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609 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.

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

Sonia Domingos-Pereira, Karthik Sathiyandan, Stefano La Rosa, Lenka Polák, Mathieu F. Chevalier, Paul Martel, Rim Hojeij, Laurent Derré, Jacques-Antoine Haefliger, Patrice Jichlinski, 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.

630 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, Xiaozhen Liu, Meng Qiao, Xiaoxia Chen, Chunxia 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.

644 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 Rodríguez-Perales, Raul Torres-Ruiz, Ganiraju C. Manyam, Carlo Visco, Yi Miao, Xiaohong Tan, Hongwei Zhang, Alexandar Tzankov, Jing Wang, Karen Dybkær, Wayne Tam, Hua You, Govind Bhagat, Eric D. Hsi, Maurilio Ponzoni, Andrés J.M. Ferreri, Michael B. Møller, 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 immunochemotherapy.

658 Autologous Lymphocyte Infusion Supports Tumor Antigen Vaccine–Induced Immunity in Autologous Stem Cell Transplant for Multiple Myeloma

Adam D. Cohen, Nikolett Lendvai, Sarah Nataraj, Naoko Imai, Achim A. Jungbluth, Ioanna Tsakos, Adeb Rahman, Anna Huo-Chang Mei, Herman Singh, Katarzyna Zarychta, Seunghee Kim-Schulze, Andrew Park, Ralph Venhaus, Katherine Alpaugh, Sacha Gnjatic, and Hearn J. Cho
Immunotherapy can include vaccines in the setting of autologous stem cell transplantation for multiple myeloma. Here, autologous lymphocyte infusion augmented immunotherapy and supported humoral and CD4⁺ helper T-cell immunity in response to a therapeutic tumor vaccine.

670 Radiotherapy and Cisplatin Increase Immunotherapy Efficacy by Enabling Local and Systemic Intratumoral T-cell Activity

Paula Kroon, Elselien Frijlink, Victoria Iglesias-Guimaraes, Andriy Volkov, Marit M. van Buuren, Ton N. Schumacher, Marcel Verheij, Jannie Borst, and Inge Verbrugge
The response to PD-1 blockade and CD137 agonism could be improved by "re-purposing" radiotherapy or cisplatin to modulate the tumor microenvironment. Chemo/radio-immunotherapy enhances CTL responses, tumor regression, and survival in a mouse model of poorly immunogenic breast cancer.

683 T-cell Activity against AML Improved by Dual-Targeted T Cells Stimulated through T-cell and IL7 Receptors

Eric Krawczyk, Sergey N. Zolov, Kevin Huang, and Challice L. Bonifant
An engineered T cell specific for two antigens shows anti-AML activity. Combining CD123 recognition and IL7R activation enhances antitumor activity and T-cell survival in preclinical models, suggesting the value of extending this strategy to other tumor types.

CORRECTION

693 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.

