanding how cancer-associated fibroblasts activated in the tumor microenvironment act to promote cancer metastasis, with implications for arresting this deadly process.

## Amplification of FRS2 and Activation of FGFR/FRS2 Signaling Pathway in High-Grade Liposarcoma

1298

Keqiang Zhang, Kevin Chu, Xiwei Wu, Hanlin Gao, Jinhui Wang, Yate-Ching Yuan, Sofia Loera, Kimberley Ho, Yafan Wang, Warren Chow, Frank Un, Peiguo Chu, and Yun Yen

**Précis:** FGFR/FRS2 signaling may play an important role in the development of high-grade liposarcoma and, therefore, represents a potential therapeutic target.

## BRMS1 Suppresses Lung Cancer Metastases through an E3 Ligase Function on Histone Acetyltransferase p300

1308

Yuan Liu, Marty W. Mayo, Alykhan S. Nagji, Emily H. Hall, Lisa S. Shock, Aizhen Xiao, Edward B. Stelow, and David R. Jones

**Précis:** Findings offer a mechanistic explanation for how the metastasis suppressor gene BRMS1 acts to suppress metastases in a lung cancer model.

## Midkine Promotes Neuroblastoma through Notch2 Signaling

1318

Satoshi Kishida, Ping Mu, Shin Miyakawa, Masatoshi Fujiwara, Tomoyuki Abe, Kazuma Sakamoto, Akira Onishi, Yoshikazu Nakamura, and Kenji Kadomatsu

**Précis:** Preclinical investigations establish a critical cell survival signaling in MYCN-driven neuroblastoma, suggesting new therapeutic directions to improve treatment.
**Inhibition of Cholinergic Signaling Causes Apoptosis in Human Bronchioalveolar Carcinoma**
Jamie K. Lau, Kathleen C. Brown, Brent A. Thornhill, Clayton M. Crabtree, Aaron M. Dom, Theodore R. Witte, W. Elaine Hardman, Christopher A. McNees, Cody A. Stover, A. Betts Carpenter, Haitao Luo, Yi C. Chen, Brandon S. Shiflett, and Piyali Dasgupta

**Precis:** Findings prompt immediate clinical testing of approved drugs that may improve the efficacy of treatments for a certain subtype of lung cancer.

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**Tasquinimod Is an Allosteric Modulator of HDAC4 Survival Signaling within the Compromised Cancer Microenvironment**

**Precis:** Findings define the mechanism of action of an antiangiogenic drug currently in phase III trials and suggest how to leverage its efficacy in combination with other drugs that target the tumor microenvironment.

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**Dual Inhibition of Bel-2 and Bel-xL Strikingly Enhances P33K Inhibition-Induced Apoptosis in Human Myeloid Leukemia Cells through a GSK3- and Bim-Dependent Mechanism**
Mohamed Rahmani, Mandy Mayo Aust, Elisa Attkisson, David C. Williams Jr, Andrea Ferreira-Gonzalez, and Steven Grant

**Precis:** This study defines a combinatorial strategy to block key nodes in cell survival signaling to greatly enhance the killing of acute myeloid leukemia cells exhibiting AKT activation.

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**Application of a Proapoptotic Peptide to Intratumorally Spreading Cancer Therapy**
Renwei Chen, Gary B. Braun, Xuejuan Luo, Kazuki N. Sugahara, Tambet Teesalu, and Erkki Ruoslahti

**Precis:** Results offer preclinical proof of concept for an injectable peptide modality that may be useful to treat tumors that are either surgically inoperable or otherwise difficult to treat systemically.

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**Targeted Cancer Therapy with a 2-Deoxyglucose–Based Adriamycin Complex**
Jie Cao, Sisi Cui, Siwen Li, Changli Du, Junmei Tian, Shunan Wan, Zhiyu Qian, Yueqing Gu, Wei R. Chen, and Guangji Wang

**Precis:** A simple conjugate of adriamycin that improves cancer cell targeting limits the cardiotoxic liabilities of this drug, offering broad applications in cancer treatment.

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**Hyperactivated JNK Is a Therapeutic Target in pVHL-Deficient Renal Cell Carcinoma**
Jiabin An, Huiren Liu, Clara E. Magyar, Yanchuan Guo, Myeore S. Veena, Eri S. Srinivasan, Jiaotu Huang, and Matthew B. Rettig

**Precis:** This study provides insight into HIFα-independent mechanisms that drive renal cancer and offers new opportunities for therapeutic targeting of this disease.

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**FGF-2 Disrupts Mitotic Stability in Prostate Cancer through the Intracellular Trafficking Protein CEP57**
Rolando Cuevas, Nina Korzeniewski, Yanis Tolstov, Markus Hohenfellner, and Stefan Duensing

**Precis:** This provocative study reveals an unexpected link between the tumor microenvironment and chromosomal instability.

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**Autocrine Motility Factor Promotes HER2 Cleavage and Signaling in Breast Cancer Cells**
Dhong Hyo Kho, Pratima Nangia-Makker, Vitaly Balan, Victor Hogan, Larry Tait, Yi Wang, and Avraham Raz

**Precis:** Insights into how resistance arises to HER2 targeting therapies in breast cancer could improve paradigms for its management.

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**Contrasting Hypoxic Effects on Breast Cancer Stem Cell Hierarchy Is Dependent on ER-α Status**
Hannah Harrison, Lynsey Rogerson, Hannah J. Gregson, Keith R. Brennan, Robert B. Clarke, and Göran Landberg

**Precis:** This study describes the response of a breast cancer subtype to hypoxia, with implications for more effective anti-hypoxic and antiangiogenic therapies.

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**miR-7 Suppresses Brain Metastasis of Breast Cancer Stem-Like Cells By Modulating KLF4**

**Precis:** This important study identifies a functional biomarker or therapeutic target for brain metastasis in breast cancer, which remains a mainly untreatable and deadly aspect of progression in this disease.
LETTER TO THE EDITOR

Oxidation-Mediated DNA Crosslinking Contributes to Toxicity of 6-Thioguanine in Human Cells — Letter
Nanne K.H. de Boer, Dirk P. van Asseldonk, Margien L. Seinen, and Adriaan A. van Bodegraven

ABOUT THE COVER

The microRNA network is considered to play critical roles in tumor progression; however, little information is available for microRNA in cancer stem-like cells (CSC). The results of microRNA profile analysis revealed that miR-7 is significantly downregulated in CSCs that are highly metastatic to the brain, and the expression of this microRNA significantly suppressed the ability of CSCs to metastasize to the brain in vivo. miR-7 was also found to be capable of modulating KLF4. Consistently, the expression of miR-7 and KLF4 in brain-metastatic lesions of breast cancer patients was found to be significantly downregulated and upregulated, respectively. High expression of KLF4 was also inversely correlated to brain-metastasis free survival of breast cancer patients. For details, see the article by Okuda and colleagues on page 1434.
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