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Rikke Sick Andersen, Charlotte Albeak Thrue, Niels Junker, Rikke Lyngaa, Marco Doria, Eva Ellebæk, Inge Marie Svane, Ton N. Schumacher, Per Thor Straten, and Sine Reker Hadrup

**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.

**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.

**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.

**Précis:** By defining the antigens recognized by tumor-infiltrating lymphocytes, one might improve their efficacy and, in turn, improve adoptive cell therapy in cancer.
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<td>Preclinical Evaluation of TriMix and Antigen mRNA-Based Antitumor Therapy</td>
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<td>Precis: 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.</td>
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<td>1672</td>
<td>Intracellular Tumor-Associated Antigens Represent Effective Targets for Passive Immunotherapy</td>
<td>Takuro Noguchi, Takuma Kato, Linan Wang, Yuka Maeda, Hiroaki Ikeda, Eiichi Sato, Alexander Knuth, Sacha Gnjatic, Gerd Ritter, Shimon Sakaguchi, Lloyd J. Old, Hiroshi Shiku, and Hiroyoshi Nishikawa</td>
<td>Precis: 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.</td>
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<td>Vascular Normalization by Loss of Siah2 Results in Increased Chemotherapeutic Efficacy</td>
<td>Christina S.F. Wong, Jaclyn Sceneay, Colin M. House, Heloise M. Halse, Mira C.P. Liu, Joshy George, Tatiana C.U. Potdevin Hunnam, Belinda S. Parker, Izak Haviv, Ze’ev Ronai, Carleen Cullinan, David D. Bowtell, and Andreas Möller</td>
<td>Precis: 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.</td>
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<td>Vanilloid Receptor-1 Regulates Neurogenic Inflammation in Colon and Protects Mice from Colon Cancer</td>
<td>Amaya G. Vinuesa, Rocío Sancho, Carmen García-Limones, Axel Behrens, Peter ten Dijke, Marco A. Calzado, and Eduardo Muñoz</td>
<td>Precis: 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.</td>
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<td>1715</td>
<td>Cancer Vaccination Drives Nanog-Dependent Evolution of Tumor Cells toward an Immune-Resistant and Stem-like Phenotype</td>
<td>Kyung Hee Noh, Young-Ho Lee, Ju-Hong Jeon, Tae Heung Kang, Chih-Ping Mao, T.-C. Wu, and Tae Woo Kim</td>
<td>Precis: 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.</td>
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<td>RORα Suppresses Breast Tumor Invasion by Inducing SEMA3F Expression</td>
<td>Gaofeng Xiong, Chi Wang, B. Mark Evers, Binhua P. Zhou, and Ren Xu</td>
<td>Precis: Findings point to an important role for the Th17 immune transcription factor RORα in preventing the establishment of an immune-suppressive tumor microenvironment in mammary tissue.</td>
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MOLECULAR AND CELLULAR PATHOBIOLOGY

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Dmp1 Physically Interacts with p53 and Positively Regulates p53’s Stability, Nuclear Localization, and Function
Donna P. Frazier, Robert D. Kendig, Fumitake Kai, Dejan Maglic, Takayuki Sugiyama, Rachel L. Morgan, Elizabeth A. Fry, Sarah J. Lagedrost, Guangchao Sui, and Kazushi Inoue

Précis: The results of this study show a novel mechanism for p53 activation through direct physical interaction between Dmp1 and p53, which plays critical roles in antagonizing Mdm2-p53 interaction.

1751

MiR-155 Is a Liposarcoma Oncogene That Targets Casein Kinase-1z and Enhances β-Catenin Signaling
Pingyu Zhang, Katelynn Bill, Juehui Liu, Eric Young, Tingsheng Peng, Svetlana Boldshakov, Aviad 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

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

1763

miRNA-130a Targets ATG2B and DICER1 to Inhibit Autophagy and Trigger Killing of Chronic Lymphocytic Leukemia Cells
Valentina Kovaeva, Rodrigo Mora, Yoon Jung Park, Christoph Plass, Abhishash I. Chiramel, Ralf Bartschelager, Hartmut Döhner, Stephan Stülbengauer, Armin Pscherer, Peter Lichter, and Martina Seiffert

Précis: 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.

1773

Hypoxia-Induced Autophagy Promotes Tumor Cell Survival and Adaptation to Antiangiogenic Treatment in Glioblastoma

Précis: 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.

1795

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

Précis: 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
Enhanced Apoptosis and Tumor Growth Suppression Elicited by Combination of MEK (Selumetinib) and mTOR Kinase Inhibitors (AZD8055)
Précis: Findings offer a preclinical proof-of-concept for combining MAPK and mTOR kinase inhibitors in clinical trials to achieve robust tumor growth inhibition while limiting risks of chemoresistance.

Paclitaxel Enhances Therapeutic Efficacy of the F8-IL2 Immunoctokine 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 Valbusa, Kathrin Schwager, Manuela Kaspar, Eveline Trachsel, Hartwig Kosmehl, Maria Rosa Bani, Dario Neri, and Raffaella Giavazzi
Précis: Findings offer a preclinical proof-of-concept for an effective application of IL-2–based immunochemotherapy for melanoma that is targeted to fibronectin, an extracellular matrix protein expressed by many melanomas.

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 Mortorelli, 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. Dautuche, 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.

Cancer Stem Cell Vaccination Confers Significant Antitumor Immunity
Ning Ning, Qin Pan, Fang Zheng, Seagal Teitz-Tennenbaum, Martin Egenti, Ji Yet, Mu Li, Christophe Genestier, Max S. Wicha, Jeffrey S. Moyer, Mark E.P. Prince, Yingxin Xu, Xiao-Lian Zhang, Shiang Huang, Alfred E. Chang, and Qiao Li
Précis: Vaccines that use purified cancer stem cells are highly immunogenic and trigger antitumor immunity with greater potency than that triggered by vaccines composed of unselected tumor cells.
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. Claret, and Huiling 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

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.