

BREAKING ADVANCES

- 1035 | **Highlights from Recent Cancer Literature**

REVIEW

- 1037 | **Heterogeneity of Neoplastic Stem Cells: Theoretical, Functional, and Clinical Implications**
Peter Valent, Dominique Bonnet, Stefan Wöhrer, Michael Andreeff, Mhairi Copland, Christine Chomienne, and Connie Eaves

MEETING REPORT

- 1046 | **Twenty-fourth Annual Pezcoller Symposium: Molecular Basis for Resistance to Targeted Agents**
Richard Marais, William Sellers, David Livingston, and Enrico Mihich

PRIORITY REPORTS

- 1050 | **Clonal Progression of Prostate Cancers from Gleason Grade 3 to Grade 4**
Adam G. Sowalsky, Huihui Ye, Glenn J. Bubley, and Steven P. Balk

Précis: Although most low grade prostate cancers appear to be indolent, this study establishes that a subset can progress to higher grades and may already harbor features that can be used to predict their progression.

- 1056 | **Unconventional Role of the Inwardly Rectifying Potassium Channel Kir2.2 as a Constitutive Activator of RelA in Cancer**

Inkyoung Lee, Sook-Ja Lee, Tong Mook Kang, Won Ki Kang, and Chaehwa Park
Précis: Expression of potassium ion channels occurs with some frequency in various human cancers, where they may offer possible therapeutic targets, but their contributions to cancer pathogenicity have not been well understood.

CLINICAL STUDIES

- 1063 | **Natural Human Plasmacytoid Dendritic Cells Induce Antigen-Specific T-Cell Responses in Melanoma Patients**
Jurjen Tel, Erik H.J.G. Aarntzen, Tetsuro Baba, Gerty Schreibelt, Barbara M. Schulte, Daniel Benitez-Ribas, Otto C. Boerman, Sandra Croockewit, Wim J.G. Oyen, Michelle van Rossum, Gregor Winkels, Pierre G. Coulie, Cornelis J.A. Punt, Carl G. Figdor, and I. Jolanda M. de Vries
Précis: This is the first clinical study to use naturally occurring plasmacytoid dendritic cells (DC) to treat metastatic melanoma, representing an important evolution in the development of more effective DC-based vaccines for cancer treatment.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1076 | **Methylome Profiling Reveals Distinct Alterations in Phenotypic and Mutational Subgroups of Myeloproliferative Neoplasms**
Sangeeta Nischal, Sanchari Bhattacharyya, Maximilian Christopheit, Yiting Yu, Li Zhou, Tushar D. Bhagat, Davendra Sohal, Britta Will, Yongkai Mo, Masako Suzuki, Animesh Pardani, Michael McDevitt, Jaroslaw P. Maciejewski, Ari M. Melnick, John M. Greally, Ulrich Steidl, Alison Moliterno, and Amit Verma
Précis: Results show that distinct patterns of DNA methylation are seen in different subgroups of myeloproliferative syndromes, defining the potential to use hypomethylating agents in certain subgroups of this disease.

- 1086 | **Impact of Tumor Progression on Cancer Incidence Curves**
E. Georg Luebeck, Kit Curtius, Jihyoung Jeon, and William D. Hazelton
Précis: A model-based analysis of cancer incidence curves reveals that they harbor significant information about several hidden processes of tumor initiation, premalignant clonal expansion, malignant transformation, and even limited information on tumor growth before clinical detection.

MICROENVIRONMENT AND IMMUNOLOGY

- 1097 **Endocan Is Upregulated on Tumor Vessels in Invasive Bladder Cancer Where It Mediates VEGF-A–Induced Angiogenesis**
Filip Roudnický, Cedric Poyet, Peter Wild, Sarah Krampitz, Fabrizia Negrini, Reto Huggenberger, Anja Rogler, Robert Stöhr, Arndt Hartmann, Maurizio Provenzano, Vivianne I. Otto, and Michael Detmar
Précis: A more tumor-selective approach to disrupt VEGF signaling is revealed as a strategy for antiangiogenic cancer therapy, focusing on a molecule that mediates VEGF action but is expressed selectively only in the tumor vasculature.
- 1107 **Targeting Galectin-1 Overcomes Breast Cancer-Associated Immunosuppression and Prevents Metastatic Disease**
Tomás Dalotto-Moreno, Diego O. Croci, Juan P. Cerliani, Verónica C. Martínez-Allo, Sebastián Dergan-Dylon, Santiago P. Méndez-Huergo, Juan C. Stupirski, Daniel Mazal, Eduardo Osinaga, Marta A. Toscano, Victoria Sundblad, Gabriel A. Rabinovich, and Mariana Salatino
Précis: Findings offer preclinical genetic validation to block an immunosuppressive lectin commonly expressed in aggressive cancers as a strategy to reverse immune escape and blunt metastatic progression.
- 1118 **Inhibition of Rapamycin-Induced AKT Activation Elicits Differential Antitumor Response in Head and Neck Cancers**
Padhma Radhakrishnan, Ulaganathan Baraneedharan, Subhadra Veluchamy, Muthu Dhandapani, Dency D. Pinto, Saravanan Thiagarajan, Allen Thayakumar, Arun Prasath, Kamal A, Ayyappan Velu, Misti Jain, Nilesh Brijwani, Prasad Narayanan, Vikram D. Kekatpure, Biswanath Majumder, and Pradip K. Majumder
Précis: This study reports a functional assay for the mTOR pathway that may be clinically useful for stratifying head and neck cancer patients who are being considered for mTOR pathway targeting therapies.

- 1128 **Targeting Tumor-Infiltrating Macrophages Decreases Tumor-Initiating Cells, Relieves Immunosuppression, and Improves Chemotherapeutic Responses**
Jonathan B. Mitchem, Donal J. Brennan, Brett L. Knolhoff, Brian A. Belt, Yu Zhu, Dominic E. Sanford, Larisa Belaygorod, Danielle Carpenter, Lynne Collins, David Piwnica-Worms, Stephen Hewitt, Girish Mallya Udupi, William M. Gallagher, Craig Wegner, Brian L. West, Andrea Wang-Gillam, Peter Goedegebuure, David C. Linehan, and David G. DeNardo
Précis: Crosstalk between tumor-infiltrating macrophages and tumor-initiating cells is a pivotal determinant of immunosuppression in pancreatic tumors, limiting the efficacy of chemotherapy, with implications on how to improve treatment in this setting.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 1142 **Moesin Is a Glioma Progression Marker That Induces Proliferation and Wnt/ β -Catenin Pathway Activation via Interaction with CD44**
Xiaoping Zhu, Fabiana C. Morales, Nitin Kumar Agarwal, Turgut Dogruluk, Mihai Gagea, and Maria-Magdalena Georgescu
Précis: This study reveals how an actin membrane-connecting protein acts as an oncogene to drive the function of an important stem cell molecule in glioblastoma, the most aggressive form of brain cancer, with implications for more effective therapy of this disease.
- 1156 **Oncogenic Activation of Pak1-Dependent Pathway of Macropinocytosis Determines BCG Entry into Bladder Cancer Cells**
Gil Redelman-Sidi, Gopa Iyer, David B. Solit, and Michael S. Glickman
Précis: Findings of this study not only reveal how an important cancer biotherapy for bladder cancer works, but also suggest clinical strategies that could personalize the therapy to predict or improve its efficacy in patients.
- 1168 **Trask Loss Enhances Tumorigenic Growth by Liberating Integrin Signaling and Growth Factor Receptor Cross-Talk in Unanchored Cells**
Danislav S. Spassov, Ching Hang Wong, Sunny Y. Wong, Jeremy F. Reiter, and Mark M. Moasser
Précis: Tumor cell growth is restricted to anchored states of the cell unless there is a loss of function in the cell surface protein Trask, which exerts a tumor-suppressing function that blocks anchorage-independent cell growth.

1180

The Noncoding RNA *MALAT1* Is a Critical Regulator of the Metastasis Phenotype of Lung Cancer Cells

Tony Gutschner, Monika Hämmerle, Moritz Eifßmann, Jeff Hsu, Youngsoo Kim, Gene Hung, Alexey Revenko, Gayatri Arun, Marion Stentrup, Matthias Groß, Martin Zörnig, A. Robert MacLeod, David L. Spector, and Sven Diederichs

Précis: Findings identify a long noncoding RNA with fundamental importance in lung cancer metastasis and potential therapeutic application in metastasis prevention.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1190

Trastuzumab-Resistant Cells Rely on a HER2-PI3K-FoxO-Survivin Axis and Are Sensitive to PI3K Inhibitors

Anindita Chakrabarty, Neil E. Bhola, Cammie Sutton, Ritwik Ghosh, María Gabriela Kuba, Bhuvanesh Dave, Jenny C. Chang, and Carlos L. Arteaga

Précis: This study reveals how PI3K inhibitors can reverse resistance to Herceptin in breast cancer cells, an important clinical challenge.

1201

CCR2 Deficiency Prevents Neuronal Dysfunction and Cognitive Impairments Induced by Cranial Irradiation

Karim Belarbi, Timothy Jopson, Carla Arellano, John R. Fike, and Susanna Rosi

Précis: Radiation-induced cognitive impairments in patients may be ameliorated by targeting CCR2 signaling, a rather surprising result, suggesting that strategies to limit proinflammatory myeloid cell responses may reduce this important side effect of cranial radiotherapy for brain tumors or metastases.

1211

Dysregulation of Cholesterol Homeostasis in Human Prostate Cancer through Loss of *ABCA1*

Byron H. Lee, Margaret G. Taylor, Peggy Robinet, Jonathan D. Smith, Jessica Schweitzer, Ephraim Sehayek, Sara M. Falzarano, Cristina Magi-Galluzzi, Eric A. Klein, and Angela H. Ting

Précis: A key cholesterol efflux transporter is hypermethylated in late stage prostate cancer, leading to higher levels of intracellular cholesterol and potentiation of tumor progression.

TUMOR AND STEM CELL BIOLOGY

1219

MYC Regulation of CHK1 and CHK2 Promotes Radioresistance in a Stem Cell-like Population of Nasopharyngeal Carcinoma Cells

Wen-Jun Wang, Si-Pei Wu, Jia-Bin Liu, Yong-Sheng Shi, Xue Huang, Qian-Bing Zhang, and Kai-Tai Yao

Précis: Targeting an important DNA-damage-checkpoint signaling axis with an important role in stem cells may offer an especially robust therapeutic strategy to reverse stem cell radioresistance.

1232

Epigenetic Repression of miR-31 Disrupts Androgen Receptor Homeostasis and Contributes to Prostate Cancer Progression

Pei-Chun Lin, Ya-Lin Chiu, Samprit Banerjee, Kyung Park, Juan Miguel Mosquera, Eugenia Giannopoulou, Pedro Alves, Ashutosh K. Tewari, Mark B. Gerstein, Himisha Beltran, Ari M. Melnick, Olivier Elemento, Francesca Demichelis, and Mark A. Rubin

Précis: This study identifies a novel biomarker for prostate cancer progression and introduces a new mechanistic concept associate with AR regulation of cell cycle progression.

1245

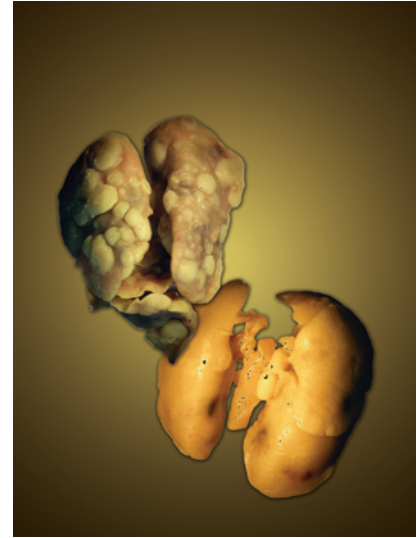
Tumor Suppressor Function of the Plasma Glutathione Peroxidase *Gpx3* in Colitis-Associated Carcinoma

Caitlyn W. Barrett, Wei Ning, Xi Chen, Jesse Joshua Smith, Mary K. Washington, Kristina E. Hill, Lori A. Coburn, Richard M. Peek, Rupesh Chaturvedi, Keith T. Wilson, Raymond F. Burk, and Christopher S. Williams

Précis: Results suggest an immunomodulatory role for an extracellular glutathione peroxidase that acts to limit the development of colitis-associated colon carcinoma.

ABOUT THE COVER

Galectin-1, a carbohydrate-binding protein, abundantly expressed at sites of tumor growth and metastasis, promotes tumor progression by influencing diverse cancer-related events including tumor cell migration, angiogenesis, and tumor-immune escape. Dalotto-Moreno and colleagues show that galectin-1 contributes to immunosuppression during progression of breast cancer. Human breast cancer biopsies expressed substantial amounts of galectin-1, which positively correlated with tumor grade. Silencing Gal1 expression in the 4T1 breast tumor model reduced tumor growth and lung metastases. This effect was accompanied by a diminished frequency and suppressive activity of $CD4^+CD25^+Foxp3^+$ regulatory T cells in both the tumor and metastatic lungs. For details, see article by Dalotto-Moreno and colleagues on page 1107.



Cancer Research

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