### WHAT WE'RE READING

347  A Sampling of Highlights from the Literature

### CANCER IMMUNOLOGY AT THE CROSSROADS

348  Antibody–Cytokine Fusions: Versatile Products for the Modulation of Anticancer Immunity

Dario Neri

### PRIORITY BRIEF

355  TIGIT and PD-1 Mark Intratumoral T Cells with Reduced Effector Function in B-cell Non-Hodgkin Lymphoma

Sarah E. Josefsson, Klaus Beiske, Yngvild N. Blaker, Mette S. Førsund, Harald Holte, Bjørn Østenstad, Eva Kimby, Hakan Köksal, Sébastien Wächli, Baoyan Bai, Erlend B. Smeland, Ronald Levy, Arne Kolstad, Kanutte Huse, and June H. Myklebust

Expression of TIGIT and PD-1 correlates with impaired T-cell effector function in intratumoral T cells. TIGIT and PD-1 ligands are expressed in the tumor microenvironment. Combinatorial blockade of TIGIT and PD-1 may be a useful therapy in NHL.

### RESEARCH ARTICLES

363  NK Cells Expressing a Chimeric Activating Receptor Eliminate MDSCs and Rescue Impaired CAR-T Cell Activity against Solid Tumors

Robin Parihar, Charlotte Rivas, Mai Huynh, Bilal Omer, Natalia Lapteva, Leonid S. Metelitsa, Stephen M. Gottschalk, and Cliona M. Rooney

Infusion of NK cells that target myeloid-derived suppressor cells of the solid tumor microenvironment can reduce immunosuppression and recruit and activate antitumor T cells, resulting in enhanced efficacy and durable responses for treatment of patients with solid tumors.

376  CCR2-Dependent Recruitment of Tregs and Monocytes Following Radiotherapy Is Associated with TNFα-Mediated Resistance

Michele Mondini, Pierre-Louis Loyer, Pauline Hamon, Marine Gerbé de Thoré, Marie Laviron, Kevin Berthelot, Céline Clémenson, Benoit I. Salomon, Christophe Combadière, Eric Deutsch, and Alexandre Boissornas

Local radiation therapy of head and neck squamous cell carcinoma tumors induces distinct CCR2-dependent waves of Treg and TNFα-producing monocyte infiltration. TNFα inhibition limits Treg functions and improves radiotherapy efficacy, paving the way for combined radioimmunotherapies.

388  Activated Eosinophils Exert Antitumorigenic Activities in Colorectal Cancer

Hadar Reichman, Michal Itan, Perri Rozenberg, Tal Yarmolovski, Eli Berezowski, Chen Varol, Nathan Gluck, Shiran Shapira, Nadir Arber, Udi Qimron, Danielle Kardo-Aatar, James J. Lee, and Ariel Muniz

Eosinophils, known from the context of allergic inflammation, are also found in various solid tumors including colorectal cancer. The antitumor activities of eosinophils in colorectal cancer are characterized here.

401  Host Immunity Following Near-Infrared Photoimmunotherapy Is Enhanced with PD-1 Checkpoint Blockade to Eradicate Established Antigenic Tumors

Tadanobu Nagaya, Jay Friedman, Yasuhiro Marusoka, Fusa Ogata, Shuhei Okuyama, Paul E. Clavijo, Peter L. Choyke, Clint Allen, and Hidatoka Kobayashi

PD-1 blockade reverses adaptive immune resistance following near-infrared photoinmunotherapy to enhance polyclonal T-cell responses, causing rejection of established syngeneic tumors in both treated and distant untreated tumors. These responses also enhanced immunologic memory development that suppressed recurrence.

414  SUV39H1 Represses the Expression of Cytotoxic T-Lymphocyte Effector Genes to Promote Colon Tumor Immune Evasion


SUV39H1, a H3K9me3-specific histone methyltransferase, was evaluated in the tumor microenvironment of human and mouse colorectal cancer tumors. CTL effector gene expression was repressed by SUV39H1, leading to impaired CTL function that allowed for tumor immune escape.
A CD40 Agonist and PD-1 Antagonist Antibody Reprogram the Microenvironment of Nonimmunogenic Tumors to Allow T-cell–Mediated Anticancer Activity

Hayley S. Ma, Bibhav Poudel, Evangelia Roussos Torres, John-William Sidhom, Tara M. Robinson, Brian Christmas, Blake Scott, Kayla Cruz, Skylar Woolman, Valerie Z. Wall, Todd Armstrong, and Elizabeth M. Jaffee

Reprogramming of the tumor microenvironment from immune resistance to responsiveness was achieved by triple combination therapy with a T cell–inducing vaccine, CD40 agonist, and PD-1 antagonist in mouse models of breast and metastatic pancreatic cancers.

IL2/Anti-IL2 Complex Combined with CTLA-4, But Not PD-1, Blockade Rescues Antitumor NK Cell Function by Regulatory T-cell Modulation

Pamela Caudana, Nicolas Gonzalo Núñez, Philippe De La Rochere, Anaïs Pinto, Jordan Denizeau, Ruby Alonso, Leticia Laura Niborski, Olivier Lantz, Christine Sedlik, and Eliane Piaggio

Combination of IL2/anti-IL2 complexes (IL2Cx) with PD-1 or CTLA-4 pathway blockade controls tumor growth and acts differentially on CD8\(^+\), NK cells, and Treg cells. Only the IL2Cx/anti-CTLA-4 combination is dependent upon NK cells.

Association of Tumor Microenvironment T-cell Repertoire and Mutational Load with Clinical Outcome after Sequential Checkpoint Blockade in Melanoma


Order matters. Clinical outcomes were associated with the mutational and neoantigen loads, and T-cell infiltrates, of pretreatment samples in a checkpoint blockade phase II trial only if nivolumab is used before ipilimumab, but not the reverse sequence.

Rapamycin Prevents Surgery-Induced Immune Dysfunction in Patients with Bladder Cancer


Data from patients and a mouse model show that surgery for bladder cancer causes immune dysfunction and decreases efficacy of immunotherapy. Low-dose rapamycin mitigates these problems through effects on the tumor and through modulating T-cell function.

Endoplasmic Reticulum Stress Contributes to Mitochondrial Exhaustion of CD8\(^+\) T Cells

Katie E. Hurst, Kyle A. Lawrence, Matthew T. Essman, Zeke J. Walton, Lee R. Leddy, and Jessica E. Thaxton

The PERK-mediated chronic stress axis contributes to the mitochondrial exhaustion that PD-1 CD8\(^+\) tumor-infiltrating T cells undergo. Targeting the PERK axis augments T-cell efficacy in tumors and aids anti-PD-1 therapy.

LIN28/let-7/PD-L1 Pathway as a Target for Cancer Immunotherapy

Yanlilian Chen, Chen Xie, Xiaohui Zheng, Xin Nie, Zining Wang, Haiying Liu, and Yong Zhao

PD-L1 expression in cancers is regulated through the LIN28/let-7 pathway and manipulated using the small compound LIN28-inhibitor C1632. Treatment with this compound increases antitumor immunity and inhibits tumor cell growth in vitro and in a mouse breast cancer model.

GM-CSF Promotes Antitumor Immunity by Inducing Th9 Cell Responses

Il-Kyu Kim, Choong-Hyun Koh, Insu Jeon, Kwang-Soo Shin, Tae-Seung Kang, Eun-Ah Ba, Hyungsuk Seo, Hyun-Ja Ko, Byung-Seok Kim, Yeonseok Chung, and Chang-Yul Kang

Granulocyte-macrophage colony-stimulating factor (GM-CSF) functions as an adjuvant for antitumor immunity through an unclear mechanism. By activating monocyte-derived dendritic cells, GM-CSF induces Th9 development and IL9 production, which facilitates antitumor cytotoxic T lymphocyte responses.

Immune-Checkpoint Blockade Opposes CD8\(^+\) T-cell Suppression in Human and Murine Cancer

Lukas W. Pfannenstiel, C. Marcela Diaz-Montero, Ye F. Tian, Joseph Scharpf, Jennifer S. Ko, and Brian R. Gastman

In this study of squamous cell carcinoma of the head and neck, checkpoint blockade therapy prevents development of suppressive CD8\(^+\) T cells that would otherwise dampen antitumor immune responses.

CORRECTION

Phage-Based Anti-HER2 Vaccination Can Circumvent Immune Tolerance against Breast Cancer

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Cytotoxic T lymphocytes (CTLs) play a key role in antitumor immunity, and the function of these cells can be suppressed in the tumor microenvironment (TME). Lu et al. show how epigenetic states in the TME suppress effector functions and can be countered by small molecule–targeted therapy in colon cancer. CTLs infiltrate tumors and have high expression of the histone methyltransferase SUV39H1, which decorates the histone H3K9me3. H3K9me3 is enriched in the promoter region of several key CTL effector genes and suppressed their expression. By specifically targeting SUV39H1 with a small-molecule inhibitor, called F5446, expression of the effector genes is enhanced, and the antitumor function of CTLs in the tumor microenvironment is increased. Read more in this issue on page 414. Original image from Fig. 1. Artwork by Lewis Long.