Metastatic Competence Can Emerge with Selection of Preexisting Oncogenic Alleles without a Need of New Mutations
Leni S. Jacob, Sakari Vanharanta, Anna C. Obenauf, Monia Pirun, Agnes Viale, Nicholas D. Soeci, and Joan Massagué

**Précis:** Changes in the ecology of metastatic niche microenvironments may be sufficient to select for metastatic capacity, without any need of for selection of new mutations in cancer cells themselves, heightening evidence of the primacy of the host microenvironment in directing cancer progression.

The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma
Paul William Harms, Pankaj Vats, Monique Elise Verhaegen, Dan R. Robinson, Yi-Mi Wu, Saravana Mohan Dhanasekaran, Nallasivam Palanisamy, Javed Siddiqui, Xuhong Cao, Fengyun Su, Rui Wang, Hong Xiao, Lakshmi P. Kunju, Rohit Mehra, Scott A. Tomlins, Douglas Randall Fullen, Christopher Keram Bichakjian, Timothy M. Johnson, Andrzej Antoni Dlugosz, and Arul M. Chinnaiyan

**Précis:** Next-generation sequencing analysis suggests two molecularly distinct etiologies for MCC, characterized by either viral-dependent or UV-dependent tumorigenic pathways.

Real-time Imaging of the Resection Bed Using a Handheld Probe to Reduce Incidence of Microscopic Positive Margins in Cancer Surgery

**Précis:** This study presents a unique web resource that enables high-quality analyses to investigate the full spectrum of long-noncoding RNAs in cancer, reducing existing barriers for biomedical researchers to access the complex genomic data, generate testable hypotheses, and make translational discoveries.

Pulsed High-Intensity Focused Ultrasound Enhances Delivery of Doxorubicin in a Preclinical Model of Pancreatic Cancer
Tong Li, Yak-Nam Wang, Tatiana D. Khokhlova, Samantha D’Andrea, Frank Starr, Hong Chen, Jeannine S. McCune, Linda J. Risler, Afshin Mashadi-Hossein, and Joo Ha Hwang

**Précis:** An ultrasound-based delivery method that causes tissue cavitation can greatly improve locally targeted delivery of drugs to tumors, such as pancreatic cancer, that have dense stroma and are poorly permeable to small molecule therapies.
A Threshold Level of Intratumor CD8+ T-cell PD1 Expression Dictates Therapeutic Response to Anti-PD1
Shin Foong Ngiow, Arabella Young, Nicolas Jacquelot, Takahiro Yamaazaki, David Enot, Laurence Zitvogel, and Mark J. Smyth
Précis: This study shows how PD1 levels in CD8+ T cells that are present in tumors can predict the treatment response to PD1 antibodies and how regulatory T cells participate in controlling this sensitivity, with immediate implications for addressing the timely question of which patients will respond best to this exciting immune checkpoint therapy.

STAT3 Inhibition Enhances the Therapeutic Efficacy of Immunogenic Chemotherapy by Stimulating Type 1 Interferon Production by Cancer Cells
Heng Yang, Takahiro Yamaazaki, Federico Pietrocola, Heng Zhou, Laurence Zitvogel, Yuting Ma, and Guido Kroemer
Précis: STAT3 inhibitors may improve the therapeutic benefits of anthracyclines through augmenting cancer cell-autonomous type 1 IFN response.

Preclinical Characterization of Novel Chordoma Cell Systems and Their Targeting by Pharmacological Inhibitors of the CDK4/6 Cell-Cycle Pathway
Adrian von Witleben, Lukas T. Goerttler, Ralf Marienfeld, Holger Barth, André Lechel, Kevin Mellett, Michael Böhm, Marko Kornmann, Regine Mayer-Steinacker, Alexandra von Baer, Markus Schulteiss, Adrienne M. Flanagan, Peter Möller, Silke Bruderlein, and Thomas F.E. Barth
Précis: This study describes how PD1 levels in CD8+ T cells

Loss of RACK1 Promotes Metastasis of Gastric Cancer by Inducing a miR-302c/IL8 Signaling Loop
Ling Chen, Lingqiang Min, Xuelei Wang, Junjie Zhao, Hua Chen, Jing Qin, Weidong Chen, Zhenbin Shen, Zhaojing Tang, Qiangjun Gan, Yuanynan Ruan, Yihong Sun, Xinyu Qin, and Jianxin Gu
Précis: This study connects epigenetics and inflammatory cytokine control during tumorigenesis in gastric tissue, showing how an epithelium state affects key mediators in establishing a master-slave relationship in the tumor microenvironment.
THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

3842 Small-Molecule NSC59984 Restores p53 Pathway Signaling and Antitumor Effects against Colorectal Cancer via p73 Activation and Degradation of Mutant p53
Précis: The p53 pathway-activating compound reported in this study is highly novel, not only stimulating p73 expression and function but also targeting gain-of-function mutants of p53 that are expressed widely in human cancers, with potentially broad-reaching implications for cancer treatment.

3853 Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies
Laurent Poirot, Brian Philip, Cecile Schiffer-Mannioui, Diane Le Clerre, Isabelle Chion-Sotinel, Sophie Demiame, Pierrick Potrel, Cecile Bas, Laetitia Lemare, Roman Galetto, Celine Lebuhotel, Justin Eyquem, Gordon Weng-Kit Cheung, Agnes Gouble, Sylvain Arnould, Karl Peggs, Martin Pule, Andrew M. Scharenberg, and Julianne Smith
Précis: This study describes methods that overcome present limitations in generating patient-derived CAR T-cell therapy by using nonalloreactive T cells from third-party donors in a scalable manufacturing process that enables an "off-the-shelf" immunotherapy to be produced.

3865 The SMARCA2/4 ATPase Domain Surpasses the Bromodomain as a Drug Target in SWI/SNF-Mutant Cancers: Insights from cDNA Rescue and PFI-3 Inhibitor Studies
Précis: These findings directly inform drug discovery efforts to translate synthetic lethal strategies into effective drugs and useful biomarkers in cancers that are driven by a mutated SWI/SNF transcription factor.

3879 ABCG2 Transporter Expression Impacts Group 3 Medulloblastoma Response to Chemotherapy
Marie Morfouace, Satish Cheepala, Sadhana Jackson, Yu Fukuda, Yogesh T. Patel, Sohira Fatima, Daisuke Kawazuci, Anang A. Shelat, Clinton F. Stewart, Brian P. Somerlin, John D. Schuetz, and Martine F. Rousel
Précis: These findings offer a preclinical rationale to block ABCG2 transporter activity as a strategy to enhance the therapeutic efficacy of topotecan used to treat Group 3 medulloblastoma, a pediatric brain tumor that is particularly challenging to address clinically.

3890 miR-634 Activates the Mitochondrial Apoptosis Pathway and Enhances Chemotherapy-Induced Cytotoxicity
Naoto Fujiiwara, Jun Inoue, Tatsuyuki Kawano, Kousuke Tanimoto, Ken-ichi Kozaki, and Ioiji Inazawa
Précis: This study shows how a little studied microRNA can alter the context in which cancer cells respond to chemotherapy-induced stress, improving efficacy in settings such as esophageal cancers, which are inherently resistant to chemotherapy.

3902 CD38 in Hairy Cell Leukemia Is a Marker of Poor Prognosis and a New Target for Therapy
Nicolas Poret, Qiangoei Fu, Soizic Guihard, Meyling Cheok, Katie Miller, Gordon Zeng, Bruno Quesnel, Xavier Troussard, Sylvie Galilic-Zouitina, and Carl Simon Shelley
Précis: This study describes for the first time a biomarker that predicts the severity of hairy cell leukemia and provides preclinical proof that the same biomarker is a powerful new therapeutic target.

TUMOR AND STEM CELL BIOLOGY

3912 Hypoxia Drives Breast Tumor Malignancy through a TET–TNFα–p38–MAPK Signaling Axis
Min-Zu Wu, Su-Feng Chen, Shin Nieh, Christopher Benner, Luo-Ping Ger, Chia-Ing Jan, Li Ma, Chien-Hung Chen, Toomaki Hishiida, Hong-Tai Chang, Yash-Shiang Lin, Nuria Montserrat, Pedro Gascon, Ignacio Sancho-Martinez, and Juan Carlos Izpisua Belmonte
Précis: These results shed new mechanistic light on how hypoxic tumor microenvironments affect epigenetic programs in cancer cells to drive stem-like character and metastasis, suggesting new ways to eradicate cancer stem-like cells that are nurtured by such microenvironments.
DNp63α Promotes Breast Cancer Cell Motility through the Selective Activation of Components of the Epithelial-to-Mesenchymal Transition Program
Tuyen T. Dang, Matthew A. Esparza, Erin A. Maine, Jill M. Westcott, and Gray W. Pearson

Précis: The transcription factor DNp63α can initiate pro-migratory components of EMT while sustaining epithelial character, perhaps explaining the aggressive invasive behavior of certain epithelial-like cancers like basal cell breast cancers.

KAT6B Is a Tumor Suppressor Histone H3 Lysine 23 Acetyltransferase Undergoing Genomic Loss in Small Cell Lung Cancer
Laia Simó-Riudalbas, Montserrat Pérez-Salvia, Fernando Setien, Alberto Villanueva, Catia Mouzinho, Anna Martínez-Caridi, Sebastián Moran, María Berradaco, Antonio Gomez, Enrique Vidal, Marta Soler, Holger Heyn, Alejandro Vaquero, Carolina de la Torre, Silvia Barceló-Batllori, August Iwakawa, Takashi Kohno, Jun Yokota, and Manel Esteller

Précis: Understanding how genetic defects in histone modifier genes contribute to human cancer can identify common pathogenic processes and new predictive and prognostic markers.

Heparanase Enhances Tumor Growth and Chemoresistance by Promoting Autophagy
Anna Shteingauz, Ilanit Boyango, Inna Naroditsky, Edward Hammond, Maayan Gruber, Ilana Doweck, Neta Ilan, and Israel Vlodavsky

Précis: These findings illuminate the function of an enzyme implicated in tumor inflammation, angiogenesis, and metastasis in modulating autophagy in cells, thereby conferring cell growth advantages under stress and resistance to chemotherapy.

Notch1 Activation or Loss Promotes HPV-Induced Oral Tumorigenesis
Rong Zhong, Riyue Bao, Pieter W. Faber, Vytautas P. Bindokas, John Bechill, Mark W. Lingen, and Michael T. Spiotto

Précis: Strikingly, a functional screen for candidate driver genes in HPV-associated squamous cancers revealed that either gain or loss of Notch1 can promote tumor growth, by distinct pathways, suggesting great caution in the interpretation of putative driver mutations linked to cancer development.

Maspin Expression in Prostate Tumor Cells Averts Stemness and Stratifies Drug Sensitivity
M. Margarida Bernardo, Alexander Kaplun, Sijana H. Dzinic, Xiaohua Li, Jonathan Irish, Adelina Mjuragic, Benjamin Jakupovic, Jessica B. Back, Eric Van Buren, Xiang Han, Ivory Dean, Yong Q. Chen, Elisabeth Heath, Wael Sakr, and Shijie Sheng

Précis: These results offer evidence that the epithelial-specific molecule maspin limits tumor cell plasticity in the prostate, thereby dictating drug sensitivity and offering a biomarker in experimental screens for curative chemotherapy.

A Molecular Portrait of High-Grade Ductal Carcinoma In Situ
Martin C. Abba, Ting Gong, Yue Lu, Jaeho Lee, Yi Zhong, Ezequiel Lacunza, Matias Butti, Yoko Takata, Sally Gaddis, Jianjun Shen, Marcos R. Estecio, Aysegul A. Sahin, and C. Marcelo Aldaz

Précis: This first comprehensive molecular profile of pre-invasive breast cancers identifies a subgroup of early-stage lesions with aggressive molecular profiles that are indistinguishable from invasive breast cancers, with immediate clinical implications for managing aggressive early-stage lesions at first diagnosis.
Mast cells located in the gut move in areas of mucosal damage during the process of resolution of acute inflammation and repair. Their activity helps the quenching of inflammatory stimuli, as demonstrated by the delayed tissue repair occurring in mast cell-deficient mice. Mucosal healing is restored upon reconstitution of tissues of mast cell-deficient mice with bone marrow-derived mast cells, as indicated by histology showing the recovered crypt architecture characterizing the intestinal mucosa of reconstituted mice. These pieces of information imply a positive role of the mast cell in the resolution of intestinal inflammation and mucosal healing, which eventually becomes detrimental when transformation towards cancer occurs. For details, see article by Rigoni and colleagues on page 3760.