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### What We’re Reading

1. **A Sampling of Highlights from the Literature**

### In the Spotlight

2. **Tumor Antigen Heterogeneity: The "Elephant in the Room" of Adoptive T-cell Therapy for Solid Tumors**
   - Steven M. Albelda
   - See related article, p. 7

### Meeting Report

3. **Translating Science into Survival: Report on the Fifth International Cancer Immunotherapy Conference**
   - Mustafa Diken, Oliver Kepp, and Arthur N. Brodsky

### Research Articles

7. **Pathogen-Boosted Adoptive Cell Transfer Therapy Induces Endogenous Antitumor Immunity through Antigen Spreading**
   - Gang Xin, Achia Khatun, Paytsar Topchyan, Ryan Zander, Peter J. Volberding, Yao Chen, Jian Shen, Chunmei Fu, Aimin Jiang, William A. See, and Weiguo Cui
   - An adoptive cell therapy approach was developed to overcome tumor antigen escape and provide durable protection against recurrence. It facilitates antigen spreading and enhances endogenous T-cell responses beyond the initially targeted antigen.
   - See related Spotlight, p. 2

19. **Tryptophan 2,3-Dioxygenase Expression Identified in Human Hepatocellular Carcinoma Cells and in Intratumoral Pericytes of Most Cancers**
   - Delia Hoffmann, Tereza Dvorakova, Vincent Stroobant, Caroline Bouzin, Aurélie Daumerie, Marie Solvay, Simon Klaessens, Marie-Claire Letellier, Jean-Christophe Renaud, Nicolas van Baren, Julie Lelotte, Etienne Marbaix, and Benoit J. Van den Eynde
   - Immunosuppressive tumor microenvironments are supported by tryptophan catabolism. Human mAbs identify expression of the catabolic enzyme TDO by a subset of tumors, including hepatocellular carcinoma, whereas other cancers restrict expression to intratumoral pericytes, suggesting a role in neoangiogenesis.
   - See related article, p. 32

32. **Inhibition of Tryptophan-Dioxygenase Activity Increases the Antitumor Efficacy of Immune Checkpoint Inhibitors**
   - Florence Schramme, Stefano Crosignani, Kim Frederix, Delia Hoffmann, Luc Pilotte, Vincent Stroobant, Julie Preillon, Gregory Driessens, and Benoit J. Van den Eynde
   - Tryptophan catabolism contributes to tumor immune escape, so inhibiting it could improve antitumor immune therapies. Response to immune checkpoint blockade is enhanced when used with the TDO inhibitor PF06845102/EOS200809 or when administered to TDO-KO mice.
   - See related article, p. 19

46. **A Neuropilin-1 Antagonist Exerts Antitumor Immunity by Inhibiting the Suppressive Function of Intratumoral Regulatory T Cells**
   - Keunok Jung, Jeong-Ah Kim, Ye-Jin Kim, Hyun Woo Lee, Chul-Ho Kim, Seokjin Haam, and Yong-Sung Kim
   - T regulatory cells (T<sub>reg</sub>) are a common immune suppressive cell in the tumor microenvironment. Inhibiting suppressive intratumoral T<sub>reg</sub> with an NRP1 antagonist improves antitumor CD8+ T-cell responses and inhibits tumor growth.
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57  A High-Avidity T-cell Receptor Redirects Natural Killer T-cell Specificity and Outcompetes the Endogenous Invariant T-cell Receptor
Elisa Landoni, Christof C. Smith, Giovanni Fucá, Yuhui Chen, Chuang Sun, Benjamin G. Vincent, Leonid S. Metelitsa, Gianpietro Dotti, and Barbara Savoldo

NKT cells expressing functional TCRs have advantages over engineered T cells. TCR+ NKT cells downregulate their invariant TCR, avoiding further engineering for optimal TCR expression and preventing TCR-chain mispairing, and show antitumor efficacy in preclinical models.

70  Combined Vaccination with NY-ESO-1 Protein, Poly-ICLC, and Montanide Improves Humoral and Cellular Immune Responses in Patients with High-Risk Melanoma
Anna Pavlick, Ana B. Blazquez, Marcia Meseck, Michael Lattanzi, Patrick A. Ott, Thomas U. Marron, Rose Marie Holman, John Mandelli, Andres M. Salazar, Christopher B. McClain, Gustavo Gimenez, Sreekumar Balan, Sacha Gnijatic, Rachel Lubong Sabado, and Nina Bhardwaj

Vaccination with NY-ESO-1, poly-ICLC, and montanide induces integrated antigen-specific humoral and cellular responses in patients at high-risk, resected melanoma. In the future, this strategy could be combined with checkpoint blockade immunotherapy, the current standard of care for these patients.

81  XCL1/Glypican-3 Fusion Gene Immunization Generates Potent Antitumor Cellular Immunity and Enhances Anti-PD-1 Efficacy
Kun Chen, Zhiyuan Wu, Hong Zhao, Yanmei Wang, Yutong Ge, Dongmei Wang, Zhengliang Li, Changming An, Yuying Liu, Fefei Wang, Xinyu Bi, Hongying Zhang, Jianqiang Cai, Chunhong Ma, and Chunfeng Qu

Enhancing tumor-specific T-cell responses with vaccination can promote antitumor efficacy. Immunization with XCL1-GPC3 delays growth of liver cancer and improves anti-PD-1 efficacy by de novo generation of GPC3-specific CD8+ T cells.

94  Assessing the Magnitude of Immunogenic Cell Death Following Chemotherapy and Irradiation Reveals a New Strategy to Treat Pancreatic Cancer
Jian Ye, Bradley N. Mills, Tony Zhao, Booyeon J. Han, Joseph D. Murphy, Ankit P. Patel, Carl J. Johnston, Edith M. Lord, Brian A. Belt, David C. Linehan, and Scott A. Gerber


108 Changes in CT Radiomic Features Associated with Lymphocyte Distribution Predict Overall Survival and Response to Immunotherapy in Non-Small Cell Lung Cancer
Mohammadhadi Khorrami, Prateek Prasanna, Amit Gupta, Pradnya Patil, Priya D. Velu, Rajat Thawani, German Corroder, Mehdi Alilou, Kaustav Bera, Pingfu Fu, Michael Feldman, Vamsidhar Velcheti, and Anant Madabhushi

An approach was developed that utilizes features of CT imaging to identify early responses to immune checkpoint blockade, help predict overall survival, and establish associations with tumor-infiltrating lymphocytes.

120 IgA-Mediated Killing of Tumor Cells by Neutrophils Is Enhanced by CD47-SIRPα Checkpoint Inhibition

Modulating myeloid effector cells can improve the efficacy of anticancer monoclonal antibody therapy. Blocking the binding of myeloid CD47 to SIRPα enhances IgA-dependent cytotoxicity against cancer cells.

131 Myeloid Cells Orchestrate Systemic Immunosuppression, Impairing the Efficacy of Immunotherapy against HPV+ Cancers
Gabriele Galliverti, Stephan Wullschleger, Mélanie Tichet, Dhaarini Murugan, Nadine Zangger, Wesley Horton, Alan J. Korman, Lisa M. Coussens, Melody A. Swartz, and Douglas Hanahan

HPV-driven cancers have immunosuppressive microenvironments, making them poorly responsive to immunotherapy. In a cervical cancer mouse model, myeloid cells inhibit CD8+ T-cell function and dendritic cell activation, limiting the efficacy of antitumor vaccination plus immune checkpoint blockade.

146 TCR Repertoire Diversity of Peripheral PD-1+ CDB+ T Cells Predicts Clinical Outcomes after Immunotherapy in Patients with Non-Small Cell Lung Cancer
Jiefei Han, Jianchun Duan, Hua Bai, Yuqi Wang, Rui Wan, Xin Wang, Si Chen, Yanhua Tian, Di Wang, Kailun Fei, Zhuoran Yao, Shuhang Wang, Zhimin Lu, Zhiyue Wang, and Jing Wang

Noninvasive predictors of responses to immune checkpoint blockade are needed. Greater T-cell receptor repertoire diversity of peripheral blood PD-1+CD8+ T cells is associated with better survival after anti-PD-1/PD-L1 therapy in the context of non-small cell lung cancers.

155 Acknowledgment to Reviewers

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ABOUT THE COVER

Tumors can utilize tryptophan catabolism, via indoleamine 2,3-dioxygenase (IDO1) or tryptophan 2,3-dioxygenase (TDO), to evade antitumor immunity. Although IDO1 is expressed in various tumors and is an antitumor therapeutic target, tumoral TDO expression is poorly characterized, so its usefulness as part of a cancer treatment remains untested. To improve the characterization of TDO, Hoffmann et al. develop TDO-specific monoclonal antibodies and find that most human cancers express TDO; TDO can be expressed on tumor cells or the pericytes of the tumor microenvironment, depending on the tumor type. Schramme et al. develop a small-molecule inhibitor of TDO that improves the antitumor efficacy of immune checkpoint blockade in a TDO-dependent manner. Together, the articles from the Van den Eynde laboratory establish the role of TDO in tumor immune evasion. To read more, Hoffmann et al. begins on page 19 and Schramme et al. begins on page 32. Original immunofluorescence imaging of TDO expression (orange) in human glioblastoma by the Van den Eynde laboratory. Artwork by Lewis Long.