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# Cancer Immunology Research

Illuminating the Interplay of Cancer and the Immune System

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Marcela V. Maus, Andrew R. Haas, Gregory L. Beatty, Steven M. Albelda, Bruce L. Levine, Xiaojun Liu, Yangbing Zhao, Michael Kalos, and Carl H. June

*Synopsis:* Chimeric antigen receptor-expressing T cells (CAR-T cells) represent a promising, novel form of adoptive immunotherapy to overcome tolerance to cancer. Using an intermittent dosing schedule of autologous CAR-T cells electroporated with mRNA encoding a hybrid single chain molecule comprising the extracellular domain of murine monoclonal antibody against human mesothelin and the human transmembrane and cytoplasmic T-cell signaling domains, Maus and colleagues characterized and reported a serious adverse event that occurred in one of four patients receiving repeated modified T-cell infusions, with proposed modifications to address and minimize future adverse occurrence.

## RESEARCH ARTICLES

- 32 | **Anti-CTLA-4 Antibodies of IgG2a Isotype Enhance Antitumor Activity through Reduction of Intratumoral Regulatory T Cells**

Mark J. Selby, John J. Engelhardt, Michael Quigley, Karla A. Henning, Timothy Chen, Mohan Srinivasan, and Alan J. Korman

*Synopsis:* The therapeutic potential of CTLA-4 blockade is evident in the ability of anti-CTLA-4 antibody to induce regression of established tumors. In an elegant set of experiments using a panel of murine immunoglobulin in various isotypes, Selby and colleagues delineated the mechanism of action of CTLA-4 blockade. Anti-CTLA-4 promotes antitumor activity by a selective reduction of intratumoral T-regulatory cells along with concomitant activation of T-effector cells.

**Chimeric Antigen Receptor T Cells with Dissociated Signaling Domains Exhibit Focused Antitumor Activity with Reduced Potential for Toxicity *In Vivo***

Evrpidis Lanitis, Mathilde Poussin, Alex W. Klattenhoff, Degang Song, Raphael Sandaltzopoulos, Carl H. June, and Daniel J. Powell Jr

*Synopsis:* To decrease therapy-induced autoimmunity due to on-target toxicity against normal tissues, Lanitis and colleagues developed a trans-signaling CAR-based immunotherapy strategy in which the T-cell activation signal is physically dissociated from the costimulatory signal in two CARs of differing antigen specificity. Their findings show that this dual-specificity, trans-signaling CAR approach can potentiate the therapeutic efficacy of CAR-T cells against cancer while minimizing parallel reactivity against normal tissues bearing single antigen.

**PD-L1 Expression in the Merkel Cell Carcinoma Microenvironment: Association with Inflammation, Merkel Cell Polyomavirus, and Overall Survival**

Evan J. Lipson, Jeremy G. Vincent, Myriam Loyo, Luciane T. Kagohara, Brandon S. Lubber, Hao Wang, Haiying Xu, Suresh K. Nayar, Timothy S. Wang, David Sidransky, Robert A. Anders, Suzanne L. Topalian, and Janis M. Taube

*Synopsis:* Using paraffin-embedded specimens from 49 patients diagnosed with various stages of Merkel cell carcinoma (MCC), Lipson and colleagues found PD-L1 expression in approximately 50% of these rare tumors. PD-L1<sup>+</sup> carcinomas were invariably associated with immune infiltrates and the presence of Merkel cell polyomavirus DNA. These findings suggest that an endogenous immune response, perhaps directed in part to MCC-related antigen, promotes PD-L1 expression in the tumor microenvironment and provide a rationale for investigating therapies blocking PD-1/PD-L1 for patients with MCC.

**Myeloid-Derived Suppressor Cells Attenuate T<sub>H</sub>1 Development through IL-6 Production to Promote Tumor Progression**

Hirotake Tsukamoto, Ryutarō Nishikata, Satoru Senju, and Yasuharu Nishimura

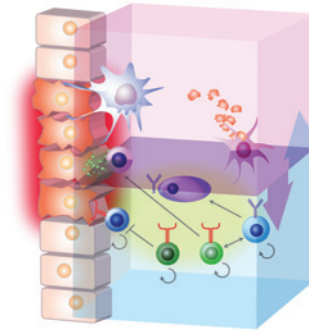
*Synopsis:* IL-6<sup>+/+</sup> MDSC dampened the induction of T<sub>H</sub>1 cells and CD4<sup>+</sup> T-cell cognate help for CD8<sup>+</sup> T cells, and temporal blockade of IL-6 activity at the T-cell priming phase restored T<sub>H</sub>1 cell differentiation. Tsukamoto and colleagues identify Gr-1<sup>+</sup> MDSC as a source of IL-6 in tumor-bearing mice and show that IL-6<sup>+/+</sup> MDSC-sensitized CD4<sup>+</sup> T cells were less potent in mounting antitumor immune responses. In the aggregate, these results suggest that MDSC-derived IL-6 contributes to the dysfunction of host antitumor responses.

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## ABOUT THE COVER

Host immune defense comprises a hard-wired mechanism for immediate generalized responses called innate immunity, and a precise circuitry for mounting specific responses called adaptive immunity. Innate immune responses include the complement cascade, macrophages, natural killer cells, and dendritic cells. Components of adaptive immune responses include plasma cells, antibodies, and lymphocytes. The two systems operate in a highly interconnected manner. Cancer arises when immune recognition, innate, and adaptive immune responses by the host fail. The cover image depicts a schematic diagram of immune surveillance and cancer. For details, see the Masters of Immunology article by Hidde Ploegh on page 5 of this issue.

[The cover image was rendered by Tom DiCesare (Whitehead Institute for Biomedical Research), and was adapted from Ploegh, HL. Viral strategies of immune evasion. *Science* 1998;280:248–53.]



## ABOUT THE MASTER

Hidde L. Ploegh is a professor of biology at Massachusetts Institute of Technology and a member of the Whitehead Institute for Biomedical Research in Cambridge, MA; prior to this appointment, he directed the immunology graduate program (1997–2005) at Harvard Medical School. He received his PhD in 1981 from the University of Leiden, the Netherlands, and performed the research for his doctoral thesis in Jack Strominger's lab at Harvard. Prior to his affiliation with Harvard, Dr. Ploegh served as a junior group leader in the immunology division led by Klaus Rajewsky at the University of Cologne in Germany. Dr. Ploegh has published over 400 papers, with topics spanning the range from how viruses evade immune surveillance to how the host innate and adaptive immune responses distinguish self from non-self and how professional antigen-presenting dendritic cells sense the presence of antigens and instruct the immune response. The Ploegh lab has contributed significantly to research on how products of the major histocompatibility complex are assembled and delivered to help initiate immune responses.



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