BREAKING ADVANCES

7073 Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENTARY

7075 Commentary on “Epithelial–to–Mesenchymal Transition Contributes to Drug Resistance in Pancreatic Cancer”
Jessica A. Beach and David D.L. Bowtell

INTEGRATED SYSTEMS AND TECHNOLOGIES

7078 Quantifying the Dynamics of Field Cancerization in Tobacco-Related Head and Neck Cancer: A Multiscale Modeling Approach
Marc D. Ryser, Walter T. Lee, Neal E. Ready, Kevin Z. Leder, and Jasmine Foo
Précis: This study demonstrates how mathematical models can be used to inform and improve current clinical practice and to reduce the rate of local relapse in head and neck cancer patients.

7089 Preclinical Evidence That 3'-Deoxy-3'-[18F]Fluorothymidine PET Can Visualize Recovery of Hematopoiesis after Gemcitabine Chemotherapy
Sonja Schelhaas, Annelena Held, Nicole Baumer, Thomas Viel, Sven Hermann, Carsten Müller-Tidow, and Andreas H. Jacobs
Précis: These findings offer preclinical proof of concept for the use of a noninvasive imaging method to monitor the status of hematopoietic tissues after administration of myelosuppressive chemotherapies, with clinical implications for its use in developing new cancer therapies.

7096 Gemcitabine Mechanism of Action Confounds Early Assessment of Treatment Response by 3'-Deoxy-3'-[18F]Fluorothymidine in Preclinical Models of Lung Cancer
Sonja Schelhaas, Annelena Held, Lydia Wachsmuth, Sven Hermann, Davina J. Honess, Kathrin Heinzmann, Donna-Michelle Smith, John R. Griffiths, Davina J. Honess, Kathrin Heinzmann, Donna-Michelle Smith, John R. Griffiths, and Andreas H. Jacobs
Précis: When using [18F]FLT as an imaging biomarker in cancer patients receiving gemcitabine therapy, factors confounding uptake of this biomarker in patients receiving gemcitabine therapy have to be taken into account.

MICROENVIRONMENT AND IMMUNOLOGY

7106 Surface Expression of TGFβ Docking Receptor GARP Promotes Oncogenesis and Immune Tolerance in Breast Cancer
Alessandra Metelli, Bill X. Wu, Caroline W. Fugle, Saleh Rachidi, Shaoli Sun, Yongliang Zhang, Jennifer Wu, Stephen Tomlinson, Philip H. Howe, Yi Yang, Elizabeth Garrett-Mayer, Bei Liu, and Zihai Li
Précis: A cell surface docking receptor for latent TGFβ deposited in the tissue microenvironment is shown to exert both cancer-intrinsic and cancer-extrinsic roles in oncogenesis, with notable impacts on tumor immunity and metastasis.

MOLECULAR AND CELLULAR PATHOBIOLGY

7118 IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity
Précis: This study reports molecular biomarkers for a rare form of breast cancer by identifying IDH2 and PIK3CA driver mutations that may help diagnose this disease and possibly direct its more effective treatment.

7130 TSC2 Deficiency Unmasks a Novel Necrosis Pathway That Is Suppressed by the RIP1/RIP3/MLKL Signaling Cascade
Piotr T. Filipczak, Cindy Thomas, Wenshu Chen, Andrew Salzman, Jacob D. McDonald, Yong Lin, and Steven A. Belinsky
Précis: These findings define a necrotic death pathway that involves mitochondrial homeostasis, possibly offering a promising therapeutic target for tumors marked by inactivation of the tumor suppressor gene TSC.
Dysregulation of RUNX2/Activin-A Axis upon miR-376c Downregulation Promotes Lymph Node Metastasis in Head and Neck Squamous Cell Carcinoma

Precis: This study uncovers a novel oncogenic transcriptional axis that enables lymph node metastasis in head and neck squamous carcinoma.

A Study of TP53 RNA Splicing Illustrates Pitfalls of RNA-seq Methodology
Sunali Mehta, Peter Tsai, Annette Lasham, Hamish Campbell, Roger Reddel, Antony Braithwaite, and Cristin Print

Precis: This study draws attention to limitations of RNA sequencing to understand the biological function of spliced variants expressed at wide-ranging levels from transcriptionally complex loci, such as the p53 gene.

Pancreatic Cancer Risk Associated with Prediagnostic Plasma Levels of Leptin and Leptin Receptor Genetic Polymorphisms
Ana Babic, Ying Bao, Zhi Rong Qian, Chen Yuan, Edward L. Giovannucci, Hugues Aschard, Peter Kraft, Laufey T. Amundadottir, Rachael Stolzenberg-Solomon, Vicente Morales-Oyarvide, Kimmie Ng, Meir H. Stampfer, John Michael Gaziano, Nader Rifai, Michael N. Pollak, Matthew L. Anderson, Barbara B. Cochrane, and Brian M. Wolpin

Precis: A prospective, nested case-control study among participants from five U.S. cohorts identifies prediagnostic leptin levels as a risk factor for pancreatic cancer in men, but not women.

ERK and p38 MAPK Activities Determine Sensitivity to PI3K/mTOR Inhibition via Regulation of MYC and YAP

Precis: This study offers a preclinical proof of concept for the utility of MAPK inhibitors to relieve cancer cell resistance to PI3K/mTOR inhibitors, which evolve in tumors.

Nucleolin Targeting Impairs the Progression of Pancreatic Cancer and Promotes the Normalization of Tumor Vasculature
Maud-Emmanuelle Gilles, Federica Maione, Mélissandre Cossutta, Gilles Carpenter, Laure Caruana, Silvia Di Maria, Claire Houatte, Damien Destouches, Ksenya Shchors, Christopher Prochasson, Fabien Mongelard, Simona Lamba, Alberto Bardelli, Philippe Bouvet, Anne Couvelard, José Courty, Enrico Giraudo, and Ilaria Cascone

Precis: These findings highlight an actionable target in pancreatic cancer that coordinates tumor progression and angiogenesis, in which inhibition might be therapeutically exploited to improve drug delivery and efficacy.

Ubiquitous Release of Exosomal Tumor Suppressor miR-6126 from Ovarian Cancer Cells
Pinar Kanlikilicer, Mohammed H. Rashid, Recep Bayraktar, Rahul Mitra, Cristina Ivan, Burcu Aslan, Xia Zhan, Justyna Filant, Andrea M. Silva, Cristian Rodriguez-Aguayo, Emine Bayraktar, Martin Pichler, Bulent Ozpolat, George A. Calin, Anil K. Sood, and Gabriel Lopez-Berestein

Precis: These findings provide new insights into the role of exosomal miRNA-mediated tumor progression and suggest a new therapeutic approach to disrupt oncogenic phenotypes in ovarian tumors.

A Hyaluronidase-Responsive Nanoparticle-Based Drug Delivery System for Targeting Colon Cancer Cells
Mingzhen Zhang, Changlong Xu, Liuqing Wen, Moon Kwon Han, Bo Xiao, Jun Zhou, Yuchen Zhang, Zhan Zhang, Emilie Viennois, and Didier Merlin

Precis: These findings offer preclinical proof of concept for a novel carrier system for targeted drug delivery to treat cancer.

FOXD1–ALDH1A3 Signaling Is a Determinant for the Self-Renewal and Tumorigenicity of Mesenchymal Glioma Stem Cells

Precis: These findings define a core pathway controlling the clonogenic and tumorigenic potential of an aggressive mesenchymal subtype of stem-like cells in glioblastoma.
Alternative Polyadenylation in Triple-Negative Breast Tumors Allows NRAS and c-JUN to Bypass PUMILIO Posttranscriptional Regulation
Wayne O. Miles, Antonio Lembo, Angela Volorio, Elena Brachtel, Bin Tian, Dennis Sgroi, Paolo Provero, and Nicholas Dyson
Précis: These findings highlight nongenetic changes that contribute to triple-negative breast tumor transcription and downstream signaling modifications.

Mechanisms through Which Hypoxia-Induced Caveolin-1 Drives Tumorigenesis and Metastasis in Hepatocellular Carcinoma
Xiaowen Mao, Sivia Yuen Sze Wong, Edith Yuk Ting Tse, Frankie Chi Fat Ko, Sze Keong Tey, Yin Shan Yeung, Kwan Man, Regina Cheuk-Lam Lo, Irene Oi-Lin Ng, and Judy Wai Ping Yam
Précis: These important findings reveal how hypoxia in liver cancer enhances its invasive and metastatic potential.

Glucose Metabolism Reprogrammed by Overexpression of IKKe Promotes Pancreatic Tumor Growth
Haseeb Zubair, Shaqquat Azim, Sanjeev Kumar Srivastava, Aamir Ahmad, Arun Bhardwaj, Mohammad Aslam Khan, Grijesh Kumar Patel, Sumit Arora, James Elliot Carter, Seema Singh, and Ajay Pratap Singh
Précis: These findings establish the kinase IKKe as a novel regulator of c-MYC and glucose metabolism, also offering a preclinical mechanistic rationale for its targeting to attack pancreatic cancers, where IKKe is upregulated.

Transglutaminase Interaction with α6/β4-Integrin Stimulates YAP1-Dependent ΔNp63Δ Stabilization and Leads to Enhanced Cancer Stem Cell Survival and Tumor Formation
Matthew L. Fisher, Candace Kerr, Gautam Adhikary, Dan Grun, Wen Xu, Jeffrey W. Keillor, and Richard L. Eckert
Précis: These findings advance understanding of the mechanisms that sustain the survival of cancer stem-like cells, identifying a mechanism involving the targetable factor transglutaminase-2.

CBX4 Suppresses Metastasis via Recruitment of HDAC3 to the Runx2 Promoter in Colorectal Carcinoma
Xin Wang, Liping Li, Yuanzhong Wu, Ruhua Zhang, Meilang Zhang, Dan Liao, Gang Wang, Ge Qin, Rui-hua Xu, and Tiebang Kang
Précis: These findings suggest a strategy to treat colorectal cancer patients with metastases by stabilizing a novel histone deacetylase complex.

LETTERS TO THE EDITOR

RECQL4 Modulates MDR1 Expression and Chemoresistance—Letter
Paola Perego

RECQL4 Modulates MDR1 Expression and Chemoresistance—Response
Yongliang Zhao

CORRECTIONS

Correction: Autocrine Production of Interleukin-4 and Interleukin-10 Is Required for Survival and Growth of Thyroid Cancer Cells

Correction: IFN-β Down-Regulates the Expression of DNA Repair Gene MGMT and Sensitizes Resistant Glioma Cells to Temozolomide

Acknowledgment to Reviewers
About the Cover

FOXD1 and ALDH are evolutionarily conserved genes that contribute to central nervous system tumorigenesis. Glioblastoma shows cellular heterogeneity linked to glioma stem cells (GSC) of the mesenchymal (MES) or proneural subtype. Analysis of the MES-GSC regulatory machinery led to the identification of ALDH1 as a specific marker for MES GSCs that is transcriptionally regulated by FOXD1. Upregulation of Fd59A (Drosophila FoxD1 ortholog) correlates with formation of invasive glial neoplasms. Using immunohistochemistry in Drosophila larval central nervous system, it was found that Fd59A expression is upregulated in glial neoplasms from repoGAL4 UASPTEN^RNAi UASRas^V12 as compared with normal larvae. For details, see article by Cheng and colleagues on page 7219.
Cancer Research

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