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Cancer Research

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MEETING REPORT

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Pedro Berraondo, Viktor Umansky, and Ignacio Melero

PRIORITY REPORTS

- 5165 | **RALBP1/RLIP76 Depletion in Mice Suppresses Tumor Growth by Inhibiting Tumor Neovascularization**
Seunghyung Lee, Jeremy G. T. Wurtzel, Sharad S. Singhal, Sanjay Awasthi, and Lawrence E. Goldfinger
Précis: A widely expressed multifunctional protein that binds to Ral and R-Ras small GTPases is essential to support the blood vasculature in tumors, supporting its candidacy as a generalized anticancer target.

- 5174 | **Autologous Ectopic Grafting of Cryopreserved Testicular Tissue Preserves the Fertility of Prepubescent Monkeys That Receive Sterilizing Cytotoxic Therapy**
Kirsi Jahnukainen, Jens Ehmcke, Mirja Nurmio, and Stefan Schlatt

Précis: This study addresses an important survivorship issue for pediatric male cancer patients in developing a proof-of-principle for methods to allow engraftment of immature testis tissue following therapy as a strategy to reduce or eliminate risks of future infertility.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5179 | **An NMR Metabolomics Approach for the Diagnosis of Leptomeningeal Carcinomatosis**
Hye Rim Cho, He Wen, Young Jin Ryu, Yong Jin An, Hyo Cheol Kim, Woo Kyung Moon, Moon Hee Han, Sunghyoun Park, and Seung Hong Choi

Précis: Preclinical proof-of-concept for metabolic typing of cerebral spinal fluid offers a tool to improve diagnostic accuracy of one of the more common types of metastatic invasion into the central nervous system, immediately prompting clinical testing of this approach.

MICROENVIRONMENT AND IMMUNOLOGY

- 5188 | **Impaired IFN- α Production by Plasmacytoid Dendritic Cells Favors Regulatory T-cell Expansion That May Contribute to Breast Cancer Progression**
Vanja Sisirak, Julien Faget, Michael Gobert, Nadège Goutagny, Nelly Vey, Isabelle Treilleux, Sarah Renaudineau, Gaelle Poyet, Sana Intidhar Labidi-Galy, Sophie Goddard-Leon, Isabelle Durand, Isabelle Le Mercier, Agathe Bajard, Thomas Bachelot, Alain Puisieux, Isabelle Puisieux, Jean-Yves Blay, Christine Ménétrier-Caux, Christophe Caux, and Nathalie Bendriss-Vermare

Précis: This study unravels the mechanistic basis for the negative impact of pDC infiltration in breast tumor and offers perspectives for new therapeutic strategies by targeting pDC to overcome immune tolerance in breast cancer.

5198 **Stromal Progenitor Cells from Endogenous Adipose Tissue Contribute to Pericytes and Adipocytes That Populate the Tumor Microenvironment**

Yan Zhang, Alexes C. Daquinag, Felipe Amaya-Manzanares, Olga Sirin, Chieh Tseng, and Mikhail G. Kolonin

Précis: This report suggests that obesity promotes cancer progression by providing a wellspring of adipose cells for tumors to recruit to their microenvironment, where they support angiogenesis and malignant outgrowth.

5209 **PD-1 Blockade Enhances T-cell Migration to Tumors by Elevating IFN- γ Inducible Chemokines**

Weiyi Peng, Chengwen Liu, Chunyu Xu, Yanyan Lou, Jieqing Chen, Yan Yang, Hideo Yagita, Willem W. Overwijk, Gregory Lizée, Laszlo Radvanyi, and Patrick Hwu

Précis: Blocking immune escape mechanisms mediated by the PD-1 pathway may enhance a variety of cancer therapies, including adoptive T-cell treatments that have shown promise over the years but induce durable responses in a minority of patients.

5219 **TNF- α Mediates Macrophage-Induced Bystander Effects through Netrin-1**

Yonghong Yang, Xingmin Wang, Danny R. Moore, Stanley A. Lightfoot, and Mark M. Huycke

Précis: Commensal intestinal infections that may program inflammation in the colon tumor microenvironment influence a neuronal pathway with emerging importance in cancer.

5230 **A Retinoic Acid—Rich Tumor Microenvironment Provides Clonal Survival Cues for Tumor-Specific CD8⁺ T Cells**

Yanxia Guo, Karina Pino-Lagos, Cory A. Ahonen, Kathy A. Bennett, Jinshan Wang, Joseph L. Napoli, Rune Blomhoff, Shanthini Sockanathan, Roshantha A. Chandraratna, Ethan Dmitrovsky, Mary Jo Turk, and Randolph J. Noelle

Précis: These findings reveal that tumor growth elevates retinoic acid within the tumor microenvironment and that this event is critical to maintain tumor-specific CD8⁺ T-cell clonal survival and to facilitate antitumor immunity, with mechanistic implications for immunoediting.

5240 **Plasmacytoid Dendritic Cells Promote Immunosuppression in Ovarian Cancer via ICOS Costimulation of Foxp3⁺ T-Regulatory Cells**

Curdin Conrad, Josh Gregorio, Yi-Hong Wang, Tomoki Ito, Stephan Meller, Shino Hanabuchi, Sonya Anderson, Neely Atkinson, Pedro T. Ramirez, Yong-Jun Liu, Ralph Freedman, and Michel Gilliet

Précis: Findings identify a signaling pathway controlled by the T-cell coreceptor ICOS as a pivotal driver of immunosuppression in ovarian cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

5250 **53BP1 Is a Haploinsufficient Tumor Suppressor and Protects Cells from Radiation Response in Glioma**

Massimo Squatrito, Fabio Vanoli, Nikolaus Schultz, Maria Jasin, and Eric C. Holland

Précis: These findings suggest that components of the nonhomologous end-joining system of DNA repair may be good therapeutic targets to improve treatment of aggressive brain tumors.

5261 **Clusterin Mediates TGF- β -Induced Epithelial–Mesenchymal Transition and Metastasis via Twist1 in Prostate Cancer Cells**

Masaki Shiota, Anousheh Zardan, Ario Takeuchi, Masafumi Kumano, Eliana Beraldi, Seiji Naito, Amina Zoubeidi, and Martin E. Gleave

Précis: These findings identify a new link between TGF- β and the epithelial–mesenchymal transition that could be targeted to block prostate cancer metastasis.

5273 **Multilevel Whole-Genome Analysis Reveals Candidate Biomarkers in Clear Cell Renal Cell Carcinoma**

Andrew H. Girgis, Vladimir V. Iakovlev, Ben Beheshti, Jane Bayani, Jeremy A. Squire, Anna Bui, Marina Mankaruos, Youssef Youssef, Bishoy Khalil, Heba Khella, Maria Pasic, and George M. Yousef

Précis: In addition to mutation and expression analyses, the analysis of gene methylation and gene-copy number as part of an integrated whole-genome analysis may provide a more comprehensive understanding of cancer heterogeneity to improve diagnosis, prognosis, and therapy.

5285

Hypoxia-Induced Gene Expression in Chemoradioresistant Cervical Cancer Revealed by Dynamic Contrast-Enhanced MRI

Cathinka Halle, Erlend Andersen, Malin Lando, Eva-Katrine Aarnes, Grete Hasvold, Marit Holden, Randi G. Syljuasen, Kolbein Sundfør, Gunnar B. Kristensen, Ruth Holm, Eirik Malinen, and Heidi Lyng

Précis: A noninvasive imaging strategy has been found to identify patients who might benefit from hypoxic modification of chemoradiotherapy in cervical cancers.

5296

Protein Tyrosine Phosphatase Shp2 (Ptpn11) Plays an Important Role in Maintenance of Chromosome Stability

Xia Liu, Hong Zheng, and Cheng-Kui Qu

Précis: These findings reveal how deregulation of an important tyrosine phosphatase that modifies many pathways of cancer cell signaling contributes to malignant development.

5307

Molecular Subsets of Mantle Cell Lymphoma Defined by the IGHV Mutational Status and SOX11 Expression Have Distinct Biologic and Clinical Features

Alba Navarro, Guillem Clot, Cristina Royo, Pedro Jares, Anastasia Hadzidimitriou, Andreas Agathangelidis, Vasilis Bikos, Nikos Darzentas, Theodora Papadaki, Itziar Salaverria, Magda Pinyol, Xavier Puig, Jara Palomero, Maria Carmela Vegliante, Virginia Amador, Alejandra Martinez-Trillos, Lenka Stefancikova, Adrian Wiestner, Wyndham Wilson, Christiane Pott, Maria Jose Calasanz, Nicola Trim, Wendy Erber, Birgitta Sander, German Ott, Andreas Rosenwald, Dolores Colomer, Eva Giné, Reiner Siebert, Armando Lopez-Guillermo, Kostas Stamatopoulos, Silvia Beà, and Elías Campo

Précis: This large multidisciplinary study of mantle cell lymphoma reveals 2 previously unrecognized subtypes that may have distinct origins and clinical implications.

5317

In Vivo Regulation of TGF- β by R-Ras2 Revealed through Loss of the RasGAP Protein NF1

Deanna M. Patmore, Sara Welch, Patricia C. Fulkerson, Jianqiang Wu, Kwangmin Choi, David Eaves, Jennifer J. Kordich, Margaret H. Collins, Timothy P. Cripe, and Nancy Ratner

Précis: Findings that link the functions of TGF- β and R-Ras2/TC21, a little-studied member of the Ras superfamily, might explain why TGF- β suppresses tumors at early stages of development but later acts to promote tumor progression.

PREVENTION AND EPIDEMIOLOGY

5328

Leptin and Soluble Leptin Receptor in Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition Cohort

Krasimira Aleksandrova, Heiner Boeing, Mazda Jenab, H. Bas Bueno-de-Mesquita, Eugene Jansen, Fränzel J. B. van Duijnhoven, Sabina Rinaldi, Veronika Fedirko, Isabelle Romieu, Elio Riboli, Marc J. Gunter, Sabine Westphal, Kim Overvad, Anne Tjønneland, Jytte Halkjær, Antoine Racine, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon, Rudolf Kaaks, Annetkatrin Lukanova, Antonia Trichopoulou, Pagona Lagiou, Dimitrios Trichopoulos, Amalia Mattiello, Valeria Pala, Domenico Palli, Rosario Tumino, Paolo Vineis, Genevieve Buckland, María-José Sánchez, Pilar Amiano, José María Huerta, Aurelio Barricarte, Virginia Menéndez, Petra H. Peeters, Stefan Söderberg, Richard Palmqvist, Naomi E. Allen, Francesca L. Crowe, Kay-Tee Khaw, Nickolas Wareham, and Tobias Pischon

Précis: Elucidation of the etiologic pathways linking obesity and colorectal cancer risk may improve risk assessment and opportunities for lifestyle interventions.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5338

ROCK1 and ROCK2 Are Required for Non-Small Cell Lung Cancer Anchorage-Independent Growth and Invasion

Dominico Vigil, Tai Young Kim, Ana Plachco, Andrew J. Garton, Linda Castaldo, Jonathan A. Pachter, Hanqing Dong, Xin Chen, Brianna Tokar, Sharon L. Campbell, and Channing J. Der

Précis: These findings define a specific small-molecule inhibitor of the Rho kinases and reveal the potential therapeutic benefits of targeting them in a model of lung adenocarcinoma.

5348

Sorafenib Has Potent Antitumor Activity against Multiple Myeloma In Vitro, Ex Vivo, and In Vivo in the 5T33MM Mouse Model

Pedram Kharaziha, Hendrik De Raeve, Charlotte Fristedt, Qiao Li, Astrid Gruber, Per Johnsson, Georgia Kokaraki, Maria Panzar, Edward Laane, Anders Österborg, Boris Zhivotovsky, Helena Jernberg-Wiklund, Dan Grandér, Fredrik Celsing, Magnus Björkholm, Karin Vanderkerken, and Theocharis Panaretakis

Précis: Sorafenib, an approved broad-spectrum kinase inhibitor, might be repositioned to treat multiple myeloma, a highly aggressive cancer.

5363 **Natural Product Triptolide Mediates Cancer Cell Death by Triggering CDK7-Dependent Degradation of RNA Polymerase II**

Stefano Giustino Manzo, Zhao-Li Zhou, Ying-Qing Wang, Jessica Marinello, Jin-Xue He, Yuan-Chao Li, Jian Ding, Giovanni Capranico, and Ze-Hong Miao

Précis: This study offers an explanation for how a key component of traditional Chinese medicine may mediate diverse medical effects, including anticancer effects.

5374 **GF-15, a Novel Inhibitor of Centrosomal Clustering, Suppresses Tumor Cell Growth *In Vitro* and *In Vivo***

Marc S. Raab, Iris Breikreutz, Simon Anderhub, Mads H. Rønneest, Blanka Leber, Thomas O. Larsen, Ludmila Weiz, Gleb Konotop, Patrick J. Hayden, Klaus Podar, Johannes Fruehauf, Felix Nissen, Walter Mier, Uwe Haberkorn, Anthony D. Ho, Hartmut Goldschmidt, Kenneth C. Anderson, Mads H. Clausen, and Alwin Krämer

Précis: This study reports the characterization of a first-in-class inhibitor of centrosomal clustering and its unique mechanistic approach to cancer cell killing.

TUMOR AND STEM CELL BIOLOGY

5386 **Mammalian Sterile 20-like Kinase 1 Suppresses Lymphoma Development by Promoting Faithful Chromosome Segregation**

Tae-Shin Kim, Da-Hye Lee, Sang Kyum Kim, So Youn Shin, Eul-Ju Seo, and Dae-Sik Lim

Précis: The Hippo pathway has been implicated in oncogenesis of solid tumors, but these findings reveal that its core component may exert a tumor-suppressive function in blood cell tumors based on its ability to prevent chromosomal instability in lymphocytes.

5396 **The Unfolded Protein Response Induces the Angiogenic Switch in Human Tumor Cells through the PERK/ATF4 Pathway**

Yugang Wang, Goleeta N. Alam, Yu Ning, Fernanda Visioli, Zhihong Dong, Jacques E. Nör, and Peter J. Polverini

Précis: These results offer new mechanistic insights into the links between angiogenesis and the unfolded protein response, which may be activated nearly universally in cancer cells.

5407 **Inhibition of Stathmin1 Accelerates the Metastatic Process**

Karin Williams, Ritwik Ghosh, Premkumar Vummidi Giridhar, Guangyu Gu, Thomas Case, Scott M. Belcher, and Susan Kasper

Précis: These findings challenge the concept of stathmin as a cancer-promoting protein with evidence that it can restrain the invasive movement of metastatic cancer cells.

5418 **Inactivating All Three Rb Family Pocket Proteins Is Insufficient to Initiate Cervical Cancer**

Myeong-Kyun Shin, Julien Sage, and Paul F. Lambert

Précis: These results provide a powerful argument that the HPV E7 oncoprotein drives cancer by binding to proteins other than the Rb family members, challenging central and long-standing assumptions in the field.

LETTERS TO THE EDITOR

5428 **Melanoma Cells Inhibit NK Cell Functions—Letter**

Giuseppe Sconocchia, Roberto Arriga, Luigi Tornillo, Luigi Terracciano, Soldano Ferrone, and Giulio C. Spagnoli

5430 **Melanoma Cells Inhibit NK Cell Functions—Response**

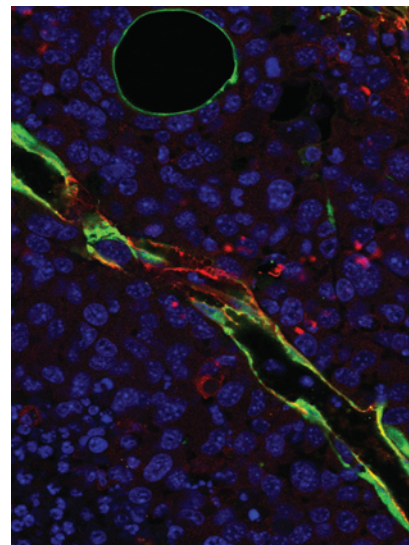
Gabriella Pietra, Massimo Vitale, Claudia Manzini, Mirna Balsamo, Lorenzo Moretta, and Maria Cristina Mingari

CORRECTION

5431 **Correction: Combination Therapy with HSP90 Inhibitor 17-DMAG Reconditions the Tumor Microenvironment to Improve Recruitment of Therapeutic T Cells**

ABOUT THE COVER

Obesity, caused by overgrowth of fat tissue, was shown to be associated with expansion and mobilization of adipose progenitor cells and with increased tumor growth. Animal experiments show that adipose progenitors are recruited by tumors, where they incorporate into the blood vessels and differentiate into adipocytes. A confocal section micrograph of a breast tumor grown in an obese mouse shows vascular/perivascular cells and adipocytes derived from GFP-labeled (green) adipose cells. Vascular endothelium was costained with a CD31 antibody (red), while nuclear staining (blue) identified malignant cells lacking GFP and CD31. For details, see article by Zhang and colleagues on page 5198.



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