### Cancer Research

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

1319 A Novel Radiotracer to Image Glycogen Metabolism in Tumors by Positron Emission Tomography
Timothy H. Witney, Laurence Carroll, Israt S. Alam, Anil Chandrashekaran, Quang-Dé Nguyen, Roberta Sala, Robert Harris, Ralph J. DeBerardinis, Roshan Agarwal, 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

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

#### INTEGRATED SYSTEMS AND TECHNOLOGIES

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#### 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, Domantas 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 eIF4E2-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, Andrew J. Caton, William Fredericks, Bruce Malkowicz, Christopher S. Paterno, Alexandra S. Carolin, David W. Speicher, Emmanuel Skordalakes, Qihong Huang, Shoukat Dedhar, Katherine L.B. Borden, and Frank J. Rauscher III

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 Andries 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
Thais Quadros, 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 Guarnieri, Liang Lei, Benjamin Amendolara, Craig Soderquist, Richard Leung, Jonathan Yen, Benjamin Kennedy, Julia Sisti, Samuel Bruce, Rachel Bruce, Reena Shakya, Thomas Ludwig, Steven Rosenfeld, Peter A. Sims, Jeffrey N. Bruce, Andrea Califano, and Peter Canoll

Précis: Perturbing a transcriptional network associated with glial progenitor transformation alters the course of glioma progression and prevents the selection of proneural-specific genetic alterations, demonstrating a functional interplay between tumor phenotype and genotype.
1452 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

**Précis:** 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.

1463 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

**Précis:** 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.

1475 Molecular Rules Governing \textit{De Novo} Methylation in Cancer
Deborah Nejman, Ravid Straussman, Israel Steinfeld, Michael Ruvolo, Douglas Roberts, Zohar Yakhini, and Howard Cedar

**Précis:** 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.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

1484 Differential Regulation of Estrogen Receptor \(\alpha\) Expression in Breast Cancer Cells by Metastasis-Associated Protein 1
Hyun-Jin Kang, Min-Ho Lee, Hae-Lim Kang, Sung-Hye Kim, Jung-Ran H Ahn, Hyelin Nā, Tae-Young Na, Yo Na Kim, Je Kyeung Seong, and Mi-Ock Lee

**Précis:** This study shows how a nucleosome remodeling complex differentially affects ER\(\alpha\)-positive and ER\(\alpha\)-negative breast cancer cells, potentially determining their sensitivity to hormone therapy.

1495 LEF1 and B9L Shield \(\beta\)-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

**Précis:** 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.

1506 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. Faizkili, Jin Wang, Ruong 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

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