

IN THE SPOTLIGHT

643 Remote Controlled CARs: Towards a Safer Therapy for Leukemia

Carl H. June

[See related article, p. 658.](#)

CANCER IMMUNOLOGY MINIATURES

644 Effector Regulatory T Cells Reflect the Equilibrium between Antitumor Immunity and Autoimmunity in Adult T-cell Leukemia

Hiroshi Ureshino, Takero Shindo, Hiroyoshi Nishikawa, Nobukazu Watanabe, Eri Watanabe, Natsuko Satoh, Kazutaka Kitaura, Hiroaki Kitamura, Kazuko Doi, Kotaro Nagase, Hiromi Kimura, Makoto Samukawa, Susumu Kusunoki, Masaharu Miyahara, Tadasu Shin-I, Ryuji Suzuki, Shimon Sakaguchi, and Shinya Kimura
Anti-CCR4 treatment of ATL destroys leukemic and normal Tregs, which can lead to autoimmunity. Only leukemic Tregs expressed CADM1, distinguishing the two populations. Treg depletion was associated with autoimmunity and Treg reemergence with relapse of ATL.

PRIORITY BRIEF

650 Interferon- γ Production by Peripheral Lymphocytes Predicts Survival of Tumor-Bearing Mice Receiving Dual PD-1/CTLA-4 Blockade

Michael J. McNamara, Ian Hilgart-Martiszus, Diego M. Barragan Echenique, Stefanie N. Linch, Melissa J. Kasiewicz, and William L. Redmond
PD-1/CTLA-4 dual blockade has shown substantial promise against refractory tumors in some patients. Biomarkers were sought to identify patients early in treatment who are responding positively. Strong production of IFN γ shortly after treatment commenced significantly correlated with survival.

RESEARCH ARTICLES

658 A Tet-On Inducible System for Controlling CD19-Chimeric Antigen Receptor Expression upon Drug Administration

Reona Sakemura, Seitaro Terakura, Keisuke Watanabe, Jakrawadee Julamanee, Erina Takagi, Kotaro Miyao, Daisuke Koyama, Tatsunori Goto, Ryo Hanajiri, Tetsuya Nishida, Makoto Murata, and Hitoshi Kiyoi
On-target/off-tumor effects can be problematic if the antigen target for CAR T-cell therapy is also expressed on normal tissue. An inducible CAR expression strategy was used that controlled CAR expression and shows promise in discriminating between tumor and B-cell expression of CD19.
[See related Spotlight, p. 643.](#)

669 Durable Complete Response from Metastatic Melanoma after Transfer of Autologous T Cells Recognizing 10 Mutated Tumor Antigens

Todd D. Prickett, Jessica S. Crystal, Cyrille J. Cohen, Anna Pasetto, Maria R. Parkhurst, Jared J. Gartner, Xin Yao, Rong Wang, Alena Gros, Yong F. Li, Mona El-Gamil, Kasia Trebska-McGowan, Steven A. Rosenberg, and Paul F. Robbins
The T cells from a patient with a complete durable response after autologous TIL therapy were examined. They recognized multiple mutated tumor antigens and persisted long term, providing evidence for the mechanisms behind efficacious TIL therapy.

679 Immune Profiling of Adenoid Cystic Carcinoma: PD-L2 Expression and Associations with Tumor-Infiltrating Lymphocytes

Vishwajith Sridharan, Evisa Gjini, Xiaoyun Liao, Nicole G. Chau, Robert I. Haddad, Mariano Severgnini, Peter Hammerman, Adel El-Naggar, Gordon J. Freeman, F. Stephen Hodi, Scott J. Rodig, Glenn Dranoff, and Jonathan D. Schoenfeld
PD-1 ligand expression and T-cell infiltration may predict responsiveness to PD-1 pathway inhibitors. ACC tumors expressed PD-L2 and the Wnt and PI3K pathways but had little immune infiltration. Chemoradiotherapy promoted antitumor responses, suggesting potential synergies with PD-1 blockade.

688 HER2-Targeted Polyinosine/Polycytosine Therapy Inhibits Tumor Growth and Modulates the Tumor Immune Microenvironment

Maya Zigler, Alexei Shir, Salim Joubran, Anna Sagalov, Shoshana Klein, Nufar Edinger, Jeffrey Lau, Shang-Fan Yu, Gabriel Mizraji, Anat Globerson Levin, Mark X. Sliwkowski, and Alexander Levitzki
HER2 is overexpressed in many breast tumors. A therapy was developed that targeted pIC (a TLR3 ligand) to HER2-positive tumors. Tumor growth was significantly inhibited, and antitumor immunity was activated via multiple signaling pathways.

Table of Contents

698 Lenalidomide Induces Interleukin-21 Production by T Cells and Enhances IL21-Mediated Cytotoxicity in Chronic Lymphocytic Leukemia B Cells

Rebekah L. Browning, William H. Byrd, Nikhil Gupta, Jeffrey Jones, Xiaokui Mo, Erin Hertlein, Lianbo Yu, Natarajan Muthusamy, and John C. Byrd
Lenalidomide is a potential therapy for patients with CLL. It induces IL21 production by T cells while increasing IL21 receptors on CLL B cells, with concomitant cytotoxicity to CLL B cells, operating through multiple mechanisms.

708 Cross-talk between 4-1BB and TLR1–TLR2 Signaling in CD8⁺ T Cells Regulates TLR2's Costimulatory Effects

Ann Mary Joseph, Ratika Srivastava, Jovanny Zabaleta, and Eduardo Davila

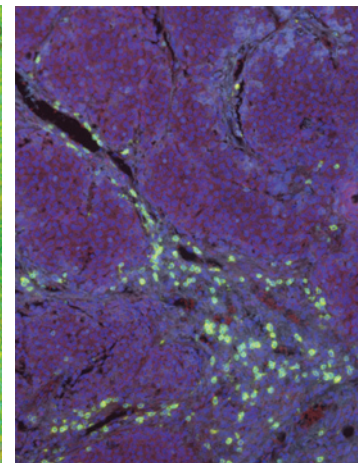
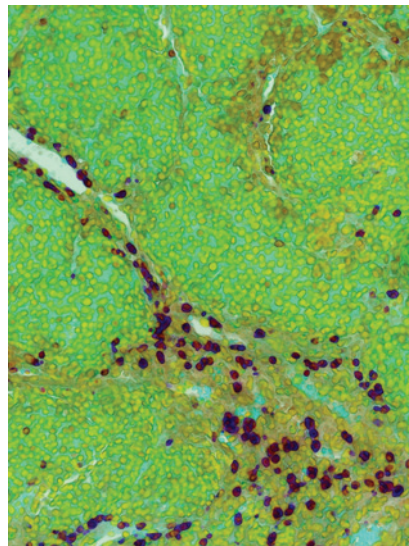
The mechanisms underlying the costimulatory effects of TLR2 engagement on T cells are poorly understood. Costimulatory TLR1–TLR2 signaling in CD8⁺ T cells was found to be largely mediated by 4-1BB and contributes to mounting an antitumor immune response.

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ABOUT THE COVER

At their best, T cells kill tumors and can provide long-term protection against recurrence. However, T cells need to overcome two major obstacles. First, after T-cell stimulation, CTLA-4 is expressed and suppresses further proliferation. Second, activated T cells upregulate the inhibitory receptor PD-1, the ligands for which are frequently found within tumors, shutting down infiltrating T cells. Blocking either of these checkpoints initiates antitumor immune responses in a segment of the patient population. To increase the percentage of responding patients, clinicians are testing combinations of these two checkpoint inhibitors, but this dual treatment increases the number and severity of immune-related complications. Early identification of which patients are responding would be key. McNamara and colleagues have screened multiple mouse models early in the course of treatment for prognostic biomarkers in blood. Peripheral blood lymphocytes of responders produced large amounts of IFN γ and were better at predicting response than other markers that were assayed. The cover art (left) is based on an original micrograph (right) showing CD3⁺CD8⁺ T cells (green/yellow) infiltrating a murine breast tumor that had been treated with combination anti-checkpoint therapies. This image was captured by Mohammad Farhad and supplied by the Redmond laboratory at the Earle A. Chiles Research Institute, Portland, Oregon. Artwork is by Lewis Long. Read more starting on page 650 of this issue of *Cancer Immunology Research*.



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