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## Integrated Systems and Technologies

**2607** Quantifying the Landscape for Development and Cancer from a Core Cancer Stem Cell Circuit  
Chunhe Li and Jin Wang  
**Précis:** A pictorial “cancer landscape” theory described in this study offers quantitative insights into underlying mechanisms of cancer stem-like cell formation and the interplay with normal development, with possible applications to a variety of disease-related regulatory networks.

## Microenvironment and Immunology

**2619** Blocking Tumor Necrosis Factor α Enhances CD8 T-cell–Dependent Immunity in Experimental Melanoma  
Florian Bertrand, Julia Rochotte, Céline Colacios, Anne Montfort, Anne-Françoise Tilkin-Mariamé, Christian Touriol, Philippe Rochais, Isabelle Lajoie-Mazenc, Nathalie Andrieu-Abadie, Thierry Levade, Hervé Benoist, and Bruno Séguin  
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**2629** Chemotherapy-Derived Inflammatory Responses Accelerate the Formation of Immunosuppressive Myeloid Cells in the Tissue Microenvironment of Human Pancreatic Cancer  
Shintaro Takeuchi, Muhammad Baghdadi, Takahiro Tsuchikawa, Haruka Wada, Toru Nakamura, Hirotake Abe, Sayaka Nakanishi, Yuu Usui, Kohtarou Higuchi, Mizuna Takahashi, Kazuho Inoko, Syoki Sato, Hiroshi M. Takano, Tomohiro Shichinohe, Ken-Ichi Seino, and Satoshi Hirano  
**Précis:** These findings challenge the use of therapeutic regimens employing GM-CSF as part of a cancer vaccine by providing preclinical evidence that GM-CSF ablation may benefit patients with pancreatic cancer, who generally respond poorly to chemotherapy, through helping defeat a powerful immune escape mechanism.
2641  Genetic Regulation of Fate Decisions in Therapeutic T Cells to Enhance Tumor Protection and Memory Formation  
Pedro Velića, Mathias Zech, Sian Henson, Angelika Holler, Teresa Manzo, Rebecca Pike, Pedro Santos e Sousa, Lei Zhang, Bernhard Schiedlmier, Martin Pule, Hans Stauss, and Ronjon Chakraverty  

Précis: These findings suggest translational strategies to generate heterogeneous T-cell immunity against cancer by manipulating functions of mTORC1 subunits that balance T-effector cell differentiation and self-renewal.

2653  Neutrophil Extracellular Traps Accumulate in Peripheral Blood Vessels and Compromise Organ Function in Tumor-Bearing Animals  
Jessica Cedervall, Yanyu Zhang, Hua Huang, Lei Zhang, Julia Femel, Anna Dimberg, and Anna-Karin Olsson  

Précis: These findings suggest seminal insights into why organ failure occurs in cancer patients, including those with limited tumor loads, due to the collateral damage that tumors inflict systemically on inflammation and vascular function in organs unaffected by metastasis.

2663  Macrophages Regulate the Systemic Response to DNA Damage by a Cell Nonautonomous Mechanism  
Anat Geiger-Maor, Avital Guedj, Sharona Even-Ram, Yoav Smith, Ethan Galun, and Jacob Rachmilewitz  

Précis: This study reveals how macrophages act non-cell autonomously to assist neighboring cells to repair damaged DNA, illuminating a novel physiologic mechanism that helps maintain genomic integrity.

2674  miR-181a-5p Inhibits Cancer Cell Migration and Angiogenesis via Downregulation of Matrix Metalloproteinase-14  
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Précis: This study provides important new information about the regulation of a critical cell surface protease in mediating invasion and metastasis by many types of human solid cancers.

2686  NKX3.1 Suppresses TMPRSS2–ERG Gene Rearrangement and Mediates Repair of Androgen Receptor–Induced DNA Damage  
Cai Bowen, Tian Zheng, and Edward P. Gelmann  

Précis: Loss of the suppressor gene NKX3.1 in premalignant prostate cells predisposes them to defective DNA repair, thereby increasing risks of TMPRSS2-ERG oncogene rearrangement that is critical early in malignant transformation.

2699  Repair versus Checkpoint Functions of BRCA1 Are Differentially Regulated by Site of Chromatin Binding  
Michael Goldstein and Michael B. Kastan  

Précis: These findings demonstrate that spatially distinct forms of the tumor suppressor BRCA1 are recruited to sites of DNA double-strand breaks with distinctive differential functions in DNA repair and checkpoint signaling.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

2708  NUAK2 Amplification Coupled with PTEN Deficiency Promotes Melanoma Development via CDK Activation  

Précis: This study defines a novel gene activation event that is critical for progression of cutaneous melanomas, with implications that rationalize their treatment with CDK2 inhibitors.

2716  A Novel Cinnamon-Related Natural Product with Pim-1 Inhibitory Activity Inhibits Leukemia and Skin Cancer  
Jong-Eun Kim, Joe Eun Son, Hyein Jeong, Dong Joon Kim, Sang Gwon Seo, Eunjung Lee, Tae Gyu Lim, Jong Rhan Kim, Yengo Raymond Kimbung, Hongyong Chen, Ann M. Bode, Ki Won Lee, and Zigang Dong  

Précis: These results offer preclinical proof of concept for a cinnamon compound with potent anticancer activity based on direct targeting of a pro-oncogenic kinase.
2729 Hepatocellular Shuttling and Recirculation of Sorafenib-Glucuronide Is Dependent on Abcc2, Abcc3, and Oatp1a/1b
Aksana Vasilyeva, Selvi Durmus, Lie Li, Els Wagenaar, Shuiving Hu, Alice A. Gibson, John C. Panetta, Sridhar Mani, Alex Sparreboom, Sharyn D. Baker, and Alfred H. Schinkel
Précis: These results suggest broad relevance of a hepatocyte shuttling process known as “hepatocyte hopping”—a novel concept in clinical pharmacology—for detoxification of targeted cancer drugs that undergo hepatic glucuronidation, such as sorafenib.

2737 Paracrine Effect of NRG1 and HGF Drives Resistance to MEK Inhibitors in Metastatic Uveal Melanoma
Hanyin Cheng, Mizue Terai, Ken Kageyama, Shinji Ozaki, Peter A. McCue, Takami Sato, and Andrew E. Aplin
Précis: These findings offer a preclinical proof of concept for the combination of MEK inhibitor plus a growth factor receptor targeting antibody in the treatment of highly aggressive uveal melanomas.

2749 Tracking and Functional Characterization of Epithelial–Mesenchymal Transition and Mesenchymal Tumor Cells during Prostate Cancer Metastasis
Marcus Ruscetti, Bill Quach, Eman L. Dadashian, David J. Mulholland, and Hong Wu
Précis: EMT prostate tumor cells, which transition readily between epithelial and mesenchymal states, can recapitulate each stage of the metastatic cascade, supporting the use of therapeutic agents that target tumor cell plasticity for the treatment of lethal metastatic prostate cancer.

2759 Retraction: Concurrent Suppression of Integrin α5, Radixin, and RhoA Phenocopies the Effects of miR-31 on Metastasis

2760 Correction: miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL6-Mediated Paracrine Effects in Head and Neck Cancer

ABOUT THE COVER
TNFα plays a central, but still enigmatic, role in melanoma. Using immunofluorescence, it was found that TNF deficiency or blockade enhanced intratumor content of high endothelial venules surrounded by high CD8+ T lymphocyte density. Consequently, the tumor growth of melanoma cell lines expressing MHC-I molecules at high levels was dramatically impaired. Counteracting TNF signaling may potentiate the immune response in melanoma. For details, see article by Bertrand and colleagues on page 2619.
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