Tumor-Specific Cytotoxic T Cells Are Crucial for Efficacy of Immunomodulatory Antibodies in Patients with Lung Cancer

Joachim G. Aerts and Joost P. Hegmans

Understanding Phenotypic Variation in Rodent Models with Germline $Apc$ Mutations

Maged Zeineldin and Kristi L. Neufeld

**PERSPECTIVES**

2400  Siah: A Promising Anticancer Target  
Christina S.F. Wong and Andreas Müller

2407  The Model Muddle: In Search of Tumor Growth Laws  
Philip Gerlee

**MEETING REPORT**

2412  Challenges and Key Considerations of the Enhanced Permeability and Retention Effect for Nanomedicine Drug Delivery in Oncology  
Uma Prabhakar, Hiroshi Maeda, Rakesh K. Jain, Eva M. Sevick-Muraca, William Zamboni, Omid C. Farokhzad, Simon T. Barry, Alberto Gabizon, Piotr Grodzinski, and David C. Blakey

**PRIORITY REPORTS**

2418  Epithelial-to-Mesenchymal Transition and Autophagy Induction in Breast Carcinoma Promote Escape from T-cell–Mediated Lysis  
Intissar Akalay, Bassam Janji, Meriem Hasmim, Muhammad Zaeem Noman, Fabrice André, Patricia De Cremoux, Philippe Bertheau, Cécile Badoual, Philippe Vielh, Annette K. Larsen, Michèle Sabbah, Tuan Zea Tan, Joan Harr Keira, Nicole Tsang Ying Hung, Jean Paul Thiery, Fathia Mami-Chouaib, and Salem Chouaib

**PRÉCIS:** This seminal study shows how the acquisition of EMT and autophagy in cancers promotes their ability to escape T-cell immunity, revealing new mechanistic perspectives on how immune escape and metastatic progression are linked.

2428  EGFR-TKI Resistance Due to $BIM$ Polymorphism Can Be Circumvented in Combination with HDAC Inhibition  
Takayuki Nakagawa, Shini Takeuchi, Tadakki Yamada, Hiromichi Ebi, Takako Sano, Shigeki Nanjo, Daisuke Ishikawa, Mitsuo Sat0, Yoshinori Hasegawa, Yoshitaka Sekido, and Seiji Yano

**PRÉCIS:** This study unravels the mechanistic basis for EGFR inhibitor resistance in patients who harbor a common BIM polymorphism that prevents BIM induction needed for a robust drug response and shows how to restore sensitivity by epigenetic reprogramming with an HDAC inhibitor.

2435  Higher Frequencies of GARP$^+$ CTLA-4$^+$ Foxp3$^+$ T Regulatory Cells and Myeloid-Derived Suppressor Cells in Hepatocellular Carcinoma Patients Are Associated with Impaired T-Cell Functionality  
Suresh Kalathil, Amit A. Lugade, Austin Miller, Renuka Iyer, and Yasmin Thanavala

**PRÉCIS:** This is one of the first studies to confirm the expectation that multiple immunosuppressive phenotypes are present in patients with advanced cancer, with results that also greatly encourage testing of combinatorial approaches to degrade these phenotypes in this most challenging population as a rational strategy of immunotherapy.

2445  Automated Tracking of Nanoparticle-labeled Melanoma Cells Improves the Predictive Power of a Brain Metastasis Model  
Terje Sundstrøm, Inderjit Daphu, Ingvild Wendelbo, Erland Hadneland, Arvid Lundervold, Heike Immervoll, Kai Ove Skaftnesmo, Michal Babic, Pavla Jendelova, Eva Sykova, Morten Lund-Johansen, Rolf Bjerkvig, and Frits Thorsen

**PRÉCIS:** This study describes a model that can improve upon the predictive elements derived from preclinical studies of brain metastasis, perhaps ultimately helping reduce the number of clinical trials that fail to show patient benefit.
Selective Blockade of Matrix Metalloprotease-14 with a Monoclonal Antibody Abrogates Invasion, Angiogenesis, and Tumor Growth in Ovarian Cancer
Rajani Kaimal, Raid Aljumaily, Sarah L. Tressel, Rutika V. Pradhan, Lidija Covic, Athan Kuliopulos, Corrine Zarwan, Young B. Kim, Sheida Sharifi, and Anika Agarwal
Précis: Targeting MMP-14 with a monoclonal antibody may be important for antiangiogenic therapy not only in ovarian cancer but also in other solid tumors.

Interleukin 21–Induced Granzyme B–Expressing B Cells Infiltrate Tumors and Regulate T Cells
Stefanie Lindner, Karen Dahlke, Kai Sontheimer, Magdalena Hagn, Christof Kaltenmeier, Thomas F. Barth, Thamara Barth, Frank Reister, Dorit Fabricius, Ramin Lotfi, Oleg Lanov, G. Ulrich Nienhaus, Thomas Simmet, Rolf Kreienberg, and Bernd Jahrsdorfer
Précis: This potentially seminal study establishes the existence and control of human B regulatory cells in the tumor microenvironment, which under the control of IL-21 may contribute significantly to Treg-dependent mechanisms of local immune escape.

Chemotherapy Alters Monocyte Differentiation to Favor Generation of Cancer-Supporting M2 Macrophages in the Tumor Microenvironment
Précis: Chemotherapy-induced activation of the NFκB pathway reinforces immune suppression in tumor microenvironments where prostanglandins E2 and IL-6 are being produced, suggesting combination strategies with inhibitors of COX-2 or IL-6 signaling to improve chemotherapeutic efficacy.

Chemotherapy Acts as an Adjuvant to Convert the Tumor Microenvironment into a Highly Permissive State for Vaccination-Induced Antitumor Immunity
Tae Heung Kang, Chih-Jen Wang, Crystal D. Lin, Yi-Hsin Tseng, Chung-Ying Tsai, Sheng-Ming Wu, Sheng-Yi Chen, Hsiang-Cheng Chi, Chen-Hsin Liao, Chia-Jung Liao, and Kwang-Huei Lin
Précis: This study identifies Src as the critical oncogenic driver and potential druggable target of juvenile myelomonocytic leukemia, an aggressive myeloid malignancy without an effective cure.

Thyroid Hormone Regulation of miR-21 Enhances Migration and Invasion of Hepatoma
Précis: Mechanistic findings reveal how the thyroid hormone can drive the growth and invasion of liver cancer cells by directly regulating an oncogenic microRNA that mediates the hormone’s procarcinogenic effects.

SRC Signaling Is Crucial in the Growth of Synovial Sarcoma Cells
Sebastian Michels, Marcel Trautmann, Elisabeth Sievers, Dagmar Kindler, Sebastian Huss, Marcus Renner, Nicolaus Friedrichs, Jutta Kirfel, Susanne Steiner, Elnara Endl, Peter Wurst, Lukas Heukamp, Roland Penzel, Olle Larsson, Akira Kawai, Shinya Tanaka, Hiroshi Sonobe, Peter Schirmacher, Gunhild Mechtshersheimer, Eva Wardelmann, Reinhard Bütter, and Wolfgang Hartmann
Précis: SRC activation is a critical signaling component of synovial sarcomas and represents a promising therapeutic target in this disease setting.

PARI Overexpression Promotes Genomic Instability and Pancreatic Tumorigenesis
Kevin W. O’Connor, Donniphat Dejsuphong, Eummi Park, Claudia M. Nicolae, Alec C. Kimmelman, Alan D. D’Andrea, and George-Lucian Moldovan
Précis: This study offers preclinical proof-of-concept for a novel element in the homologous recombination pathway of DNA repair widely elevated in pancreatic cancer as a candidate therapeutic target to treat this deadly disease.

Inhibition of SRC Corrects GM-CSF Hypersensitivity That Underlies Juvenile Myelomonocytic Leukemia
Severa Bunda, Michelle W. Kang, Stephanie S. Sybingco, Julie Weng, Helene Favre, Danielle H. Shin, Meredith S. Irwin, Mignon L. Loh, and Michael Ohl
Précis: This study identifies Src as the critical oncogenic driver and potential druggable target of juvenile myelomonocytic leukemia, an aggressive myeloid malignancy without an effective cure.
Endocrine Fibroblast Growth Factor FGF19 Promotes Prostate Cancer Progression
Shu Feng, Olga Dakhova, Chad J. Creighton, and Michael Ittmann

Précis: Expression of an endocrine FGF in prostate cancers is found to promote tumor progression, suggesting it may offer a novel therapeutic target.

CYP24A1 and CYP27B1 Polymorphisms Modulate Vitamin D Metabolism in Colon Cancer Cells
Elizabeth T. Jacobs, Chad Van Pelt, Ryan E. Forster, Wasiq Zaidi, Elizabeth A. Hibler, Michael A. Galligan, Mark R. Haussler, and Peter W. Jurutka

Précis: These results illustrate how naturally occurring genetic variations in vitamin D metabolic pathways may influence the risk of colon cancer.

Characterization of Torin2, an ATP-Competitive Inhibitor of mTOR, ATM, and ATR
Qingsong Liu, Chunxiao Xu, Swapriya Kirubakaran, Xin Zhang, Wooyoung Hur, Yan Liu, Nicholas P. Kwiatkowski, Jinhua Wang, Kenneth D. Westover, Wasiq Zaidi, Elizabeth A. Hibler, Michael A. Galligan, Mark R. Haussler, and Peter W. Jurutka

Précis: An mTOR inhibitor with superior pharmacologic properties in vivo is found to inhibit PI3K family kinases involved in DNA damage signaling and to cooperate strongly with MEK kinase inhibition in killing mouse and human cancer cells.

MDM2 Small-Molecule Antagonist RG7112 Activates p53 Signaling and Regresses Human Tumors in Preclinical Cancer Models

Précis: The first p53 activator to reach clinical trials is shown in preclinical testing to shrink human tumors, offering a proof-of-concept for eradication of tumors with wild-type forms of this tumor suppressor.

Ex Vivo Expansion of Highly Cytotoxic Human NK Cells by Cocultivation with Irradiated Tumor Cells for Adoptive Immunotherapy
Seon Ah Lim, Tae-Jin Kim, Jung Eun Lee, Chung Hee Sonn, Kwanghee Kim, Jiyoung Kim, Jong Gwon Choi, Il-Kyu Choi, Chae-Ok Yun, Jae-Hong Kim, Cassian Yee, Vinay Kumar, and Kyung-Mi Lee

Précis: This article shows how to activate and expand human NK cells, providing the basis for a straightforward strategy to expand a highly cytotoxic effector cell population that may help treat advanced cancers refractory to conventional therapy.

Ex Vivo Activation of CD56+ Immune Cells That Eradicate Neuroblastoma
Piya Rujkijyanont, Wing Keung Chan, Paul W. Eldridge, Timothy Lockey, Martha Holladay, Barbara Rooney, Andrew M. Davidoff, Wing Keung, and Queenie Yong

Précis: These results show a clinically expedient strategy to generate activated NK cells that are highly cytotoxic to neuroblastoma with minimal risk of GvHD.

scFv-Based "Grababody'' as a General Strategy to Improve Recruitment of Immune Effector Cells to Antibody-Targeted Tumors
Zheng Cai, Ting Fu, Yasuhiro Nagai, Lian Lam, Marla Yee, Zhiqiang Zhu, and Hongtao Zhang

Précis: A novel recombinant molecule combining the specificity of an antibody variable chain with the IgG binding domain facilitates the ability to enable tumor specific killing by endogenous immune effector cells.

AMPK Activation by Oncogenesis Is Required to Maintain Cancer Cell Proliferation in Astrocytic Tumors
Marcos Rios, Marc Foretz, Benoit Viollet, Angel Prieto, Maximo Fraga, Jose A. Costoya, and Rosa Señarís

Précis: Whether AMPK is essential or not for cancer cell proliferation has been somewhat controversial, but this preclinical study offers a clear rationale for its further exploration as a therapeutic target in brain cancers.
### Rhythmic Control of the ARF-MDM2 Pathway by ATF4 Underlies Circadian Accumulation of p53 in Malignant Cells

Michiko Horiguchi, Satoru Koyanagi, Ahmed M. Hamdan, Keisuke Kakimoto, Naoya Matsunaga, Chikamasa Yamashita, and Shigehiro Ohdo

**Précis:** Circadian rhythms that determine the accumulation of p53 in malignant cells can result, with potential implications for increasing therapeutic efficacy by optimizing the time of drug administration in patients.

### Menin Epigenetically Represses Hedgehog Signaling in MEN1 Tumor Syndrome

Buddha Gurung, Zijie Feng, Daniel V. Iwamoto, Austin Thiel, Guanghui Jin, Chen-Min Fan, Jessica M.Y. Ng, Tom Curran, and Xianxin Hua

**Précis:** Mechanistic results suggest a way to treat parathyroid, pituitary, pancreatic, and other tumors that characterize the MEN1 syndrome, offering a unified treatment approach.

### Hepatocyte Growth Factor Activator Inhibitor Type 1 Is a Suppressor of Intestinal Tumorigenesis

Shinri Hoshiko, Makiko Kawaguchi, Tsunoshii Fukushima, Yukihiro Haruyama, Kenji Yorita, Hiroyuki Tanaka, Motoharu Seiki, Haruhiko Inatsu, Kazuo Kitamura, and Hiroaki Kataoka

**Précis:** A membrane-associated tumor suppressor in the intestinal tract is defined that may stimulate novel therapeutic approaches to prevent progression of benign colon tumors.

### Inherited Variation in miR-290 Expression Suppresses Breast Cancer Progression by Targeting the Metastasis Susceptibility Gene Arid4b

Natalie Goldberger, Renard C. Walker, Chang Hee Kim, Scott Winter, and Kent W. Hunter

**Précis:** This is the first study to show that inherited differences in microRNA expression can modify susceptibility to metastatic progression in breast cancer.

### CD44-Positive Cancer Stem Cells Expressing Cellular Prion Protein Contribute to Metastatic Capacity in Colorectal Cancer

Lei Du, Guanhua Rao, Hongyi Wang, Baowei Li, Weili Tian, Jiantao Cui, Leya He, Brian Laffin, Xiuyan Tian, Chunyi Hao, Hongmin Liu, Xin Sun, Yushan Zhu, Dean G. Tang, Maryam Mehrpour, Youyong Lu, and Quan Chen

**Précis:** Prions may be functional markers of a highly metastatic subpopulation of cancer stem cells in colorectal cancer, where they might be targeted to treat metastatic disease.

### Regulation of Lung Cancer Metastasis by Klf4-Numb–like Signaling

Valentina Vaira, Alice Faversani, Nina M. Martin, David S. Garlick, Stefano Ferrero, Mario Nosotti, Joseph L. Kissil, Silvano Bosari, and Dario C. Altieri

**Précis:** These findings uncover a novel signaling network centered on the polarity protein Numb-like, which dually promotes abnormal cell motility needed for metastasis along with the persistence of cancer-initiating, stem-like cells that reduce overall survival in lung cancer.

### ABOUT THE COVER

Cancer stem cells are implicated in tumor metastasis although the exact mechanisms remain poorly understood. The expression of cellular prion protein (PrPc), a highly conserved glycoprotein that has the same protein sequence as the scrapie prion protein, is positively correlated with an increased risk of metastasis in colorectal cancer. By double immunofluorescence staining of CD44 (green) and PrPc (red), CD44⁺PrPc⁺ cells were detected in the cryosections of colorectal cancers. PrPc⁺CD44⁺ colorectal cancer stem cells displayed high liver metastatic capability. For details, see article by Du and colleagues on page 2682.