


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
Yves A. 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
Akshata R. Udyavar, David J. Wooten, Megan Hoeksema, Mukesh Bansal, Andrea Califano, 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 Verkarre, Saïk Urien, Cécile Badoual, Hélène Roussel, Marion Mandavit, Patrice Ravel, Mathilde Sibony, Lucie Biard, Camélia Radulescu, Emeline Vinatier, Nadine Benhamouda, 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** ROR γ ⁺ Innate Lymphoid Cells Promote Lymph Node Metastasis of Breast Cancers
Sheeba Irshad, Fabian Flores-Borja, Katherine Lawler, James Monypenny, Rachel Evans, Victoria Male, Peter Gordon, Anthony Cheung, Patrycja Gazinska, Farzana Noor, Felix Wong, Anita Grigoriadis, Gilbert O. Fruhwirth, Paul R. Barber, Natalie Woodman, Dominic Patel, Manuel Rodriguez-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 N.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
Benoit Manfroi, Thomas McKee, Jean Francois Mayol, Sebastien Tabruyn, Sebastien Moret, Christian Villiers, Christian Righini, Martin Dyer, Mary Callanan, Pascal Schneider, Alexandar Tzankov, Thomas Matthes, Nathalie Sturm, and Bertrand Huard
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 costimulatory 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.

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1127 Anti-folate Receptor- α IgE but not IgG Recruits Macrophages to Attack Tumors via TNF α /MCP-1 Signaling



Debra H. Josephs, Heather J. Bax, Tihomir Dodev, Mirella Georgouli, Mano Nakamura, Giulia Pellizzari, Louise Saul, Panagiotis Karagiannis, Anthony Cheung, Cecilia Herraiz, Kristina M. Ilieva, Isabel Correa, Matthew Fittall, Silvia Crescioli, Patrycja Gazinska, Natalie Woodman, Silvia Mele, Giulia Chiaruttini, Amy E. Gilbert, Alexander Koers, Marguerite Bracher, Christopher Selkirk, Heike Lentfer, Claire Barton, Elliott Lever, Gareth Muirhead, Sophia Tsoka, Silvana Canevari, Mariangela Figini, Ana Montes, Noel Downes, David Dombrowicz, Christopher J. Corrigan, Andrew J. Beavil, Frank O. Nestle, Paul S. Jones, Hannah J. Gould, Victoria Sanz-Moreno, Philip J. Blower, James F. Spicer, and Sophia N. Karagiannis

Précis: IgE antibodies, which mediate anti-parasite responses, have been little explored in cancer therapy, and this seminal report shows how they can be used to extend monoclonal antibody technology confined mainly to IgG at present to powerfully reprogram and recruit macrophages to eradicate cancer cells.

MOLECULAR AND CELLULAR PATHOBIOLOGY

1142 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

Précis: This mechanistic study suggests a novel prognostic marker and therapeutic target for improving the personalized management cervical cancer.

1155 Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation

Pushkar Malakar, Asaf Shilo, Adi Mogilevsky, Ilan Stein, Eli Pikarsky, Yuval Nevo, Hadar Benyamini, Sharon Elgavish, Xinying Zong, Kannanganattu V. Prasanth, and Rotem Karni

Précis: These findings show how a proto-oncogenic long noncoding RNA acts in liver cancer to modulate alternative RNA splicing and malignant progression through upregulation of the splice factor SRSF1.

1168 SRSF2 Regulates Alternative Splicing to Drive Hepatocellular Carcinoma Development

Chunling Luo, Yuanming Cheng, Yuguo Liu, Linlin Chen, Lina Liu, Ning Wei, Zhiqin Xie, Wenwu Wu, and Ying Feng

Précis: 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.

PREVENTION AND EPIDEMIOLOGY

1179 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

Précis: A habitual proinflammatory diet during adolescent and early adult years may increase the risk of premenopausal breast cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

1188 Cetuximab Resistance in Head and Neck Cancer Is Mediated by EGFR-K₅₂₁ Polymorphism

Friederike Braig, Malte Kriegs, Minna Voigtlaender, Beate Habel, Tobias Grob, Karina Biskup, Veronique Blanchard, Markus Sack, Anja Thalhammer, Isabel Ben Batalla, Ingke Braren, Simon Laban, Antje Danielczyk, Steffen Goletz, Elzbieta Jakubowicz, Bruno Märkl, Martin Trepel, Rainald Knecht, Kristoffer Riecken, Boris Fehse, Sonja Loges, Carsten Bokemeyer, and Mascha Binder

Précis: These findings correlate cetuximab resistance in head and neck cancer with a frequent EGFR genetic polymorphism, potentially illuminating how to overcome this resistance through other methods to target EGFR.

1200 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 Hyeon Kim, Trevor G. Bivona, and Jae Cheol Lee

Précis: While many EGFR kinase inhibitors exist, the novel compounds described here exhibit improved mutant selectivity and superior potency against brain metastases in multiple preclinical models of lung cancer.

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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 Matri, Walid Moghrabi, Lindsay S. Cooley, Marc Ettaiche, Emmanuel Chamorey, Julien Parola, Valerie Vial, Marilena Lupu-Plesu, Jean Christophe Bernhard, Alain Ravaud, Delphine Borchiellini, Jean-Marc Ferrero, Andréas Bikfalvi, John M. Ebos, Khalid Saad Khabar, Renaud Grépin, and Gilles Pagès

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.

TUMOR AND STEM CELL BIOLOGY

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, Yuanyuan Lu, Yongzhan Nie, Kaichun Wu, Yongquan Shi, and Daiming Fan

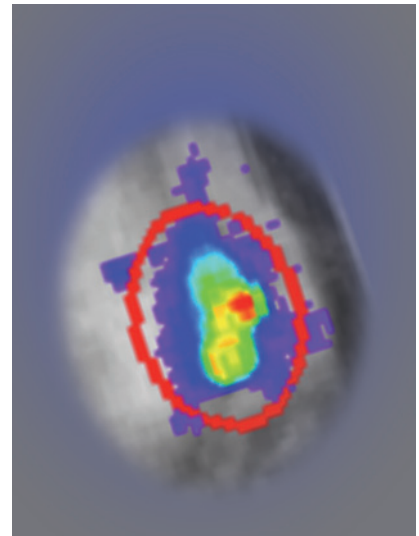
Précis: These findings define a positive feedback loop that drives gastric carcinogenesis, as influenced by H. pylori infections that involve stimulation of the procancerous inflammatory cytokine IL6.

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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.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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