INTEGRATED SYSTEMS AND TECHNOLOGIES

3136 Darwinian Dynamics of Intratumoral Heterogeneity: Not Solely Random Mutations but Also Variable Environmental Selection Forces
Mark C. Lloyd, Jessica J. Cunningham, Marilyn M. Bui, Robert J. Gillies, Joel S. Brown, and Robert A. Gatenby
Précis: Regional heterogeneity of molecular properties of tumor cells is governed by local variation in environmental selection forces rather than random accumulating mutations

MICROENVIRONMENT AND IMMUNOLOGY

3145 NFAT1 Directly Regulates IL8 and MMP3 to Promote Melanoma Tumor Growth and Metastasis
Einav Shoshan, Russell R. Braeuer, Takafumi Kamiya, Aaron K. Mobley, Li Huang, Mayra E. Vasquez, Guermarie Velazquez-Torres, Nimit Chakravarti, Cristina Ivan, Victor Prieto, Gabriel J. Villares, and Menashe Bar-Eli
Précis: This study reports a new role for a T-cell transcription factor in melanoma progression and provides mechanistic insights into the downstream factors endowing cancer cells with metastatic behaviors.

3156 Myeloid-Derived Suppressor Cells Endow Stem-like Qualities to Breast Cancer Cells through IL6/STAT3 and NO/NOTCH Cross-talk Signaling
Dongjun Peng, Takashi Tanikawa, Wei Li, Lili Zhao, Yin Wang, Yan Liu, Elzbieta Staroslawska, Franciszek Sztubatska, Jacek Rolinski, Ewelina Grywalska, Andrzej Stanislawek, Wojciech Polkowski, Andrzej Kurylcio, Celina Kleer, Allan E. Chang, Max Wicha, Michael Sabel, Weiping Zou, and Ilona Kryczek
Précis: This seminal study illuminates an immune-associated mechanism that extrinsically confers cancer cell stemness properties along with immune escape, suggesting the opportunity to therapeutically target a pivotal coupled process in the tumor microenvironment.

3166 Guidance Molecule SEMA3A Restricts Tumor Growth by Differentially Regulating the Proliferation of Tumor-Associated Macrophages
Majken Wallerius, Tatjana Wallmann, Margarita Barish, Jeanette Osling, Artur Mezheyevetski, Nicholas P. Tobin, Emma Nygren, Pradeepa Pangigadde, Paola Pellegrini, Mario Leonardo Squadrato, Fredrik Pomiens, Johan Hartman, Jonas Bergh, Angelo De Millo, Michele De Palma, Arne Ostman, John Andersson, and Charlotte Rolny
Précis: These results illuminate a mechanism whereby the phenotype of tumor-associated macrophages is controlled and identify a cell surface tissue guidance molecule as a candidate for therapeutic targeting in the tumor microenvironment.
Inhibition of PAI-1 Limits Tumor Angiogenesis
Regardless of Angiogenic Stimuli in Malignant Pleural Mesothelioma
Yusuke Takayama, Noboru Hattori, Hirokazu Hamada, Takeshi Masuda, Keitaro Omori, Shin Akita, Hiroshi Iwamoto, Kazunori Fujitaka, and Nobuoki Kohno

AMPK Activation and Metabolic Reprogramming by Tamoxifen through Estrogen Receptor–Independent Mechanisms Suggests New Uses for This Therapeutic Modality in Cancer Treatment
Natalie A. Daurio, Andrew J. Worth, Ethan Y. Song, Christopher Destandins, Yanke Yu, George Lai, Larisa Reyderman, Nancy Wong, and Barbara S. Slusher

AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ERα-Mutant Breast Tumors in Preclinical Models
Hazel M. Weir, Robert H. Bradbury, Mandy Lawson, Alfred A. Rabow, David Buttar, Rowena J. Callis, Ion O. Curwen, Camila de Almeida, Peter Ballard, Michael Hulme, Craig S. Donald, Lyman J.L. Feron, Galith Karouchi, Philip MacFaul, Thomas Moss, Richard A. Norman, Stuart E. Pearson, Michael Tonge, Gareth Davies, Graeme E. Walker, Zena Wilson, Rachel Rowlinson, Steve Powell, Claire Sadler, Graham Richmond, Brendan Ladd, Erimira Pazolli, Anne Marie Mazzola, Celina D’Cruz, and Chris De Savi

Proteasomal Inhibition by Ixazomib Induces CHK1 and MYC-Dependent Cell Death in T-cell and Hodgkin Lymphoma
Dashnamoorthy Ravi, Afshin Beheshti, Nasséra Abermil, Frank Passero, Jaya Sharma, Michael Coyle, Athena Kritikaris, Irawati Kandela, Lynn Hlatky, Michael V. Sitkovsky, Andrew Mazar, Ronald B. Gartenhaus, and Andrew M. Evans

Sustained Accumulation of Microtubule-Binding Chemotherapy Drugs in the Peripheral Nervous System: Correlations with Time Course and Neurotoxic Severity
Krystyna M. Wozniak, James I. Vornov, Ying Wu, Kensichi Nomoto, Bruce A. Littlefield, Christopher Destandins, Yanke Yu, George Lai, Larisa Reyderman, Nancy Wong, and Barbara S. Slusher

Novel Protein Disulfide Isomerase Inhibitor with Anticancer Activity in Multiple Myeloma
Sergei Vatolin, James G. Phillips, Babal K. Jha, Shrawya Govindgari, Jennifer Hu, Dale Grabowski, Yvonne Parker, Daniel J. Lindner, Fei Zhong, Clark W. Distelhorst, Mitchell R. Smith, Claudio Cotta, Yan Xu, Sujatha Chilakala, Rebecca R. Kuang, Samantha Tall, and Frederic J. Reu
TUMOR AND STEM CELL BIOLOGY

3351 p120 Catenin Suppresses Basal Epithelial Cell Extrusion in Invasive Pancreatic Neoplasia
Audrey M. Hendley, Yue J. Wang, Kishore Polireddy, Janivette Alsina, Ishrat Ahmed, Kelly J. Lafaro, Hao Zhang, Nilotpal Roy, Samuel G. Savidge, Yanna Cao, Matthias Hebrok, Anirban Maitra, Albert B. Reynolds, Michael Goggins, Mamoun Younes, Christine A. Iacobuzio-Donahue, Steven D. Leach, and Jennifer M. Bailey
Précis: These results provide insight into mechanisms controlling early events in the metastatic process, suggesting cancer progression is enhanced by regulating epithelial cell invasion.

3364 c-Myb Enhances Breast Cancer Invasion and Metastasis through the Wnt/β-Catenin/Axin2 Pathway
Yihao Li, Ke Jin, Gabi W. van Pelt, Hans van Dam, Xiao Yu, Wilma E. Mesker, Peter ten Dijke, Fangfang Zhou, and Long Zhang
Précis: These results identify a pathway of breast cancer invasion and metastasis that may provide a general strategy for therapeutic targeting of aggressive disease.

3376 Ly6E/K Signaling to TGFβ Promotes Breast Cancer Progression, Immune Escape, and Drug Resistance
Midrar AlHossiny, Linlin Luo, William R. Frazier, Noriko Steiner, Yuriy Gusev, Bhaskar Kallakury, Eric Glasgow, Karen Creswell, Subha Madhavan, Rakesh Kumar, and Geeta Upadhyay
Précis: This seminal study illustrates the deep connections between the evolution of stem-like cells in cancer and immune escape, also suggesting a rationale for their eradication by immune checkpoint agents.

3387 Ribosomal Protein Rpl22 Controls the Dissemination of T-cell Lymphoma
Précis: Varying the copy number of ribosomal protein Rpl22 produces unexpectedly divergent effects on how and where lethal lymphoid tumors develop.

3397 Autophagy Differentially Regulates Distinct Breast Cancer Stem-like Cells in Murine Models via EGFR/Stat3 and Tgfβ/Smad Signaling
Syn Kok Yeo, Jian Wen, Song Chen, and Jun-Lin Guan
Précis: These preclinical findings uncover a differential dependence of heterogeneous breast cancer stem-like cell populations on two different signaling pathways, with implications on how drug combinations might be better tailored to eradicate these cells and improve therapeutic efficacy.

3411 NOTCH Signaling Regulates Asymmetric Cell Fate of Fast- and Slow-Cycling Colon Cancer–Initiating Cells
Tara Srinivasan, Jewell Walters, Pengcheng Bu, Elaine Bich Than, Kuei-Ling Tung, Kai-Yuan Chen, Nicole Panarelli, Jeff Mihsom, Leonard Augenlicht, Steven M. Lipkin, and Xiling Shen
Précis: These results illuminate the basis for cancer stem-like cell heterogeneity and plasticity in colon cancers by defining slow-cycling and fast-cycling cell subpopulations and a mechanism of interconversion between each.

3422 Oncogenic Mutation of AIMP2/p38 Inhibits Its Tumor-Suppressive Interaction with Smurf2
Dae Gyu Kim, Jin Young Lee, Ji-Hyun Lee, Ha Yeon Cho, Beom Sik Kang, Song-Yee Jang, Myung Hee Kim, Min Gao, Jung Min Han, Seong Jin Kim, and Sung Hoon Kim
Précis: This study provides new insight into the mechanisms controlling MYC-driven oncogenic transformation, highlighting important contributions of tumor suppressive TGFβ signaling.

CORRECTION

3437 Correction: Delivery of Therapeutics Targeting the mRNA-Binding Protein HuR Using 3DNA Nanocarriers Suppresses Ovarian Tumor Growth
ABOUT THE COVER

Myeloid-derived suppressor cells (MDSC) inhibit tumor immunity, prompt breast cancer stemness, and enhance tumorigenic potential. Mechanistically, MDSC-derived IL6 initiates STAT3 phosphorylation, and MDSC-derived nitric oxide activates NOTCH and NOTCH subsequently and collaboratively acts with IL6 to promote prolonged STAT3 activation. Using immunofluorescence, it was found that MDSCs increased ALDH1 expression in tumor cells. For details, see article by Peng and colleagues on page 3156.