### VEGF and c-Met Blockade Amplify Angiogenesis Inhibition in Pancreatic Islet Cancer

Weon-Kyoo You, Barbara Sennino, Casey W. Williamson, Beverly Falcon, Hiroya Hashizume, Li-Chin Yao, Dana T. Aftab, and Donald M. McDonald

**Précis:** Cancer cell-targeted therapeutic agents may achieve efficacy in part by also attacking the tumor microenvironment, as illustrated by this study revealing the antiangiogenesis benefits of MET inhibitors in promoting blood vessel regression, in addition to direct effects against tumor cells themselves.

### Podoplanin-Positive Fibroblasts Enhance Lung Adenocarcinoma Tumor Formation: Podoplanin in Fibroblast Functions for Tumor Progression

Ayuko Hoshino, Genichiro Ishii, Takashi Ito, Kazuhiro Aoyagi, Yoichi Ohtaki, Kanji Nagai, Hiroki Sasaki, and Atsushi Ochiai

**Précis:** Findings define a fibroblast cell type in the perivascular tumor microenvironment that creates a specific niche for tumor progression, suggesting new strategies to block tumor invasion and metastasis.

### IL-7 Contributes to the Progression of Human T-cell Acute Lymphoblastic Leukemias

Ana Silva, Angelo B.A. Laranjeira, Leila R. Martins, Bruno A. Cardoso, Jocelyne Demengeot, J. Andrees Yunes, Benedict Seddon, and Joao T. Barata

**Précis:** Blocking IL-7 may constitute an effective therapeutic strategy to improve treatment of an aggressive form of T cell leukemia.

### Memory Type 2 Helper T Cells Induce Long-Lasting Antitumor Immunity by Activating Natural Killer Cells

Masayuki Kitajima, Toshihiro Ito, Damon J. Tumes, Yusuke Endo, Atsushi Onodera, Kahoko Hashimoto, Shinichiro Motohashi, Masakatsu Yamashita, Takashi Nishituma, Steven F. Ziegler, and Toshinori Nakayama

**Précis:** Cancer immunotherapies that recruit an IL4-dependent class of memory T helper cells that can activate antitumor natural killer cells may achieve more potent and durable clinical outcomes.
CDS⁺ T Cells Regulate Bone Tumor Burden Independent of Osteoclast Resorption
Kaihua Zhang, Seokho Kim, Viviana Cremasco, Angela C. Hirbe, Deborah V. Novack, Katherine Weilbaecher, and Roberta Faccio

Précis: This is the first report analyzing the relative contribution of osteoclasts and immune cells in development of bone metastases.

Pivotal Role of Innate and Adaptive Immunity in Anthracycline Chemotherapy of Established Tumors
Stephen R. Mattarollo, Sherene Loi, Helene Duret, Yuting Ma, Laurence Zitvogel, and Mark J. Smyth

Précis: This study adds to growing evidence that the therapeutic efficacy of cytotoxic chemotherapy relies upon antitumor contributions of the innate and adaptive immune systems.

Human Tumor Cells Killed by Anthracyclines Induce a Tumor-Specific Immune Response
Jitka Fucikova, Petra Králíková, Anna Fialova, Tomas Brtnický, Lukas Rob, Jirina Bartunkova, and Radek Špíšek

Précis: Findings define the qualities of ‘immunogenic’ cancer cell deaths that chemotherapeutic drugs may need to trigger in order to elicit efficacious clinical responses, with implications for the design of effective regimens of immunochemotherapy.

Human Neural Stem Cell Transplantation Ameliorates Radiation-Induced Cognitive Dysfunction
Munjal M. Acharya, Lori-Ann Christie, Mary L. Lan, Erich Giedzinski, John R. Fike, Susanna Rosi, and Charles L. Limoli

Précis: Cognitive dysfunction is a common and serious side-effect of radiotherapy in brain cancer patients which the findings of this study suggest might be reversed by stem cell transplantation.

Engagement of I-Branching β-1, 6-N-Acetylglucosaminyltransferase 2 in Breast Cancer Metastasis and TGF-β Signaling
Haijun Zhang, Fanyan Meng, Sherwin Wu, Bas Kreike, Seema Sethi, Wei Chen, Fred R. Miller, and Guojun Wu

Précis: Findings reveal that breast cancer metastasis driven by TGF-β signaling relies upon the activity of a novel glycosyltransferase, identifying a tractable therapeutic target to the development of broad-acting treatments for advanced disease.

The MeF/Elf4 Transcription Factor Fine Tunes the DNA Damage Response
Goro Sasaki, Narae Bac, Silvana Di Giandomenico, Takashi Asai, Nadia Gurvich, Elena Bazzoli, Yan Liu, Gang Huang, Xinyang Zhao, Silvia Menendez, and Stephen D. Nimer

Précis: This mechanistic study shows how a member of the ETS transcription family fine tunes the DNA damage response that is orchestrated by the central regulatory kinase ATM, with implications for understanding cancer susceptibility and chemotherapeutic responses.

CCI-779 Inhibits Cell-Cycle G2–M Progression and Invasion of Castration-Resistant Prostate Cancer via Attenuation of UBE2C Transcription and mRNA Stability
Hongyan Wang, Chaungpeng Zhang, Anna Borick, Dayong Wu, Ming Chiu, Jennifer Thomas-Ahner, Zhong Chen, Hongyan Chen, Steven K. Clinton, Kenneth K. Chan, and Qianben Wang

Précis: This study of the mechanism of action of an mTOR inhibitor defines an androgen receptor target gene that may be a critical driver of advanced prostate cancers.

Two Novel Determinants of Etoposide Resistance in Small Cell Lung Cancer
Malcolm H. Lawson, Natalie M. Cummings, Doris M. Rassl, Roslin Russell, James D. Brenton, Robert C. Rintoul, and Gillian Murphy

Précis: The identification of two new genes that mediate resistance to etoposide chemotherapy may offer rational strategies to prevent or relieve chemoresistance that causes the demise of patients suffering relapse.

Notch Signaling in CD66⁺ Cells Drives the Progression of Human Cervical Cancers
Jeevisha Bajaj, Tessa Thomas Maliekal, Eric Vivien, Chitra Pattabiraman, Sweta Srivastava, H. Krishnamurthy, V. Giri, Deepa Subramaniam, and Suddhir Krishna

Précis: This study presents a powerful mechanistic rationale to inhibit Notch signaling as a generalized therapeutic strategy to treat metastatic cancers.
### Prevention and Epidemiology

**Prediagnostic Serum Levels of Cytokines and Other Immune Markers and Risk of Non-Hodgkin Lymphoma**

Mark P. Purdue, Qing Lan, Rachel Bagui, William G. Hocking, Dalsu Baris, Douglas J. Reding, and Nathaniel Rothman

**Précis:** This prospective study identifies elevations in serologic markers associated with future risk of non-Hodgkin lymphoma.

### Therapeutics, Targets, and Chemical Biology

**SPARC Stimulates Neuronal Differentiation of Medulloblastoma Cells via the Notch1/STAT3 Pathway**

Praveen Bhopathi, Chandramu Chetty, Ranadheer Dontula, Meena Gujrati, Dzung H. Dinh, Jasti S. Rao, and Sajani S. Lakka

**Précis:** This study suggests a differentiation-inducing strategy to increase therapeutic responses in a commonly deadly form of pediatric brain cancer.

**Insights into ALK-Driven Cancers Revealed through Development of Novel ALK Tyrosine Kinase Inhibitors**

Christine M. Lovly, Johannes M. Heuckmann, Elisa de Stanchina, Heidi Chen, Roman K. Thomas, Chris Liang, and William Pao

**Précis:** Acquired resistance arising in ALK-fusion positive cancers to a first generation ALK tyrosine kinase inhibitor in clinical trials might be addressed by a novel, more potent, and specific second generation inhibitor.

**Caveolin-1 Upregulation Mediates Suppression of Primary Breast Tumor Growth and Brain Metastases by Stat3 Inhibition**

Wen-Tai Chiu, Hsueh-Te Lee, Feng-Ju Huang, Kenneth D. Aldape, Jun Yao, Patricia S. Steeg, Cheng-Yang Chou, Zhimin Lu, Ke ping Xie, and Suyun Huang

**Précis:** The mediator of brain metastasis identified in this study is likely a core modifier node of many cancer signaling pathways, since it functions in controlling the formation of plasma membrane lipid rafts that organize many cell surface adhesion and signaling complexes.

**Poly(ADP-Ribose) Polymerase Inhibition Synergizes with 5-Fluorodeoxyuridine but not 5-Fluorouracil in Ovarian Cancer Cells**

Amelia M. Huehls, Jill M. Wagner, Catherine J. Huntto, Liyi Geng, Charles Erlichman, Anand G. Patel, Scott H. Kaufmann, and Larry M. Karnitz

**Précis:** An analysis of the checkpoint and DNA repair pathway responses activated by floxuridine reveals how to combine these existing chemotherapeutic agents with PARP inhibitors to achieve the best therapeutic efficacy.

**Sorafenib Enhances Pemetrexed Cytotoxicity through an Autophagy-Dependent Mechanism in Cancer Cells**


**Précis:** This study defines a novel combination of clinically approved drugs that may prove to be highly effective in the treatment of many types of solid tumors, prompting immediate clinical attention.

**Effect of ON 01910.Na, an Anticancer Mitotic Inhibitor, on Cell-Cycle Progression Correlates with RanGAP1 Hyperphosphorylation**

Irina A. Oussenko, James F. Holland, E. Premkumar Reddy, and Takao Ohnuma

**Précis:** This drug mechanism study offers evidence of a new therapeutic pathway that can achieve pathobiological selectivity for cancer cells.

**Small-Molecule Anticancer Compounds Selectively Target the Hemopexin Domain of Matrix Metalloproteinase-9**

Antoine Dufour, Nicole S. Sampson, Jian Li, Cem Kuscu, Robert C. Rizzo, Jennifer L. DeLeon, Jizu Zhi, Nadia Jaber, Eric Liu, Stanley Zucker, and Jian Cao

**Précis:** Although early MMP inhibitors moved into clinical development were not successful, the central importance of MMPs in cancer invasion and metastasis has driven the development of later generation inhibitors that offer considerable therapeutic potential.
Positive Feedback Loop Between PI3K-Akt-mTORC1 Signaling and the Lipogenic Pathway Boosts Akt Signaling: Induction of the Lipogenic Pathway by a Melanoma Antigen

Yoshio Yamauchi, Keiko Furukawa, Kazunori Hamamura, and Koichi Furukawa

Precise: This study suggests a mechanistic explanation for why cancer cells synthesize high levels of cholesterol and fatty acids, which by promoting formation of plasma membrane lipid rafts can reinforce signaling events that sustain cancer cell survival.

Suppression of Apoptosis by PIF1 Helicase in Human Tumor Cells

Mary E. Gagou, Anil Ganesh, Ruth Thompson, Geraldine Phear, Cyril Sanders, and Mark Meuth

Precise: Findings define the function of a DNA helicase that is crucial for the viability of cancer cells under DNA replication stress, with potential implications for how to increase cancer chemosensitivity.

Notch Signaling Activated by Replication Stress–Induced Expression of Midkine Drives Epithelial–Mesenchymal Transition and Chemoresistance in Pancreatic Cancer

Cenap Gungor, Hlike Zander, Katharina E. Effenberger, Yogesh K. Vashist, Tatyana Kalinina, Jakob R. Izbicki, Emre Yekebas, and Maximilian Bockhorn

Precise: Findings suggest that overexpression of the growth factor Midkine plays a role in the inherent chemoresistance of pancreatic cancer cells, suggesting that depleting this factor might heighten their sensitivity to chemotherapy.

STAT3 Plays a Critical Role in KRAS-Induced Pancreatic Tumorigenesis

Ryan B. Corcoran, Gianmarco Contino, Vikram Deshpande, Alexandros Tzatsos, Claudius Conrad, Cyril H. Benes, David E. Levy, Jeffrey Settleman, Jeffrey A. Engelman, and Nabeel Bardeesy

Precise: Findings show that JAK2-STAT3 signaling is required for pancreatic cancer initiation, progression, and maintenance, and that this pathway predicts the response to JAK2 inhibitors in clinical development.

Myeloid Suppressor Cells Regulate the Lung Environment—Letter

Momir Bosiljcic, Melisa J. Hamilton, Judith P. Banath, Nancy E. LePard, Denise C. McDougal, Jessica X. Jia, Gerald Krystal, and Kevin L. Bennewith

Myeloid Suppressor Cells Regulate the Lung Environment—Response

Hannah H. Yan, Michael Pickup, Yanli Pang, Agnieszka E. Gorska, Zhaoyang Li, Anna Chyttil, Yipeng Geng, Jerome W. Gray, Harold L. Moses, and Li Yang

Correction: Hsp27 Promotes Insulin-Like Growth Factor-I Survival Signaling in Prostate Cancer via p90Rsk-Dependent Phosphorylation and Inactivation of BAD

Zhumur Ghosh, Mei Huang, Shijun Hu, Kitchener D. Wilson, Devaveena Dey, and Joseph C. Wu

Precise: Differentiation of pluripotent stem cell derivatives may not limit all their oncogenic properties, implying the need for additional testing prior to use in regenerative therapy.

Ex Vivo Graft Purging and Expansion of Autologous Blood Progenitor Cell Products from Patients with Multiple Myeloma


Precise: The study describes a novel ex vivo purging strategy to improve the quality of autologous peripheral blood progenitor cell transplant used to treat patients with myeloma.
ABOUT THE COVER

Tumor antigen-reactive CTLs by programming iPS cells infiltrated into tumor tissue. Tumor antigen TCR gene-transduced iPS cells were adoptively transferred into C57BL/6 mice, which were subjected to challenge with E. G7 tumor cells. On day 35 after tumor challenge, tumor tissues were examined for tumor-reactive T-cell infiltration by immunohistological staining. Tumor antigen-specific CTLs (red) infiltrated into lymphoma tissue (green). For details, see the article by Lei and colleagues on page 4742 of this issue.