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      Giulio Donati, Lorenzo Montanaro, and Massimo Derenzini

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      John M. Harrold, Robert M. Straubinger, and Donald E. Mager

MICROENVIRONMENT AND IMMUNOLOGY
1642  Dissection of T-cell Antigen Specificity in Human Melanoma
      Rikke Sick Andersen, Charlotte Albek Thrus, Niels Junker, Rikke Lyngaa, Marco Donia, Eva Elkebak, Inge Marie Svane, Ton N. Schumacher, Per thor Straten, and Sine Reker Hadrup

Precis: 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 variation in key pathways can limit a targeting principle depending on its proportional involvement in the tumor.
**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**

**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, Jaclyn Sceneay, Colin M. House, Heloise M. Halse, Mira C.P. Liu, Joshy George, Titaina C.U. Potdevin Hunnam, Belinda S. Parker, Izak Haviv, Z'e'ev Ronai, Carleen Cullinane, David D. Bortell, 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.

**RORα 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 RORα in preventing the establishment of an immune-suppressive tumor microenvironment in mammary tissue.
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<td>MiR-155 Is a Liposarcoma Oncogene That Targets Casein Kinase-1 and Enhances β-Catenin Signaling</td>
<td>Pingyu Zhang, Katellyn Bill, Juehui Liu, Eric Young, Tingsheng Peng, Svetlana Boldshakov, Avidai Hoffan, 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</td>
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**MOLECULAR AND CELLULAR PATHOBIOLOGY**

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


**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.

**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.

**Précis:** Findings suggest a feedback loop involving miR-155 and β-catenin signaling with implications for prognosis and therapy of dedifferentiated deadly forms of this disease.

**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.

**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.
### CHEMICAL BIOLOGY

**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 Alferez, Sarah Runswick, Sarah Fenton, Christine M. Chresta, Yi Gu, Jingchuan Zhang, Yi-Long Wu, Robert W. Wilkinson, Sylvie M. Guichard, and Paul D. Smith

*Precis: Findings establish a significant association between genomic variants at 19p13.1 and triple-negative breast cancer, providing convincing evidence that there is a genetic susceptibility to different breast tumor subtypes and that they arise through distinct etiologic pathways.*

**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, Edosardo Micotti, Giovanni Valbusa, Kathrin Schwager, Manuela Kaspar, Eveline Trachsel, Hartwig Kosmehl, Maria Rosa Bani, Dario Neri, and Raffaella Giavazzi

*Precis: Findings offer a preclinical proof-of-concept for an effective application of IL-2-based immunocytokine therapy for melanomas that is targeted to fibronectin, an extracellular matrix protein expressed by many melanomas.*

### TUMOR AND STEM CELL BIOLOGY

**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, Daniana Antonia Fae, Elena Muraro, Debora Martorelli, Giorgio Inghiram, and Riccardo Dolcetti

*Precis: 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. Daurtiche, Hillary Schneller, Lester Zambrana, and Andrew R. Marks

*Precis: 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

*Precis: 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.*

**Cancer Stem Cell Vaccination Confers Significant Antitumor Immunity**

Ning Ning, Qin Pan, Fang Zheng, Seagal Teitz-Tennenbaum, Martin Egenti, Ji Yet, Mu Li, Christophe Ginestier, Max S. Wicha, Jeffrey S. Moyer, Mark E.P. Prince, Yingxin Xu, Xiao-Lian Zhang, Shiang Huang, Alfred E. Chang, and Qiao Li

*Precis: 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, Qingxiu 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 Fatima 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.