Human T<sub>reg</sub>17 Immune Cells Specific for the Tumor Antigen MAGE-A3 Convert to IFN-γ–Secreting Cells as They Differentiate into Effector T Cells
In Vivo
Ahmed Hamai, Pascale Pignon, Isabelle Raimbaud, Karine Duperrier-Amouriaux, Hélène Senellart, Sandrine Hiret, Jean-Yves Douillard, Jaafar Bennouna, Maha Ayyoub, and Danila Valmori

Précis: Naturally arising T<sub>reg</sub>17 helper T cells that are specific for a common tumor antigen in cancer patients tend to convert into IFN-γ-secreting cells as they differentiate into effector T cells, a finding that encourages the development of methods to amplify them through immunotherapy.

Exploiting the Mutanome for Tumor Vaccination
John C. Castle, Sebastian Kreiter, Jan Diekmann, Martin Löwer, Niels van de Roemer, Jos de Graaf, Abderraouf Selmi, Mustafa Diken, Sebastian Boegel, Claudia Paret, Michael Koslowski, Andreas N. Kuhn, Cedrik M. Britten, Christoph Huber, Özlem Türeci, and Ugur Sahin

Précis: This important study heralds strategies for personalized vaccinations of cancer patients, through the use of deep sequencing analysis, which shows that many nonsynonymous somatic mutations in a tumor are sufficient to confer antitumor activity to a peptide vaccine.
MOLECULAR AND CELLULAR PATHOBIOLOGY

Upregulation of miR-196a and HOTAIR Drive Malignant Character in Gastrointestinal Stromal Tumors
Takeshi Niihuma, Hirozu Suzuki, Masanori Nojima, Katsuhiko Nosho, Hiroyuki Yamamoto, Hiroyuki Takamaru, Eiichiro Yamamoto, Reo Maruyama, Takayuki Nohbu, Yasuaki Miyazaki, Toshihisa Nishida, Takeshi Yamada, Tatsuo Kanda, Yoichi Akioka, Takahiro Taguchi, Satoshi Okahara, Hiroaki Takahashi, Yasunori Nishida, Masaaki Hosokawa, Tadashi Hasegawa, Takashi Tokino, Koichi Hirata, Kohzoh Imay, Minoru Toyota, and Yasuhisa Shinomura
Précis: This study is among the first to reveal an important role in human cancer for HOTAIR, a member of an as yet little studied new category of long noncoding RNAs that may have broad applications as biomarkers or therapeutic targets in oncology.

KR-POK Interacts with p53 and Represses Its Ability to Activate Transcription of p21WAF1/CDKN1A
Bu-Nam Jeon, Min-Kyeong Kim, Won-Il Choi, Dong-In Koh, Sung-Yi Hong, Kyung-Sup Kim, Minjung Kim, Chae-Ok Yun, Jung-Yoon, Kang-Yell Choi, Kyung-Ryul Lee, Kenneth P. Nephe, and Man-wook Hur
Précis: Findings provide important novel insights into how the transcriptional activation function of p53 is repressed in cells, with implications for understanding a new oncogenic pathway in kidney cancers.

ATR–ATRIP Kinase Complex Triggers Activation of the Fanconi Anemia DNA Repair Pathway
Tomoko Shigechi, Junya Tomida, Koichi Sato, Masahiko Kobayashi, John K. Eykelenboom, Fabio Pessina, Yanbin Zhang, Emi Uchida, Masamichi Ishida, Heil F. Lowndes, Kenichi Yamamoto, Hitoshi Kurumizaka, Yoshikiko Maehara, and Minoru Takata
Précis: Findings advance pathophysiologic understanding of a cancer-disposing disorder, Fanconi anemia, and reveal key insights into fundamental control pathways for S-phase DNA repair and cell-cycle checkpoint defective in cancer.
Kaposi Sarcoma Herpesvirus Promotes Endothelial-to-Mesenchymal Transition through Notch-Dependent Signaling
Paola Gasperini, Georgina Espigol-Frigole, Peter J. McCormick, Ombretta Salvucci, Dragan Marie, Thomas S. Uldrick, Mark N. Polizzotto, Robert Yarchano, and Giovanna Tosato

Précis: This study identifies a basis to understand the aggressiveness of a mesenchymal cancer that occurs commonly in AIDS patients, with implications for its better treatment with Notch pathway inhibitors currently being explored in clinical trials.

DNA Methylation Does Not Stably Lock Gene Expression but Instead Serves as a Molecular Mark for Gene Silencing Memory

Précis: Chromatin is a target for epigenetic cancer therapies that reactivate gene expression, but removal of DNA methylation signals is required first to achieve durable long-term effects.

PREVENTION AND EPIDEMIOLOGY

Novel Genetic Markers of Breast Cancer Survival Identified by a Genome-Wide Association Study

Précis: Genetic variants in the RAD51L1 gene implicated in DNA repair along with a second locus on chromosome 16 appear to predict the survival of breast cancer patients.

Impact of Circulating Vitamin D Binding Protein Levels on the Association between 25-Hydroxyvitamin D and Pancreatic Cancer Risk: A Nested Case-Control Study
Stephanie J. Weinstein, Rachael Z. Stolzenberg-Solomon, William Kopp, Helen Rager, Jarmo Virtamo, and Demetrius Albanes

Précis: Findings suggest an explanation for the adverse influence of vitamin D on risk of pancreatic cancer, which contrasts with some other solid tumors, with implications for how future risk association studies of vitamin D may be designed.

RNAi-Mediated Targeting of Noncoding and Coding Sequences in DNA Repair Gene Messages Efficiently Radiosensitizes Human Tumor Cells
Zhiming Zheng, Wooi Loon Ng, Xiangning Zhang, Jeffrey J. Olson, Chunhui Hao, Walter J. Curran, and Ya Wang

Précis: This study defines a generalized approach for highly efficient RNAi-based gene silencing, using a combinatorial targeting strategy to illustrate how knockdown of DNA repair genes can effectively radiosensitize tumor cells.

LRIG1 Modulates Cancer Cell Sensitivity to Smac Mimetics by Regulating TNFα Expression and Receptor Tyrosine Kinase Signaling
Longchuan Bai, Donna McEachern, Chao-Yie Yang, Jianfeng Lu, Haiying Sun, and Shaomeng Wang

Précis: This study provides key insights into the basis for resistance to IAP inhibitors, possibly critical to the successful clinical development of this new class of cancer drugs.
Adoptive Cell Therapy for Lymphoma with CD4 T Cells Depleted of CD137-Expressing Regulatory T Cells
Matthew J. Goldstein, Holbrook E. Kohrt, Roch Houot, Bindu Varghese, Jack T. Lin, Erica Swanson, and Ronald Levy

"This important study provides knowledge that can immediately be translated into the clinical setting to optimize cell-based cancer immunotherapies based on adoptive transfer of CD4+ T lymphocytes."

TUMOR AND STEM CELL BIOLOGY

Targeting Pioneering Factor and Hormone Receptor Cooperative Pathways to Suppress Tumor Progression
Supriya Shah, Shikha Prasad, and Karen E. Knudsen

"Findings reveal that the turmeric spice component curcumin can act in a combinatorial manner to disrupt histone modification and androgen receptor signaling to control prostate cancer growth."

PRAS40 Is a Functionally Critical Target for EWS Repression in Ewing Sarcoma
Lin Huang, Yuji Nakai, Iku Kuwahara, and Ken Matsumoto

"An Akt substrate is identified as a critical oncogenic mediator in an aggressive type of pediatric cancer that has had an elusive molecular pathobiology."

p53 Inhibits Angiogenesis by Inducing the Production of Arresten
Sarah Assadian, Wissal El-Assaad, Xue Q.D. Wang, Phillippe O. Gannon, Véronique Barris, Mathieu Latour, Anne-Marie Mes-Masson, Fred Saad, Yoshikazu Sado, Josée Dostie, and Jose G. Teodoro

"In addition to its well studied effects on tumor cell growth, senescence, and survival, p53 also acts in many ways to modify the cellular microenvironment, including through regulation of antiangiogenic factors."

CORRECTIONS

Correction: Increased Survival of Glioblastoma Patients Who Respond to Antiangiogenic Therapy with Elevated Blood Perfusion

Correction: Regulation of Matrix Metalloproteinase Genes by E2F Transcription Factors: Rb–Raf-1 Interaction as a Novel Target for Metastatic Disease
ABOUT THE COVER

A number of cathepsin proteases have been documented to promote tumor invasion and metastasis. However, the role of specific proteases in breast cancer metastasis and the therapeutic potential of their selective inhibition in clinically relevant models are not clear. Using 3D and in vivo models, Withana and colleagues have shown that the cysteine protease cathepsin B has important roles in breast cancer metastasis and that therapeutic inhibition of this protease using small-molecule inhibitors dramatically decreases metastasis to lung and bone. The cover image was produced with fluorescent whole-body imaging using a cysteine cathepsin activity–based fluorescent probe (GB123) and the fluorescent diphosphonate probe Osteosense 750, which detects bone remodeling. The image shows cysteine cathepsin activity along the spine of mice bearing bone metastatic tumors. This activity is reduced in mice treated with the cathepsin B selective small-molecule inhibitor CA-074. For details, see the article by Withana and colleagues on page 1199 of this issue.