### Table of Contents

**March 1, 2014 • Volume 74 • Number 5**

### BREAKING ADVANCES

1285  **Highlights from Recent Cancer Literature**

### REVIEWS

1287  **Monocyte Subpopulations in Angiogenesis**  
Heather J. Dalton, Guillermo N. Armaiz-Pena,  
Vianey Gonzalez-Villasana, Gabriel Lopez-Berestein,  
Menashe Bar-Eli, and Anil K. Sood

1294  **Ganetespib and HSP90: Translating Preclinical Hypotheses into Clinical Promise**  
David A. Proia and Richard C. Bates

1301  **RNA Editome Imbalance in Hepatocellular Carcinoma**  
Lihua Qi, Tim Hon Man Chan, Daniel G. Tenen, and Leilei Chen

### MEETING REPORT

1307  **Future Opportunities in Cancer Nanotechnology—NCI Strategic Workshop Report**  
Piotr Grodzinski and Dorothy Farrell

### CLINICAL STUDIES

1311  **Fusobacterium in Colonic Flora and Molecular Features of Colorectal Carcinoma**  
Tomomitsu Tahara, Eichihiro Yamamoto,  
Hiromu Suzuki, Reo Maruyama, Woonbok Chung,  
Judith Garriga, Jaroslav Jelinek, Hiro-o Yamano,  
Tamotsu Sugai, Byonggu An, Imad Shureiqi,  
Minoru Toyota, Yutaka Kondo, Marcos R.H. Estécio, and Jean-Pierre J. Issa

**Précis:** Particular alterations of the bacterial species in the gut microbiome are linked to molecular features of colon cancer, highlighting the potential utility of these species as biomarkers and prevention targets.

### INTEGRATED SYSTEMS AND TECHNOLOGIES

1319  **A Novel Radiotracer to Image Glycogen Metabolism in Tumors by Positron Emission Tomography**  
Timothy H. Witney, Laurence Carroll, Israt S. Alam,  
Anil Chandrashekar, Quang-Dé Nguyen,  
Roberta Sala, Robert Harris, Ralph J. DeBerardinis,  
Roshanagarwal, and Eric O. Aboagye

**Précis:** By exploiting the little-studied process of glycogen synthesis in tumors, a novel radiotracer for PET scans was developed in this study to evaluate tumoral quiescence.

1329  **Fragmented Sleep Accelerates Tumor Growth and Progression through Recruitment of Tumor-Associated Macrophages and TLR4 Signaling**  
Fahed Hakim, Yang Wang, Shelley X.L. Zhang,  
Jiamao Zheng, Esma S. Yolcu, Alba Carreras,  
Abdelnaby Khalyfa, Haval Shirwan,  
Isaac Almendros, and David Gozal

**Précis:** Sleep apnea caused by breathing difficulties in obese individuals may be a contributing factor in how obesity promotes cancer, given links between sleep disruption and a higher incidence of cancer prevalence and mortality.

1338  **Genetic and Phenotypic Diversity in Breast Tumor Metastases**  
Vanessa Almendro, Hee Jung Kim, Yu-Kang Cheng,  
Mithat Gönen, Shalev Itzkovitz, Pedram Argani,  
Alexander van Oudenaarden, Saraswati Sukumar,  
Franziska Michor, and Kornelia Polyak

**Précis:** Understanding changes in cancer cell populations during malignant progression is a critical first step toward the design of improved therapies for advanced cancers.

### MICROENVIRONMENT AND IMMUNOLOGY

1349  **Novel Bispecific Antibodies Increase γδ T-Cell Cytotoxicity against Pancreatic Cancer Cells**  
Hans-Heinrich Oberg, Matthias Peipp,  
Christian Kellner, Susanne Sebens, Sarah Krause,  
Dominantas Petrick, Sabine Adam-Klages,  
Christoph Röcken, Thomas Becker, Ilka Vogel,  
Dietrich Weisner, Sandra Freitag-Wolf,  
Martin Gramatzki, Dieter Kabelitz, and Daniela Wesch

**Précis:** These results show how bispecific antibodies that selectively recruit γδ T cells to pancreatic tumors can exploit the immunotherapeutic potential of this type of T cell from pancreatic cancer patients.
Induction of Immunoregulatory CD271+ Cells by Metastatic Tumor Cells That Express Human Endogenous Retrovirus H
Chie Kudo-Saito, Masahiro Yura, Ryusuke Yamamoto, and Yutaka Kawakami

Précis: An expressed endogenous retrovirus present in the human genome is found to be a critical determinant of immune escape and metastasis, acting to organize immunosuppressive mesenchymal stem cells and myeloid-derived suppressor cells in the tumor microenvironment.

P14ARF Suppresses Tumor-Induced Thrombosis by Regulating the Tissue Factor Pathway
Abdessamad Zerrouqi, Beata Pyrzynska, Daniel J. Brat, and Erwin G. Van Meir

Précis: This study links an important suppressor pathway to the vascular microenvironment of tumors, suggesting how necrotic areas that promote progression can develop.

Cancer Cells Exploit elf4E2-Directed Synthesis of Hypoxia Response Proteins to Drive Tumor Progression
James Uniacke, J. Kishan Perera, Gabriel Lachance, Camille B. Francisco, and Stephen Lee

Précis: Cancer cells shift their use of translation initiation factors to adapt to hypoxic microenvironments where aggressive characters are selected, with implications for understanding and preventing the malignant progression of subclinical lesions.

LIMD2 Is a Small LIM-Only Protein Overexpressed in Metastatic Lesions That Regulates Cell Motility and Tumor Progression by Directly Binding to and Activating the Integrin-Linked Kinase
Hongzhuang Peng, Mehdi Talebzadeh-Farrooji, Michael J. Osborne, Jeremy W. Prokop, Paul C. McDonald, Jayashree Karar, Zhaoyuan Hou, Mei He, Electron Kebebew, Torben Orntoft, Meenhard Herlyn, and Andrew J. Caton

Précis: A signaling component that links integrin-mediated signaling to cell motility and metastatic behavior may offer a new target to control tumor spread.

ALCAM/CD166 Is a TGF-β Responsive Marker and Functional Regulator of Prostate Cancer Metastasis to Bone
Amanda G. Hansen, Shanna A. Arnold, Ming Jiang, Trenis D. Palmer, Tatiana Ketova, Alyssa Merkel, Michael Pickup, Susan Samaras, Yu Shyr, Harold L. Moses, Simon W. Hayward, Julie A. Sterling, and Andrés Zijlstra

Précis: These findings demonstrate that a molecular regulator of tumor cell migration not only contributes functionally to skeletal metastasis but also acts as a biomarker of disease progression.

HAVCR/KIM-1 Activates the IL-6/STAT-3 Pathway in Clear Cell Renal Cell Carcinoma and Determines Tumor Progression and Patient Outcome
Thaïs Cuadros, Enric Trilla, Eduard Sarró, Maya R. Vilà, Jordi Vilardell, Inés de Torres, Mayte Salcedo, Joan López-Hellin, Alex Sánchez, Santiago Ramón y Cajal, Emilio Itarte, Juan Morote, and Anna Meseguer

Précis: This study suggests novel insights into the mechanisms by which deadly clear cell renal cancers are driven, with implications for prognosis and follow-up care.

Suppression of MicroRNA-9 by Mutant EGFR Signaling Upregulates FOXP1 to Enhance Glioblastoma Tumorigenicity
German G. Gomez, Stefano Volinia, Carlo M. Croce, Ciro Zanca, Ming Li, Ryan Emnett, David H. Gutmann, Cameron W. Brennan, Frank B. Furnari, and Webster K. Cavenee

Précis: These findings identify an important new mechanism through which a common EGFR mutant acts to drive advanced brain cancer.

The Transcriptional Regulatory Network of Proneural Glioma Determines the Genetic Alterations Selected during Tumor Progression
Adam M. Sonabend, Mukesh Bansal, Paolo Guarneri, Liang Lei, Benjamin Amendolara, Craig Soderquist, Richard Leung, Jonathan Yun, Benjamin Kennedy, Julia Sisti, Samuel Bruce, Rachel Bruce, Reena Shakya, Thomas Ludvig, Steven Rosenfeld, Peter A. Sims, Jeffrey N. Bruce, Andrea Califano, and Peter Canoll

Précis: Perturbing a transcriptional network associated with glioblastoma tumorigenicity alters the course of glioma progression and prevents the selection of proneural-specific genetic alterations, demonstrating a functional interplay between tumor phenotype and genotype.
Overexpression of the Transcription Factor MEF2D in Hepatocellular Carcinoma Sustains Malignant Character by Suppressing G2–M Transition Genes
Leina Ma, Jia Liu, Limei Liu, Guangjie Duan, Qingliang Wang, Yannin Xu, Feng Xia, Juanjuan Shan, Junjie Shen, Zhi Yang, Ping Bie, Youhong Cui, Xiu-Wu Bian, Jesus Prieto, Matías A. Avila, and Cheng Qian

Precis: A transcription factor implicated in leukemia cell survival is shown in this report to be an important oncogenic driver in liver cancer, with clinical implications for etiology and treatment.

Invasive Lobular Carcinoma Cell Lines Are Characterized by Unique Estrogen-Mediated Gene Expression Patterns and Altered Tamoxifen Response
Matthew J. Sikora, Kristine L. Cooper, Amir Bahreini, Soumya Luthra, Guoying Wang, Uma R. Chandran, Nancy E. Davidson, David J. Dabbs, Alana L. Welm, and Steffi Oesterreich

Precis: These results offer explanatory power to understand recent clinical observations in lobular breast cancer, where, despite favorable biomarkers, patients do not necessarily consistently exhibit favorable outcomes.

Molecular Rules Governing De Novo Methylation in Cancer
Deborah Nejman, Ravid Straussman, Israel Steinfeld, Michael Ruvolo, Douglas Roberts, Zohar Yakhini, and Howard Cedar

Precis: This study offers new knowledge into how de novo DNA methylation is controlled at CpG islands in the genome, a process widely altered in human cancer, with implications for how to develop broadly applicable epigenetic therapies for cancer prevention and treatment.

Differential Regulation of Estrogen Receptor α Expression in Breast Cancer Cells by Metastasis-Associated Protein 1
Hyun-Jin Kang, Min-Ho Lee, Hae-Lim Kang, Sung-Hye Kim, Jung-Ran Hahn, Hyelin Na, Tae-Young Na, Yo Na Kim, Je Kyeong Seong, and Mi-Ock Lee

Precis: This study shows how a nucleosome remodeling complex differentially affects ERα positive and ERα-negative breast cancer cells, potentially determining their sensitivity to hormone therapy.

LEF1 and B9L Shield β-Catenin from Inactivation by Axin, Desensitizing Colorectal Cancer Cells to Tankyrase Inhibitors
Marc de la Roche, Ashraf E.K. Ibrahim, Juliusz Mieszczanek, and Mariann Bienz

Precis: These findings suggest that chronic Wnt pathway activation can render cancer cells insensitive to tankyrase inhibitors, a novel class of clinical experimental therapeutics, possibly limiting their potential therapeutic impact in colorectal cancer where Wnt activation is common.

Bufalin Is a Potent Small-Molecule Inhibitor of the Steroid Receptor Coactivators SRC-3 and SRC-1
Ying Wang, David M. Lonard, Yang Yu, Dar-Chone Chow, Timothy G. Falzkill, Jin Wang, Ruogu Qi, Alexander J. Matzuk, Xianzhou Song, Franck Madoux, Peter Hodder, Peter Chase, Patrick R. Griffin, Suding Zhou, Lan Liao, Jianming Xu, and Bert W. O’Malley

Precis: Steroid receptor coactivators are key oncogenes and attractive drug targets for cancer therapy that can be effectively inhibited with the small-molecule inhibitor bufalin.

BRCA2 Phosphorylated by PLK1 Moves to the Midbody to Regulate Cytokinesis Mediated by Nonmuscle Myosin IIC
Miho Takaoka, Hiroko Saito, Katsuya Takenaka, Yoshio Miki, and Akira Nakashima

Precis: This study suggests that BRCA2 may prevent cancer in part by enforcing checkpoint controls on cytokinesis, the last step in mitosis, where it may be possible to prevent aneuploidy and multinucleation leading to cancer.

Axon Guidance Factor SLIT2 Inhibits Neural Invasion and Metastasis in Pancreatic Cancer
Andreas Göhrig, Katharina M. Detjen, Georg Hilfenhaus, Jan L. Körner, Martina Welzel, Ruza Arsenic, Rosa Schmuck, Marcus Bahra, Jane Y. Wu, Bertram Wiedenmann, and Christian Fischer

Precis: A cell surface receptor system that guides neuronal migration appears to be dysfunctions co-opted during development of pancreatic cancer, possibly driving its propensity to metastasize from the pancreas along nerve tracts.
1541 microRNA-148a Is a Prognostic oncomiR That Targets MIG6 and BIM to Regulate EGFR and Apoptosis in Glioblastoma
Jungeun Kim, Ying Zhang, Michael Skalski, Josie Hayes, Benjamin Kefas, David Schiff, Benjamin Purrow, Sarah Parsons, Sean Lawler, and Roger Abounader

Précis: These findings provide a comprehensive analysis of the prognostic value and oncogenic function of a microRNA in aggressive brain cancer, with further implications as a potential target for therapy.

1554 CD133+ Cancer Stem-like Cells in Small Cell Lung Cancer Are Highly Tumorigenic and Chemoresistant but Sensitive to a Novel Neuropeptide Antagonist
Sana Sarvi, Alison C. Mackinnon, Nicolaos Avlonitis, Mark Bradley, Robert C. Rintoul, Doris M. Rassl, Wei Wang, Stuart J. Forbes, Christopher D. Gregory, and Tariq Sethi

Précis: Small-cell lung cancer has neuroendocrine features that suggest its targeting by neuropeptide antagonists, an idea that is strongly reinforced by the findings of this study.

1566 VEGF-Mediated Angiogenesis Links EMT-Induced Cancer Stemness to Tumor Initiation
Anna Fantozzi, Dorothea C. Gruber, Laura Pisarsky, Chantal Heck, Akiko Kunita, Mahmut Yilmaz, Nathalie Meyer-Schaller, Karen Cornille, Ulrike Hopfer, Mohamed Bentires-Alj, and Gerhard Christofori

Précis: This study offers provocative findings suggesting that the ability of cancer stem-like cells to initiate cancer relies on their ability to promote angiogenesis.

1576 Mesenchymal Stem Cells Use IDO to Regulate Immunity in Tumor Microenvironment
Weifang Ling, Jimin Zhang, Zengrong Yuan, Guangwen Ren, Liying Zhang, Xiaodong Chen, Arnold B. Rabson, Arthur I. Roberts, Ying Wang, and Yufang Shi

Précis: This study corroborates the concept that IDO offers a pivotal mediator of immune escape in human cancer by showing that IDO expression in mesenchymal stem cells in the tumor microenvironment is sufficient to drive tumor formation.

1588 Sequential Gene Targeting to Make Chimeric Tumor Models with De Novo Chromosomal Abnormalities

Précis: This study describes a rapid method to generate mouse models of cancer, providing a flexible platform to tag cancer-initiating cells and a means to learn how chromosomal abnormalities interact with other mutations.

1598 Integrin αvβ6 Promotes an Osteolytic Program in Cancer Cells by Upregulating MMP2

Précis: This study shows how expression of a single integrin can contribute to osteolysis by cancer cells by triggering matrix degradation in bone.

1609 Interactions between MUC1 and p120 Catenin Regulate Dynamic Features of Cell Adhesion, Motility, and Metastasis
Xiang Liu, Chunhui Yi, Yunfei Wen, Prakash Radhakrishnan, Jarrod R. Tremayne, Thongtan Dao, Keith R. Johnson, and Michael A. Hollingsworth

Précis: These findings provide new functional insights into the dynamic interplay between cell adhesion and motility and their relationship to metastasis.

CORRECTION

1621 Correction: Circadian Regulation of mTOR by the Ubiquitin Pathway in Renal Cell Carcinoma
ABOUT THE COVER

Chemoresistant small cell lung cancer (SCLC) tumors demonstrate increased expression of CD133, a known marker for cancer stem cells. The CD133 positive SCLC cells coexpress gastrin releasing peptide receptor (GRPR), which facilitates signaling and growth in response to GRP while rendering cells more sensitive to neuropeptide antagonists. Confocal microscopic analysis of chemoresistant human SCLC xenografts show clusters of CD133 positive cells (green) within the tumor that were shown to coexpress GRPR (red). Antagonists such as the one described by Sarvi and colleagues may provide a new avenue for the treatment of chemoresistant SCLC tumors. For details, see article by Sarvi and colleagues on page 1554.