BREAKING ADVANCES

1049 Highlights from Recent Cancer Literature

PERSPECTIVE

1051 The Tumor Microenvironment at a Turning Point—Knowledge Gained Over the Last Decade, and Challenges and Opportunities Ahead: A White Paper from the NCI TME Network
Yeasmin DeClerck, Kenneth J. Pienta, Elisa C. Woodhouse, Dinah S. Singer, and Suresh Mohla

MEETING REPORT

1060 Pancreatic Cancer: Progress and Challenges in a Rapidly Moving Field
Eric A. Collisson and Kenneth P. Olive

INTEGRATED SYSTEMS AND TECHNOLOGIES

1063 Novel Hybrid Phenotype Revealed in Small Cell Lung Cancer by a Transcription Factor Network Model That Can Explain Tumor Heterogeneity
Akhata R. Udyavar, David J. Wooten, Megan Hoeksema, Mukesh Bansal, Andrea Calilano, Lourdes Estrada, Santiago Schnell, Jonathan M. Irish, Pierre P. Massion, and Vito Quaranta
Précis: A systems biology gene regulatory network approach reveals a drug-evading phenotype in small cell lung cancer that may ultimately inform our understanding of cancer heterogeneity and its impact on relapse.

MICROENVIRONMENT AND IMMUNOLOGY

1075 Tim-3 Expression on Tumor-Infiltrating PD-1+ CD8+ T Cells Correlates with Poor Clinical Outcome in Renal Cell Carcinoma
Clémence Granier, Charles Dariane, Pierre Combe, Virginie Verkappe, Saik Uti, Séverine Badoual, Hélène Roussel, Marion Mandavitt, Patrice Ravel, Mathilde Sibony, Lucie Bian, Camélia Radulescu, Emeline Vinatier, Nadine Benhamou, Michael Peyromaure, Stéphane Oudard, Arnaud Méjean, Marc-Olivier Timsit, Alain Gey, and Eric Tartour
Précis: This study establishes the negative impact of Tim-3 expression on intratumoral PD1+ CD8+ T cells on the outcome of kidney cancer patients, using a novel automated immunofluorescence technology to identify this T-cell subset.

1083 ROByt+ Innate Lymphoid Cells Promote Lymph Node Metastasis of Breast Cancers
Sheeba Ireshad, Fabian Flores-Borja, Katherine Lawler, James Monpeynery, Rachel Evans, Victoria Male, Peter Gordon, Anthony Cheung, Patrycia Gazinska, Farzana Noor, Felix Wong, Anita Grigoradiis, Gilbert O. Fruhwirth, Paul R. Barber, Natalie Woodman, Dominic Patel, Manuel Rodríguez-Justo, Julie Owen, Stewart G. Martin, Sarah E. Pinder, Cheryl E. Gillett, Simon P. Poland, Simon Ameer-Beg, Frank McCaughan, Leo M. Carlin, Uzma Hasan, David R. Withers, Peter Lane, Borivoj Vojnovic, Sergio A. Quezada, Paul Ellis, Andrew J. Tutt, and Tony Ng
Précis: This seminal study reveals a critical role in lymph node metastasis for innate lymphoid cells, a peculiar class of lymphocytes lacking B- or T-cell receptors whose accumulation in the tumor microenvironment promotes a chemokine milieu that drives invasion of cancer cells into lymphatics.

1097 CXCL-8/IL8 Produced by Diffuse Large B-cell Lymphomas Recruits Neutrophils Expressing a Proliferation-Inducing Ligand APRIL
Sheeba Ireshad, Fabian Flores-Borja, Katherine Lawler, James Monpeynery, Rachel Evans, Victoria Male, Peter Gordon, Anthony Cheung, Patrycia Gazinska, Farzana Noor, Felix Wong, Anita Grigoradiis, Gilbert O. Fruhwirth, Paul R. Barber, Natalie Woodman, Dominic Patel, Manuel Rodríguez-Justo, Julie Owen, Stewart G. Martin, Sarah E. Pinder, Daniel J. Cua, and Renu Jain
Précis: This study identifies a chemokine-directed neutrophil pathway through which tumors of B-cell origin can increase their aggressiveness.

1108 Dual Roles for Regulatory T-cell Depletion and Costimulatory Signaling in Agonistic GITR Targeting for Tumor Immunotherapy
Ashley E. Mahne, Smita Mauze, Barbara Joyce-Shaikh, Jane Xia, Edward P. Bowman, Amy M. Beebe, Daniel J. Cua, and Renu Jain
Précis: These findings from this study help guide the clinical development of GITR antibodies for cancer immunotherapy by identifying important roles for Treg depletion and co-stimulatory signaling in this therapeutic approach to engage antitumor T-cell attack.

1119 IL6 Signaling in Peripheral Blood T Cells Predicts Clinical Outcome in Breast Cancer
Lei Wang, Andrea K. Miyahira, Diana L. Simons, Xuyang Lu, Andrew Y. Chang, Carrie Wang, Maria A. Suni, Vernon C. Maino, Frederick M. Dirbas, John Yim, James Waisman, and Peter P. Lee
Précis: In the peripheral blood of breast cancer patients at diagnosis, naive T cells may display altered cytokine signals that portend immune dysfunction and future relapse.
Anti-folate Receptor-α IgE but not IgG Recruits Macrophages to Attack Tumors via TNFα/MCP-1 Signaling

MOLECULAR AND CELLULAR PATHOBIOLOGY

Cervical Cancer Growth Is Regulated by a c-ABL–PLK1 Signaling Axis
Xu Yang, Gang Chen, Wei Li, Changmin Peng, Yue Zhu, Xiaoming Yang, Teng Li, Cheng Cao, and Huadong Pei

Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation
Pushkar Malakar, Asaf Shilo, Adi Mogilevsky, Ilan Stein, Eli Pilarsky, Yuval Nevo, Hadar Benyamini, Sharona Elgavish, Xinying Zong, Kannanganattu V. Prasanth, and Rotem Karni

SRSF2 Regulates Alternative Splicing to Drive Hepatocellular Carcinoma Development
Chunding Luo, Yuanming Cheng, Yuguo Liu, Linlin Chen, Lina Liu, Ning Wei, Zhiqin Xie, Wenwu Wu, and Ying Feng

PREVENTION AND EPIDEMIOLOGY

An Adolescent and Early Adulthood Dietary Pattern Associated with Inflammation and the Incidence of Breast Cancer
Holly R. Harris, Walter C. Willett, Rita L. Vaidya, and Karin B. Michels

Therapeutics, Targets, and Chemical Biology

Cetuximab Resistance in Head and Neck Cancer Is Mediated by EGFR-K521 Polymorphism

Superior Efficacy and Selectivity of Novel Small-Molecule Kinase Inhibitors of T790M-Mutant EGFR in Preclinical Models of Lung Cancer
Jin Kyung Rho, In Yong Lee, Yun Jung Choi, Chang-Min Choi, Jae-Young Hur, Jong Sung Koh, Jaekyoo Lee, Byung-Chul Suh, Ho-Juhn Song, Paresh Salgaonkar, Jungmi Lee, Jaesang Lee, Dong Sik Jung, Sang-Yeob Kim, Dong-Cheol Woo, In-Jeoung Baek, Joo-Yong Lee, Chang Hoon Ha, Young Hoon Sung, Jeong Kon Kim, Woo Sung Kim, Joon Seon Song, Cheol Heyon Kim, Trever G. Bivona, and Jae Cheol Lee

SRSF2 regulates alternative splicing to drive hepatocellular carcinoma development. These findings identify the splicing factor SRSF2 as a determinant of aberrant RNA splicing in cancer, with possible clinical implications as a candidate prognostic factor in hepatoma patients.
1212  Sunitinib Stimulates Expression of VEGFC by Tumor Cells and Promotes Lymphangiogenesis in Clear Cell Renal Cell Carcinomas
Maeva Dufies, Sandy Giuliano, Damien Ambrosetti, Audrey Claren, Papa Diogop Ndiaye, Michalis Mastri, Walid Moghrabi, Lindsay S. Cooley, Marc Ettaiche, Emmanuel Chamorey, Julien Parola, Valerie Vial, Marilena Lupu-Plesu, Jean Christophe Bernhard, Alain Ravaud, Delphine Borchelli, Jean-Marc Ferrero, Andréas Bikfalvi, John M. Ebos, Khalid Saad Khabar, Renaud Grepin, and Gilles Pages
Précis: These provocative findings concerning the antiangiogenic drug sunitinib used to treat kidney cancer reveal how it can also increase risks of nodal invasion and metastasis, suggesting ideas about how treatment failures may occur.

1227  Gastric Cancer Cell Proliferation and Survival Is Enabled by a Cyclophilin B/STAT3/miR-520d-5p Signaling Feedback Loop
Ting Li, Hanqing Guo, Xiaodi Zhao, Jiang Jin, Lifeng Zhang, Hong Li, Yuanjuan Lu, Yongzhan Nie, Kaichun Wu, Yongquan Shi, and Daiming Fan
Précis: These findings define a positive feedback loop that drives gastric carcinogenesis, as influenced by H. pylori infections that involve stimulation of the procancerous inflammatory cytokine IL6.

ABOUT THE COVER
Agonistic monoclonal antibodies targeting the T-cell receptor coregulatory molecule GITR exert potent therapeutic activities in preclinical tumor models. In this study, the authors show how anti-GITR mAb shifts Treg populations to enable immune attack on tumors. Using bioluminescence as a readout of Tregs in MC38 tumor-bearing Foxp3-GDL mice, in which Foxp3 drives expression of GFP, human diphtheria toxin receptor, and luciferase, the authors observed significant reduction in intratumoral Treg numbers in anti-GITR mAb (DTA-1)-treated mice. For details, see article by Mahne and colleagues on page 1108.