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Matej Krajcovic and Michael Overholtzer

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Ribosome Biogenesis and Control of Cell Proliferation: p53 Is Not Alone
Giulio Donati, Lorenzo Montanaro, and Massimo Derenzini

**PRIORITY REPORTS**

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PARP-1 Inhibition as a Targeted Strategy to Treat Ewing's Sarcoma
J. Chad Brenner, Felix Y. Feng, Sumin Han, Sonam Patel, Siddharth V. Goyal, Laura M. Bou-Maroun, Meilan Liu, Robert Lonigro, John R. Prensner, Scott A. Tomlins, and Arul M. Chinnaiyan

Précis: This study prompts immediate attention to reposition small-molecule inhibitors of the DNA damage response protein PARP-1, a new class of experimental agents currently in trials in the adult oncology clinic, for treatment of a particularly aggressive and deadly class of pediatric sarcomas.

1614

Receptor Tyrosine Kinase Genes Amplified in Glioblastoma Exhibit a Mutual Exclusivity in Variable Proportions Reflective of Individual Tumor Heterogeneity
Suzanne E. Little, Sergey Popov, Alexa Jury, Dorine A. Bax, Lawrence Doey, Safa Al-Sarraj, Juliane M. Jurgensmeier, and Chris Jones

Précis: A major challenge facing the development of molecular cancer therapeutics is the complex heterogeneity of tumors at the cellular level, a factor poorly modeled in preclinical systems currently used in drug development, where molecular variegation in key pathways can limit a targeting principle depending on its proportional involvement in the tumor.

**CLINICAL STUDIES**

1621

Oncolytic Immunotherapy of Advanced Solid Tumors with a CD40L-Expressing Replicating Adenovirus: Assessment of Safety and Immunologic Responses in Patients

Précis: Clinical translation of oncolytic virotherapy has been mainly disappointing, but this study describes a modification that may improve the ability to trigger tumor clearance by defeating immune escape.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

1632

Combinatorial Chemotherapeutic Efficacy in Non-Hodgkin Lymphoma Can Be Predicted by a Signaling Model of CD20 Pharmacodynamics
John M. Harrold, Robert M. Straubinger, and Donald E. Mager

Précis: This study offers a mathematical model that can predict the efficacy of combinatorial chemotherapy regimens, which include the CD20 agonist rituximab, a drug that is being used to treat an increasing number of human cancers.

**MICROENVIRONMENT AND IMMUNOLOGY**

1642

Dissection of T-cell Antigen Specificity in Human Melanoma
Rikke Sick Andersen, Charlotte Albrek Thruve, Niels Junker, Rikke Lyngaa, Marco Donia, Eva Ellebæk, Inge Marie Svane, Ton N. Schumacher, Per thor Straten, and Sine Reker Hadrup

Précis: By defining the antigens recognized by tumor-infiltrating lymphocytes, one might improve their efficacy and, in turn, improve adoptive cell therapy in cancer.
Oncolytic Virus and Anti–4-1BB Combination Therapy Elicits Strong Antitumor Immunity against Established Cancer

**Précis:** The preclinical proof-of-concept offered by this study suggests a strategy to improve the clinical efficacy of oncolytic viruses for cancer immunotherapy by combining them with an immune agonist antibody that may help overcome tumor-mediated immune suppression.

Preclinical Evaluation of TriMix and Antigen mRNA-Based Antitumor Therapy
Sandra Van Lint, Cleo Goyvaerts, Sarah Maenhout, Lode Goethals, Aurélie Disy, Daphné Benteyn, Joeri Pen, Aude Bonehill, Carlo Heirman, Karine Breckpot, and Kris Thielemans

**Précis:** This study presents important progress in the rapid development of simpler kinds of dendritic cell vaccines, the first ever of which was approved for patient treatment in the United States last year.

Intracellular Tumor-Associated Antigens Represent Effective Targets for Passive Immunotherapy
Takuro Noguchi, Takuma Kato, Linan Wang, Yuka Maeda, Hiroshi Shiku, Hiroyoshi Nishikawa

**Précis:** Contrary to a widely held but incorrect belief in the field, intracellular tumor antigens can offer highly effective targets for monoclonal antibody–directed therapy, as shown by this preclinical study.

Reprogramming Tumor-Associated Dendritic Cells In Vivo Using miRNA Mimetics Triggers Protective Immunity against Ovarian Cancer

**Précis:** Findings suggest it may be feasible to modulate microRNA activities in leukocytes in the tumor microenvironment without need of viral vectors or difficult clinical implementations.

Vascular Normalization by Loss of Siah2 Results in Increased Chemotherapeutic Efficacy
Christina S.F. Wong, Jacob Sceney, Colin M. House, Heloise M. Halse, Mira C.P. Liu, Joshy George, Titaina C.U. Potdevin Hunnam, Belinda S. Parker, Izak Han, Ze’ev Ronai, Carleen Cullinane, David D. Bowtell, and Andreas Möller

**Précis:** Findings offer preclinical proof-of-concept that targeting the Siah2 ubiquitin ligase that regulates the hypoxia response factor HIF-1α can relieve hypoxia, normalize tumor vasculature, and improve responses to chemotherapy.

Vanilloid Receptor-1 Regulates Neurogenic Inflammation in Colon and Protects Mice from Colon Cancer
Amaya G. Vinuesa, Rocío Sancho, Carmen García-Limones, Axel Behrens, Peter ten Dijke, Marco A. Calzado, and Eduardo Muñoz

**Précis:** This important study offers compelling genetic support for the intriguing concept that neuronally controlled processes of inflammation may underlie the root inflammatory microenvironment that drives the development and progression of colon cancer, with implications for targeting neuroinflammatory receptors that control these processes as a wholly novel strategy to prevent or treat this major disease.

Cancer Vaccination Drives Nanog-Dependent Evolution of Tumor Cells toward an Immune-Resistant and Stem-like Phenotype
Kyung Hee Noh, Young-Ho Lee, Ju-Hong Jeon, Tae Heung Kang, Chih-Ping Mao, T.-C. Wu, and Tae Woo Kim

**Précis:** An important stem cell transcription factor is found to drive development of tumoral immune resistance after therapeutic vaccinations, suggesting possible strategies to enhance cancer immunotherapy.

RORx Suppresses Breast Tumor Invasion by Inducing SEMA3F Expression
Gaofeng Xiong, Chi Wang, B. Mark Evers, Binhua P. Zhou, and Ren Xu

**Précis:** Findings point to an important role for the Th17 immune transcription factor RORx in preventing the establishment of an immune-suppressive tumor microenvironment in mammary tissue.
Hypoxia-Induced Autophagy Promotes Tumor Cell Survival and Adaptation to Antiangiogenic Treatment in Glioblastoma


**Precise:** This important study has immediate clinical implications because it suggests ways that autophagy inhibitors such as chloroquine might be combined with antiangiogenic therapies to limit a mechanism of resistance and thereby extend efficacy.

MiR-155 Is a Liposarcoma Oncogene That Targets Casein Kinase-1c and Enhances β-Catenin Signaling

Pingyu Zhang, Katellyn Bill, Juehui Liu, Eric Young, Tingsheng Peng, Svetlana Boldshakov, Avid Hoffman, Yechun Song, Elizabeth G. Demicco, Dolores Lopez Terrada, Chad J. Creighton, Matthew L. Anderson, Alexander J. Lazar, George G. Calin, Raphael E. Pollock, and Dina Lev

**Precise:** Findings reveal key functions for miR-155 and β-catenin signaling in progression of liposarcoma, with implications for prognosis and therapy of dedifferentiated dead forms of this disease.

miRNA-130a Targets ATG2B and Dicer1 to Inhibit Autophagy and Trigger Killing of Chronic Lymphocytic Leukemia Cells


**Precise:** Findings suggest a feedback loop involving a microRNA that controls expression of a master microRNA regulatory gene with an impact on the autophagic susceptibility of cancer cells, thereby affecting treatment efficacy and posttreatment relapse.

Tumor Cell–Derived Angiopoietin-like Protein ANGPTL2 Is a Critical Driver of Metastasis


**Precise:** Findings have implications for a broad-based antibody-mediated strategy to blunt metastasis in various human cancers where an angiogenesis-related factor is implicated in this process.

19p13.1 Is a Triple-Negative–Specific Breast Cancer Susceptibility Locus


**Precise:** This important study has immediate functional and clinical implications for this process.
Enhanced Apoptosis and Tumor Growth Suppression Elicited by Combination of MEK (Selumetinib) and mTOR Kinase Inhibitors (AZD8055)
Sarah V. Holt, Armelle Logie, Barry R. Davies, Denis Alferes, Sarah Runswick, Sarah Fenton, Christine M. Chresta, Yi Gu, Jingchuan Zhang, Yi-Long Wu, Robert W. Wilkinson, Sylvie M. Guichard, and Paul D. Smith

Paclitaxel Enhances Therapeutic Efficacy of the F8-IL2 Immunocytokine to EDA-Fibronectin—Positive Metastatic Human Melanoma Xenografts
Michele Moschetta, Francesca Pretto, Alexander Berndt, Kerstin Galler, Petra Richter, Andrea Bassi, Paolo Oliva, Edoardo Micotti, Giovanni Vallabusa, Kathrin Schwager, Manuela Kaspar, Eveline Trachsel, Hartwig Kosmehl, Maria Rosa Bani, Dario Neri, and Raffaella Gavazzi

Retinoic Acid/Alpha-Interferon Combination Inhibits Growth and Promotes Apoptosis in Mantle Cell Lymphoma through Akt-Dependent Modulation of Critical Targets
Jessica Dal Col, Katy Mastorci, Damiana Antonia Faè, Elena Muraro, Debora Martorelli, Giorgio Inghirami, and Riccardo Dolcetti

Précis: A clinical drug combination explored for treatment of numerous types of cancer may be especially suited to treatment of a deadly type of non-Hodgkin lymphoma that remains particularly difficult to treat.

Rapamycin Resistance Is Linked to Defective Regulation of Skp2
Hana Totary-Jain, Despina Sanoudou, Cula N. Dautriche, Hillary Schneller, Lester Zambrana, and Andrew R. Marks

Précis: This study defines a candidate drug response marker for mTOR inhibitors, an important class of experimental therapeutics of growing interest for the generalized treatment of human cancer, with immediate implications for clinical evaluation in mTOR inhibitor trials.

A Universal Strategy for Adoptive Immunotherapy of Cancer through Use of a Novel T-cell Antigen Receptor
Katarzyna Urbanska, Evripidis Lantitis, Mathilde Poussin, Rachel C. Lynn, Brian P. Gavin, Sander Kelderman, Jason Yu, Nathalie Scholler, and Daniel J. Powell Jr

Précis: This study suggests a universal immune receptor strategy to tailor and vastly expand the number of tumor antigens recognized by engineered T cells for adoptive immunotherapy, perhaps greatly enhancing the general use of this technology for cancer treatment.
miRNA Signatures Associate with Pathogenesis and Progression of Osteosarcoma
Kevin B. Jones, Zaidoun Salah, Sara Del Mare, Marco Galasso, Eugenio Gaudio, Gerard J. Nuovo, Francesca Lovat, Kimberly LeBlanc, Jeff Palatini, R. Lor Randall, Stefano Volinia, Gary S. Stein, Carlo M. Croce, Jane B. Lian, and Rami I. Aqeilan
Précis: Osteosarcoma is a leading cause of death in adolescents yet remains mainly devoid of development of sounder tools to improve prognosis or therapy.

Pten Loss and RAS/MAPK Activation Cooperate to Promote EMT and Metastasis Initiated from Prostate Cancer Stem/Progenitor Cells
David J. Mulholland, Naoko Kobayashi, Marcus Ruscetti, Allen Zhi, Linh M. Tran, Jiaoti Huang, Martin Gleave, and Hong Wu
Précis: Development of a prostate cancer model that addresses the major metastatic burden accompanying late-stage human disease addresses a gap in the field that may permit the development of more effective targeted treatment strategies.

Jab1/CSN5 Negatively Regulates p27 and Plays a Role in the Pathogenesis of Nasopharyngeal Carcinoma
Yunbao Pan, Qingshu Zhang, Ling Tian, Xin Wang, Xiaohang Fan, Huizhong Zhang, Francois X. Clare, and Huling Yang
Précis: Definition of a cell-cycle regulatory role for a component of the signalosome, a protein turnover complex analogous to the proteosome but less understood, suggests new strategies to treat an aggressive cancer endemic in East Asia.

LETTERS TO THE EDITOR

Lactate-Induced IL-8 Pathway in Endothelial Cells—Letter
Céline Pinheiro, Adhemar Longatto-Filho, Rosete Nogueira, Fernando Schmitt, and Fátima Baltazar

Lactate-Induced IL-8 Pathway in Endothelial Cells—Response
Frédérique Végran, Emmanuel Seront, Pierre Sonveaux, and Olivier Feron

CORRECTION
Correction: Significance of MAD2 Expression to Mitotic Checkpoint Control in Ovarian Cancer Cells

ABOUT THE COVER
Tumor metastasis represents a major cause of cancer mortality. Despite intense effort, strategies designed to inhibit metastasis have been unsuccessful, in part due to lack of understanding of mechanisms underlying the process. In this study, a shortened period of disease-free survival was observed after surgery in lung cancer patients showing high angiopoietin-like protein 2 (ANGPTL2) expression in tumor cells within primary tumor sites. Furthermore, tumor cell–derived ANGPTL2 increased tumor cell motility and invasive capacity in an autocrine/paracrine manner, resulting in acquisition of metastatic tumor phenotypes. In tumor cell–implanted mouse models, tumor cell–derived ANGPTL2 accelerated metastasis and shortened survival periods; conversely, decreasing ANGPTL2 expression in tumor cells significantly attenuated metastasis and extended survival periods. This image represents CD44-stained human breast tumor cells expressing ANGPTL2 in lung metastasis in mice. For details, see the article by Endo and colleagues on page 1784 of this issue.