## WHAT WE'RE READING

A Sampling of Highlights from the Literature

## CANCER IMMUNOLOGY AT THE CROSSROADS

Adoptive Immunotherapy with Antigen-Specific T Cells Expressing a Native TCR

Wingchi Leung and Helen E. Heslop

## CANCER IMMUNOLOGY MINIATURE

Immunologic Recognition of a Shared p53 Mutated Neoantigen in a Patient with Metastatic Colorectal Cancer

Winifred Lo, Maria Parkhurst, Paul F. Robbins, Eric Tran, Yong-Chen Lu, Li Jia, Jared J. Gattner, Anna Pasetto, Drew Deniger, Parisa Malekzadeh, Thomas E. Skelton, Todd Prickett, Satyajit Ray, Scott Kivitz, Biman C. Paria, Isaac Kriley, David S. Schrump, and Steven A. Rosenberg

A patient with metastatic colon cancer had T-cell receptors reactive with a mutation in the tumor suppressor gene TP53. The TCRs were neoantigen-specific and HLA-A*0201-restricted and could be used to treat others with tumors sharing the same parameters.

## PRIORITY BRIEFS

Early-Life Microbiota Exposure Restricts Myeloid-Derived Suppressor Cell–Driven Colonic Tumorigenesis

Akihito Harusato, Emilie Viennois, Lucie Etienne-Mesmin, Shingo Matsuyama, Hirohito Abo, Satoru Osuka, Nicholas W. Lukacs, Yuji Naito, Yoshito Itoh, Jian-Dong Li, Didier Merlin, Andrew T. Gewirtz, and Timothy L. Denning

Mice with altered colon microbiota early in life exhibit augmented inflammatory cytokine and chemokine expression in the colon. This led to an increased susceptibility to colitis-associated cancer later in adulthood, demonstrating the microbiota's impact on colon homeostasis.

## RESEARCH ARTICLES

CD96 Is an Immune Checkpoint That Regulates CD8⁺ T-cell Antitumor Function


The antitumor activity of anti-CD96 monotherapy depends on several host factors, including CD8⁺ T cells and immune signaling. Inhibition of CD96 in combination with other immune checkpoint inhibitors shows superior antitumor activity over single or dual agent therapy.

Targeted Delivery of IL2 to the Tumor Stroma Potentiates the Action of Immune Checkpoint Inhibitors by Preferential Activation of NK and CD8⁺ T Cells

Cornelia Hutmacher, Nicolas Gonzalo Núñez, Anna Rita Liuzzi, Burkhard Becher, and Dario Neri

Treatment of murine tumors with combination checkpoint blockade and an antibody-IL2 fusion protein reduces tumor growth, an effect dependent on CD8⁺ T cells and NK cells. These data support the use of engineered IL2 products for anti-cancer therapy.

Sustained Type I Interferon Reinforces NK Cell–Mediated Cancer Immunosurveillance during Chronic Virus Infection

Ji Hoon Oh, Myeong Joon Kim, Seong Jin Choi, Young Ho Ban, Heung Kyu Lee, Eui-Cheol Shin, Kyung-Mi Lee, and Sang-Jun Ha

Chronic LCMV infection delays tumor progression as a result of sustained type I IFN signaling and enhanced NK cell–mediated immunosurveillance. This observation could improve the development of effective treatment strategies for cancer patients with chronic viral infections.

Regulatory T Cells in an Endogenous Mouse Lymphoma Recognize Specific Antigen Peptides and Contribute to Immune Escape

Fatima Ahmetli, Tanja Riedel, Nadine Hölscher, Vera Bauer, Nico Trautwein, Albert Geishauser, Tim Sparwasser, Stefan Stevanović, Martin Röcken, and Ralph Mocikat

In a mouse model of B-cell lymphoma, regulatory T cells suppressed antitumor responses. Treg cells recognized nonmutated self epitopes, which were characteristic of lymphoma and which were related to malignancy.
Automated Analysis of Lymphocytic Infiltration, Tumor Budding, and Their Spatial Relationship Improves Prognostic Accuracy in Colorectal Cancer

Ines P. Nearchou, Kate Lillard, Christos G. Gavriel, Hideki Ueno, David J. Harrison, and Peter D. Caie

Automated image analysis reveals that high tumor bud numbers, low T-cell density, and few T cells proximal to tumor buds were associated with reduced survival of CRC patients. This model provided greater prognostic value than current clinical guidelines.

Intravesical Ty21a Vaccine Promotes Dendritic Cells and T Cell–Mediated Tumor Regression in the MB49 Bladder Cancer Model

Sonia Domingos-Pereira, Karthik Sathiyanadan, Stefano La Rosa, Lenka Poláč, Mathieu F. Chevalier, Paul Martel, Rim Hojeij, Laurent Derré, Jacques-Antoine Haefliger, Patrice Ichilinski, and Denise Nardelli-Haefliger

Low-dose intravesical administration of Ty21a, a commercial typhoid vaccine, generated effective antitumor DC and T-cell responses and improved survival in a mouse model of bladder cancer. These results demonstrate the potential of Ty21a for clinical use.

Low-Dose Apatinib Optimizes Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer

Sha Zhao, Shengxiang Ren, Tao Jiang, Bo Zhu, Xuefei Li, Chao Zhao, Yijun Jia, Jinpeng Shi, Limin Zhang, Xiaoshen Liu, Meng Qiao, Xiaoxia Su, Hui Yu, Caicun Zhou, Jun Zhang, D. Ross Camidge, and Fred R. Hirsch

Both preclinical and phase Ib clinical data indicate that lower-than-conventional doses of the anti-angiogenic agent apatinib (a VEGFR2-TKI) optimized the immunosuppressive tumor microenvironment and potentiated the therapeutic response to anti-PD-1/PD-L1 immunotherapy in lung cancer.

Immune Profiling and Quantitative Analysis Decipher the Clinical Role of Immune-Checkpoint Expression in the Tumor Immune Microenvironment of DLBCL

Ziju Y. Xu-Monette, Min Xiao, Qingyan Au, Raghav Padmanabhan, Bing Xu, Nicholas Hoe, Sandra Rodriguez-Perales, Raul Torres-Ruiz, Ganiraju C. Manyam, Carlo Visco, Yi Miao, Xiaohong Tan, Hongwei Zhang, Alexandar Tzanov, Jing Wang, Kateri Dybkas, Wayne Tam, Hua You, Govind Bhagat, Eric D. Hsi, Maurilio Ponzoni, Andrés J.M. Ferreri, Michael B. Moller, Miguel A. Piris, J. Han van Krieken, Jane N. Winter, Jason R. Westin, Lan V. Pham, L. Jeffrey Medeiros, George Z. Rassidakis, Yong Li, Gordon J. Freeman, and Ken H. Young

The immune profile of the tumor microenvironment in DLBCL patients was assessed with a MultiOmyx platform. PD-1/L1 expression on T cells and PD-L1 expression on macrophages had prognostic value in identification of patients with poor survival after immunotherapy.

CORRECTION

Correction: Collapse of the Plasmacytoid Dendritic Cell Compartment in Advanced Cutaneous Melanomas by Components of the Tumor Cell Secretome

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ABOUT THE COVER

CD96 is an immune checkpoint and is known to suppress T-cell and NK cell effector functions. Thus, CD96 can impair antitumor responses in the tumor microenvironment. Mittal et al. demonstrate that CD96 blockade can inhibit primary tumor growth in multiple tumor models. The effects of anti-CD96 are dependent on several host factors, including CD8⁺ T cells, cytokines, and DNAM-1/CD226 signaling. Because CD96 is co-expressed with other immune checkpoints, especially PD-1, dual and triple blockade protocols were tested. Dual blockade of CD96 and other immune checkpoints is more effective than anti-CD96 monotherapy, and an optimal triple combination blocking CD96, PD-1, and TIGIT is superior over dual combinations. These treatments increase T-cell infiltration and enhance antitumor responses, highlighting that combining the targeting of CD96 with other immune checkpoints could be a strategy for augmenting T-cell responses that suppress tumor growth. Read more in this issue on page 559. Original image from Fig. 3A. Artwork by Lewis Long.