Highlights from Recent Cancer Literature

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

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

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

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

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

EGFR-TKI Resistance Due to BIM Polymorphism Can Be Circumvented in Combination with HDAC Inhibition
Takayuki Nakagawa, Shinni Takeuchi, Tadaaki Yamada, Hiromichi Ebi, Takako Sano, Shigeki Nanjo, Daisuke Ishikawa, Mitsuho Satoh, Yoshimori Hasegawa, Yoshitaka Sekido, and Seiji Yano

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.

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

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.

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

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, Lijija Covic, Athan Kuliopulos, Corrine Zarwan, Young B. Kim, Sheida Sharifi, and Anika Agarwal

Precis: 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.E. Barth, Thamara Beyrer, Frank Reister, Dorit Fabricius, Ramin Lotfi, Oleg Lanov, G. Ulrich Nienhaus, Thomas Simmet, Rolf Kreienberg, Peter Mohr, Hubert Schrenzeimer, and Bernd Jahrsdoerfer

Precis: 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


Precis: Chemotherapy-induced activation of the NFκB pathway reinforces immune suppression in tumor microenvironments where prostanglandin 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-Yen Lin, Yu-Ting Hung, Chih-Jen Wang, Crystal D. Lin, and Kwang-Huei Lin

Precis: Immunotherapy that simply combines cytotoxic chemotherapy with local vaccination with tumor antigens should be explored carefully, given its potential to markedly improve outcomes.

Thyroid Hormone Regulation of miR-21 Enhances Migration and Invasion of Hepatoma


Precis: Mechanistic findings reveal how the thyroid hormone can drive the growth and invasion of liver cancer cells by directly regulating an oncogetic 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, Nikolaus Friedrichs, Jutta Kirfel, Susanne Steiner, Elnara Endil, Peter Wurst, Lukas Heukamp, Roland Penzel, Olle Larsson, Akira Kawai, Shinya Tanaka, Hiroshi Sonobe, Peter Schirmacher, Gunhild Mechtler, Eva Wardelmann, Reinhard Böttner, and Wolfgang Hartmann

Precis: SRC activation is a critical signaling component of synovial sarcomas and represents a promising therapeutic target in this disease setting.

PAR1 Overexpression Promotes Genomic Instability and Pancreatic Tumorigenesis

Kevin W. O’Connor, Donniphab Dejsuphong, Emni Park, Claudia M. Nicolae, Alec C. Kimmelman, Alan D. D’Andrea, and George-Lucian Moldovan

Precis: 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. Sybingsco, Julie Weng, Helene Favre, Danielle H. Shin, Meredith S. Irwin, Mignon L. Loh, and Michael Ohl

Precis: 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.
### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**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**


*Précis:* An mTOR inhibitor with superior pharmacologic properties in vivo is found to inhibit PIKK 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 Leung, 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, Benoît Viollet, Angélique Vial, 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, Tsunoshichi Fukushima, Yukhiro 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, Jintao Cui, Leya He, Brian Laffin, Xiuyun 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⁻ colorectal cancer stem cells were detected in the cryosections of colorectal cancers. CD44⁻PrPc⁻ colorectal cancer stem cells displayed high liver metastatic capability. For details, see article by Du and colleagues on page 2682.