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**REVIEWS**

- 4669: Understanding the Unique Attributes of MUC16 (CA125): Potential Implications in Targeted Therapy
  - Srustidhar Das and Surinder K. Batra

- 4675: Application of Evolutionary Principles to Cancer Therapy
  - Pedro M. Enriquez-Navas, Jonathan W. Wojtkowiak, and Robert A. Gatenby

**PRIORITY REPORT**

- 4681: Identification of Cancer-Associated Fibroblasts in Circulating Blood from Patients with Metastatic Breast Cancer

  **Précis:** Potentially seminal findings show how circulating cancer-associated fibroblasts can be specifically and uniformly detected in the peripheral blood of patients with metastatic breast cancer, suggesting utility as a blood-borne biomarker for metastatic disease.

**CLINICAL STUDIES**

- 4688: Androgen Receptor Upregulation Mediates Radioresistance after Ionizing Radiation
  - Daniel E. Spratt, Michael J. Evans, Brian J. Davis, Michael G. Doran, Man Xia Lee, Noel Shah, John Wongvipat, Kathryn E. Carnazza, George G. Klee, William Polkinghorn, Donald J. Tindall, Jason S. Lewis, and Charles L. Sawyers

  **Précis:** In prostate cancer patients who receive radiotherapy, monitoring the levels of androgen receptor signaling may identify those most likely to benefit from an androgen-blocking adjuvant therapy in the long term.
MICROENVIRONMENT AND IMMUNOLOGY

4728 Multivalent Forms of the Notch Ligand DLL-1 Enhance Antitumor T-cell Immunity in Lung Cancer and Improve Efficacy of EGFR-Targeted Therapy
Asel K. Biktasova, Duafalia F. Dudimah, Roman V. Uzhachenko, Kyungho Park, Anwari Akhter, Rajeswara R. Arasada, Jason V. Evans, Sergey V. Novitskiy, Elena E. Tchekneva, David P. Carbone, Anil Shanker, and Mikhail M. Dikov

Précis: These findings develop mechanistic insight and demonstrate the anticancer prowess in a preclinical model of lung cancer for multivalent forms of the Notch receptor ligand Delta-like-1 as a potential biologic for use in combination immunotherapy.

4742 Macrophage Blockade Using CSF1R Inhibitors Reverses the Vascular Leakage Underlying Malignant Ascites in Late-Stage Epithelial Ovarian Cancer
Diana L. Moughon, Huanhuan He, Shiruyeh Schokrpur, Ziyue Karen Jiang, Madeeha Yaqoob, John David, Crystal Lin, M. Luisa Iruela-Arispe, Oliver Dorigo, and Lily Wu

Précis: These striking findings show how blocking macrophage infiltration in late-stage epithelial ovarian cancers can normalize their dysfunctional vasculature, thereby reducing malignant ascites that are responsible for poor treatment outcomes.

4753 Osteogenic Potential of Mesenchymal Stromal Cells Contributes to Primary Myelofibrosis
Christophe Martinaud, Christophe Desterke, Johanna Konopacki, Lisa Pieri, Frederic Torossian, Rachel Golub, Sandrine Schmutz, Adrienne Anginot, Bernadette Guerton, Nathalie Rochet, Patricia Albanese, Emilie Henault, Olivier Pierre-Louis, Jean-Baptiste Souraud, Thierry de Revel, Brigitte Dupriez, Jean-Christophe Ianotto, Marie-Françoise Bourgrede, Alessandro M. Vannucchi, Jean-Jacques Lataillade, and Marie-Caroline Le Bousse-Kerdiles

Précis: These findings strengthen the importance of the bone marrow microenvironment in the development of hematopoietic malignancies, such as primary myelofibrosis, and suggest that therapeutic strategies for this disease should aim to target malignant stromal cells in addition to hematopoietic cells.

MOLECULAR AND CELLULAR PATHOBIOLOGY

4766 Multiple Myeloma Impairs Bone Marrow Localization of Effector Natural Killer Cells by Altering the Chemokine Microenvironment
Andrea Ponzetta, Giorgia Benigni, Fabrizio Antonangeli, Giuseppe Sciumè, Emilio Saneviero, Alessandra Zingoni, Maria Rosaria Ricciardi, Maria Teresa Petrucci, Angela Santoni, and Giovanni Bernardini

Précis: Changes in chemokine expression pattern in the bone marrow microenvironment of multiple myeloma are found to reduce recruitment of natural killer cells, possibly explaining why these cells exhibit functional abnormalities in this setting and impact the development of adoptive natural killer cell immunotherapies to treat this cancer.

4778 Merlin/NF2 Suppresses Pancreatic Tumor Growth and Metastasis by Attenuating the FOXM1-Mediated Wnt/β-Catenin Signaling
Ming Quan, Jiujie Cui, Tian Xia, Zhiliang Jia, Dacheng Xie, Daoyan Wei, Suyun Huang, Qian Huang, Shaojiang Zheng, and Keping Xie

Précis: Mechanistic insights into an important oncogenic signaling pathway discovered in pancreatic cancer may guide new rational strategies to manage this mainly untreatable disease.

4790 Radioprotection of IDH1-Mutated Cancer Cells by the IDH1-Mutant Inhibitor AGI-5198
Remco J. Molenaar, Dennis Botman, Myrthe A. Smits, Vashendriya V. Hira, Sanne A. van Lith, Jan Stap, Peter Henneman, Mohammed Khursheed, Krisste Lenting, Adri N. Mul, Dionysia Dimitrakopoulou, Cornelis M. van Drunen, Ron A. Hoeb, Tomas Radivoyevitch, Johanna W. Wilmink, Jaroslav P. Maciejewski, W. Peter van der Kooi, William P. Leenders, Fonnet E. Bleeker, and Cornelis J. van Noorden

Précis: These findings may explain the relatively longer survival of glioma patients with tumors harboring a common isocitrate dehydrogenase mutation, and they also imply that therapeutics to target this mutation should not be administered with radiotherapy, which is commonly used to treat glioma.
Histone Deacetylase HDAC8 Promotes Insulin Resistance and β-Catenin Activation in NAFLD-Associated Hepatocellular Carcinoma

Précis: This important study makes a molecular connection between obesity-associated fatty liver disease and the development of liver cancer, offering a therapeutic target to tackle the rising incidence of HCC in obese individuals.

Nrf2 Activation Promotes Keratinocyte Survival during Early Skin Carcinogenesis via Metabolic Alterations
Frank Rolfs, Marcel Huber, Andreas Kuehne, Stefan Kramer, Eric Haertel, Sukalp Muzumdar, Johanna Wagner, Yasmine Tanner, Friederike Böhm, Sigrun Smola, Nicola Zamboni, Johanna Wagner, Hans-Dietmar Beer, Daniel Hohl, Sabine Werner, and Matthias Schäfer

Précis: A key regulator of cellular redox that many studies have found to prevent cancer is reported here to have an unexpected protumorigenic activity in the skin, acting at early times to promote metabolic alterations that enhance the survival of premalignant keratinocytes.

Amphiregulin Is a Critical Downstream Effector of Estrogen Signaling in ERα-Positive Breast Cancer

Précis: These findings implicate an EGF receptor ligand as a critical mediator of the estrogen response in breast cancer, emphasizing the importance of EGF receptor signaling in breast tumor pathogenesis and therapeutic responses.

Hypoxia-Induced WSB1 Promotes the Metastatic Potential of Osteosarcoma Cells
Ji Cao, Yijie Wang, Rong Dong, Guanyu Lin, Ning Zhang, Jing Wang, Nengming Lin, Yongchuan Gu, Ling Ding, Meidan Ying, Qiaojun He, and Bo Yang

Précis: These findings define a new mechanistic linkage between hypoxic conditions in a tumor and its ability to develop metastatic process, also identifying a candidate therapeutic target that may help prevent aggressive disease.

Src Inhibition Blocks c-Myc Translation and Glucose Metabolism to Prevent the Development of Breast Cancer
Shalini Jain, Xiao Wang, Chia-Chi Chang, Catherine Ibarra-Drendall, Hai Wang, Qingling Zhang, Samuel W. Brady, Ping Li, Hong Zhao, Jessica Dobbs, Matt Kyriish, Tomasz S. Tkaczuk, Adrian Ambrose, Christopher Sistrunk, Banu K. Arun, Rebecca Richards-Kortum, Wei Jia, Victoria I. Seewaldt, and Dihua Yu

Précis: Src signaling linked to breast cancer has prompted investigation into the suitability of its targeting in that setting, here corroborated by key findings that suggest a rationale to treat premalignant breast lesions with Src kinase inhibitors.

Multiplex H. pylori Serology and Risk of Gastric Cardia and Noncardia Adenocarcinomas
Ramin Shakeri, Reza Malekzadeh, Dariush Nasrollahzadeh, Michael Pawilta, Gwenn Murphy, Farhad Islami, Masoud Sotoudeh, Angelika Michel, Arash Etemadi, Tim Waterboer, Hossein Pouatchi, Paul Brennan, Paolo Roffetta, Sanford M. Dawsey, Farin Kamangar, and Christian C. Abnet

Précis: Risk of certain stomach cancers of high incidence in Asia are associated with changes in seropositivity to H. pylori bacterial antigens, with implications for population health management.
A Heritable Missense Polymorphism in CDKN2A Confers Strong Risk of Childhood Acute Lymphoblastic Leukemia and Is Preferentially Selected during Clonal Evolution

Kyle M. Walsh, Adam J. de Smith, Helen M. Hansen, Ivan V. Smirnov, Semrita Gorneth, Alyson A. Endicott, Jianqiao Xiao, Terri Rice, Cecilia H. Fu, Lucie S. McCoy, Daniel H. Lachance, Jeanette E. Eckel-Passow, John K. Wrench, Robert P. Jenkins, Margaret R. Wrench, Xiaomei Ma, Catherine Metayer, and Joseph L. Wiemels

Précis: A newly identified heritable missense polymorphism in chromosome 9p21.3 that increases risk of childhood leukemia and is preferentially retained within the leukemic blast during tumor cell evolution sheds light on genomic events underlying the emergence of this disease.

Urokinase Receptor Promotes Skin Tumor Formation by Preventing Epithelial Cell Activation of Notch1

Roberta Mazzieri, Giovanni Pietrogrande, Laura Gerasi, Alessandro Gandelli, Piergiuseppe Colombo, Davide Moi, Chiara Brombin, Alessandro Ambrosi, Silvio Danese, Paolo Mignatti, Francesco Blasi, and Silvia D’Alessio

Précis: These findings provide a strong rationale to target a cell surface receptor implicated previously in malignant progression in skin carcinomas as a valid strategy to prevent this disease.

Heightening Energetic Stress Selectively Targets LKB1-Deficient Non–Small Cell Lung Cancers

Milica Momcilovic, Robert McMickle, Evan Abt, Atsuko Seki, Sarah A. Simko, Clara Magyar, David B. Stout, David B. Shackelford

Précis: This biomarker-guided study offers preclinical proof of concept for a personalized and readily translatable clinical strategy to eradicate a common subset of lung adenocarcinomas and squamous cell carcinomas bearing LKB1 and KRAS mutations.

JX06 Selectively Inhibits Pyruvate Dehydrogenase Kinase PDK1 by a Covalent Cysteine Modification

Wenyi Sun, Zuoquan Xie, Yifu Liu, Dan Zhao, Zhixiang Wu, Dadong Zhang, Hao Lv, Shuai Tang, Na Jin, Huailiang Jiang, Minjia Tan, Jian Ding, Cheng Luo, Jian Li, Min Huang, and Meiyu Geng

Précis: These results report a small molecule that targets the enzyme responsible for switching glucose metabolism from mitochondrial oxidation to aerobic glycolysis in cancer cells, a general hallmark of neoplastic transformation termed the Warberg effect, with potentially broad implications for the general treatment of human malignancy.

Inhibition of Casein Kinase 1 Alpha Prevents Acquired Drug Resistance to Erlotinib in EGFR-Mutant Non–Small Cell Lung Cancer

Alexandra B. Lantermann, Dongshu Chen, Kaitlin McCatchee, Greg Hoffman, Elizabeth Frias, David Ruddy, Daniel Rakiec, Joshua Korn, Gregory McAllister, Frank Stenmeier, Matthew J. Meyer, and Sreenath V. Sharma

Précis: These findings suggest that acquired resistance to the EGFR receptor kinase inhibitor erlotinib can be prevented by co-inhibiting CK1, a serine/threonine kinase that may be broadly involved in resistance mechanisms to EGFR inhibitors used in the clinic.

Identification of Bone-Derived Factors Conferring De Novo Therapeutic Resistance in Metastatic Prostate Cancer

Yu-Chen Lee, Song-Chang Lin, Guoyu Yu, Chien-Jui Cheng, Bin Liu, Hsuan-Chen Liu, David H. Hawke, Nila J. Parikh, Andreas Varkaris, Paul Corn, Christopher Logothetis, Robert L. Satcher, Li-Yuan Yu-Lee, Gary E. Gallick, and Sue-Hwa Lin

Précis: These findings deepen the evidence that the tumor stroma contributes significantly to the development of drug resistance in cancer, with specific clinical implications from this study for cancers that spread to bone.

Ras Signaling Is a Key Determinant for Metastatic Dissemination and Poor Survival of Luminal Breast Cancer Patients

Katherine L. Wright, Jessica R. Adams, Jeff C. Liu, Amanda J. Loch, Ruth G. Wong, Christine E.B. Jo, Lauren A. Beck, Divya R. Santhanam, Laura Weiss, Xue Mei, Timothy F. Lane, Sergei B. Koralov, Susan J. Done, James R. Woodgett, Eldad Zacksenhaus, Pingzhuo Hu, and Sean E. Egan

Précis: Breast cancers do not tend to involve Ras pathway mutations, but the findings of this study provide preclinical evidence that Ras-targeting therapeutics may offer a supplemental strategy for improving hormone therapy in the treatment of luminal subtypes of this disease.
Mitochondrial Superoxide Dismutase Has a Protumorigenic Role in Ovarian Clear Cell Carcinoma
L.P. Madhubhani P. Hemachandra, Dong-Hui Shin, Usawadee Dier, James N. Iuliano, Sarah A. Engelberth, Larissa M. Uusitalo, Susan K. Murphy, and Nadine Hempel

Précis: This study identifies that enhanced expression of the antioxidant Sod2 is a distinguishing feature of ovarian clear cell carcinoma, which is imperative in maintaining high mitochondrial function and in shifting steady-state ROS balance to enhance tumor progression.

An Imbalance in TAZ and YAP Expression in Hepatocellular Carcinoma Confers Cancer Stem Cell–like Behaviors Contributing to Disease Progression
Hiromitsu Hayashi, Takaaki Higashi, Naomi Yokoyama, Takayoshi Kaida, Keita Sakamoto, Yukiko Fukushima, Takatsugu Ishimoto, Hideyuki Kuroki, Hidetoshi Nitta, Daisuke Hashimoto, Akira Chikamoto, Eiji Oki, Toru Beppu, and Hideo Baba

Précis: These findings describe a compensatory mechanism that allows Hippo signaling to continue to operate during HCC progression, highlighting the need for multitargeted therapies in this setting to achieve complete antitumor responses.

ABOUT THE COVER
Malignant ascites is a common and devastating complication of late stage epithelial ovarian cancer (EOC) that features dysregulated, leaky blood vasculature. Moughon and colleagues show that tumor-associated macrophages (TAM) contribute dominantly to the vascular pathology of EOC malignant ascites. Consequently, blocking TAMs’ functions by a selective CSF1R kinase inhibitor (GW2580) reversed the vascular leakage and improved vascular perfusion as indicated by the increased number of perfused, blood carrying (lectin, red) capillaries (CD31^+, green). For details, see article by Moughon and colleagues on page 4742.