


MASTERS OF IMMUNOLOGY

- 425**  The Regulatory Role of Invariant NKT Cells in Tumor Immunity
Rosanna M. McEwen-Smith, Mariolina Salio, and Vincenzo Cerundolo

CANCER IMMUNOLOGY AT THE CROSSROADS: COMPLEMENTARY THERAPEUTIC MODALITIES

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Leisha A. Emens and Gary Middleton

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CANCER IMMUNOLOGY MINIATURES

- 449** Virotherapy with a Semliki Forest Virus–Based Vector Encoding IL12 Synergizes with PD-1/PD-L1 Blockade
José I. Quetglas, Sara Labiano, M. Ángela Aznar, Elixabet Bolaños, Arantza Azpilikueta, Inmaculada Rodriguez, Erkuden Casales, Alfonso R. Sánchez-Paulete, Víctor Segura, Cristian Smerdou, and Ignacio Melero
Synopsis: Quetglas and colleagues report that intratumoral injection of cytolytic nonreplicative Semliki Forest virus vector expressing IL12, along with systemic administration of anti-PD-1/PD-L1 antibodies, induced regression of both virally injected and distal tumors and synergistically prolonged survival in mouse tumor models.

PRIORITY BRIEF

- 455** CD4⁺ T-Helper Type 1 Cytokines and Trastuzumab Facilitate CD8⁺ T-cell Targeting of HER2/*neu*-Expressing Cancers
Jashodeep Datta, Shuwen Xu, Cinthia Rosembli, Jenessa B. Smith, Jessica A. Cintolo, Daniel J. Powell Jr, and Brian J. Czerniecki
Synopsis: Datta, Xu, and colleagues show that IFN γ /TNF α and anti-HER2 antibody cooperate to restore MHC class I expression on HER2-overexpressing cancer cells, facilitating their recognition and lysis by CD8⁺ T cells, and suggest that such combinations may be used for optimal HER2-directed CD8⁺ T-cell immunotherapy.

RESEARCH ARTICLE

- 464** Survivorship in Immune Therapy: Assessing Chronic Immune Toxicities, Health Outcomes, and Functional Status among Long-term Ipilimumab Survivors at a Single Referral Center
Douglas B. Johnson, Debra L. Friedman, Elizabeth Berry, Ilka Decker, Fei Ye, Shilin Zhao, Alicia K. Morgans, Igor Puzanov, Jeffrey A. Sosman, and Christine M. Lovly
Synopsis: Johnson and colleagues performed a retrospective analysis of the medical records of 33 melanoma patients who survived more than 2 years after receiving ipilimumab for metastatic disease or as an adjuvant therapy, and report the long-term health outcomes, chronic side effects, and functional status of these patients.

COMMENTARY

- 470** Serial Killers and Mass Murderers: Engineered T Cells Are up to the Task
Carl H. June
See related articles, p. 473 and p. 483

RESEARCH ARTICLES

- 473** Individual Motile CD4⁺ T Cells Can Participate in Efficient Multikilling through Conjugation to Multiple Tumor Cells
Ivan Liadi, Harjeet Singh, Gabrielle Romain, Nicolas Rey-Villamizar, Amine Merouane, Jay R.T. Adolacion, Partow Kebriaei, Helen Huls, Peng Qiu, Badrinath Roysam, Laurence J.N. Cooper, and Navin Varadarajan
Synopsis: Liadi, Singh, and colleagues used Time-lapse Imaging Microscopy In Nanowell Grids (TIMING) to show that CD4⁺ CD19-chimeric antigen receptor (CAR⁺) T cells participate in multikilling of tumor cells with slower kinetics of killing than CD8⁺CAR⁺ T cells, but high motility subgroups of both T-cell subsets have similar kinetics.
See related commentary, p. 470
- 483** CAR-T Cells Inflict Sequential Killing of Multiple Tumor Target Cells
Alexander J. Davenport, Misty R. Jenkins, Ryan S. Cross, Carmen S. Yong, H. Miles Prince, David S. Ritchie, Joseph A. Trapani, Michael H. Kershaw, Phillip K. Darcy, and Paul J. Neeson
Synopsis: Davenport, Jenkins, and colleagues used time-lapse microscopy and CD8⁺ T cells coexpressing TCRs and CARs for different antigens to show that CAR T cells can kill multiple tumor cells; engagement via CAR or TCR did not affect killing kinetics; T cells detached faster when CAR was engaged; and CARs are downregulated over time.
See related commentary, p. 470

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- 495** **Arming the Melanoma Sentinel Lymph Node through Local Administration of CpG-B and GM-CSF: Recruitment and Activation of BDCA3/CD141⁺ Dendritic Cells and Enhanced Cross-Presentation**
Berbel J.R. Sluijter, Mari F.C.M. van den Hout, Bas D. Koster, Paul A.M. van Leeuwen, Famke L. Schneiders, Rieneke van de Ven, Barbara G. Molenkamp, Saskia Vosslamber, Cornelis L. Verweij, M. Petrousjka van den Tol, Alfons J.M. van den Eertwegh, Rik J. Scheper, and Tanja D. de Gruijl
Synopsis: Sluijter and colleagues report that intradermal injection of combined CpG/GM-CSF at the primary melanoma excision site prior to removal of sentinel lymph nodes (SLN) led to recruitment of BDCA3⁺ conventional dendritic cell (cDC) precursors from blood and enhanced DC maturation with selective increase of SLN-resident CLEC9A/BDCA3/CD141⁺ cDCs.
- 506** **Adenosine Receptor 2A Blockade Increases the Efficacy of Anti-PD-1 through Enhanced Antitumor T-cell Responses**
Paul A. Beavis, Nicole Milenkovski, Melissa A. Henderson, Liza B. John, Bertrand Allard, Sherene Loi, Michael H. Kershaw, John Stagg, and Phillip K. Darcy
Synopsis: Beavis, Milenkovski, and colleagues reveal that adenosine receptor blockade enhanced anti-PD-1 efficacy against CD73⁺ tumors in two mouse models via augmentation of tumor-infiltrating CD8⁺ T-cell effector function by increasing IFN γ and Granzyme B production and suggest CD73 expression as a biomarker for anti-PD-1 efficacy.
- 518** **T_H2-Polarized CD4⁺ T Cells and Macrophages Limit Efficacy of Radiotherapy**
Stephen L. Shiao, Brian Ruffell, David G. DeNardo, Bruce A. Faddegon, Catherine C. Park, and Lisa M. Coussens
Synopsis: Shiao and colleagues report that inhibiting either macrophage recruitment by CSF-1/CSF-1R-blockade, or macrophage polarization by IL4/13 neutralization, delayed tumor regrowth after radiotherapy or chemotherapy, demonstrating that macrophage antagonists improve responses to cytotoxic therapies.
- 526** **STAT3 Signaling Is Required for Optimal Regression of Large Established Tumors in Mice Treated with Anti-OX40 and TGF β Receptor Blockade**
 Todd A. Triplett, Christopher G. Tucker, Kendra C. Triplett, Zefora Alderman, Lihong Sun, Leona E. Ling, Emmanuel T. Akporiaye, and Andrew D. Weinberg
Synopsis: Triplett, Tucker, and colleagues show that combination cancer therapy using an OX40 agonist and TGF β receptor blockade depends in part on STAT3 signaling by OX40-expressing T cells; this combination increases intratumoral CD4 and CD8 T-cell functions, which are dampened in the absence of STAT3 signaling.
- 536** **Cytomegalovirus-Based Vaccine Expressing a Modified Tumor Antigen Induces Potent Tumor-Specific CD8⁺ T-cell Response and Protects Mice from Melanoma**
Zhijuan Qiu, Huakang Huang, Jeremy M. Grenier, Oriana A. Perez, Henry M. Smilowitz, Barbara Adler, and Kamal M. Khanna
Synopsis: Qiu and colleagues used cytomegalovirus (CMV)-based prophylactic and therapeutic vaccines expressing foreign or modified self-tumor antigens in a B16 lung metastatic melanoma model and show that these vaccines induced protective antitumor CD8⁺ T-cell responses even in the presence of preexisting anti-CMV immunity.
- 547** **Targeting Interleukin-2 to the Bone Marrow Stroma for Therapy of Acute Myeloid Leukemia Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation**
Christoph Schliemann, Katrin L. Gutbrodt, Andrea Kerkhoff, Michele Pohlen, Stefanie Wiebe, Gerda Silling, Linus Angenendt, Torsten Kessler, Rolf M. Mesters, Leonardo Giovannoni, Michael Schäfers, Bianca Altvater, Claudia Rossig, Inga Grünwald, Eva Wardelmann, Gabriele Köhler, Dario Neri, Matthias Stelljes, and Wolfgang E. Berdel
Synopsis: Schliemann and colleagues report the use of immunocytokine F16-IL2 in combination with low-dose cytarabine in four patients with relapsed AML after allogeneic hematopoietic stem-cell transplantation; antibody-mediated delivery of IL2 to the AML stroma can activate immune effector cells in the bone marrow of patients.



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- 557** Systemic Agonistic Anti-CD40 Treatment of Tumor-Bearing Mice Modulates Hepatic Myeloid-Suppressive Cells and Causes Immune-Mediated Liver Damage
José Medina-Echeverz, Chi Ma, Austin G. Duffy, Tobias Eggert, Nga Hawk, David E. Kleiner, Firouzeh Korangy, and Tim F. Greten
Synopsis: Medina-Echeverz and colleagues show that agonistic anti-CD40 activates tumor-induced CD80⁺ and CD40⁺ hepatic myeloid-derived suppressor cells (MDSC), which cause ROS-mediated hepatotoxicity; these results are recapitulated in human CD14⁺HLA⁻DR^{low} MDSCs, which lose arginase expression and suppressor function in vitro.

- 567** *Ex Vivo* Antibody-Dependent Cellular Cytotoxicity Inducibility Predicts Efficacy of Cetuximab
Rodney J. Taylor, Vassiliki Saloura, Ajay Jain, Olga Goloubeva, Stuart Wong, Shari Kronsberg, Madhavi Nagilla, Lorna Silpino, Jonas de Souza, Tanguy Seiwert, Everett Vokes, Victoria Villaflor, and Ezra E.W. Cohen
Synopsis: Taylor and colleagues studied patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with cetuximab and lenalidomide and report that enhanced ex vivo antibody-dependent cellular cytotoxicity and innate immunity best predicted clinical responses.

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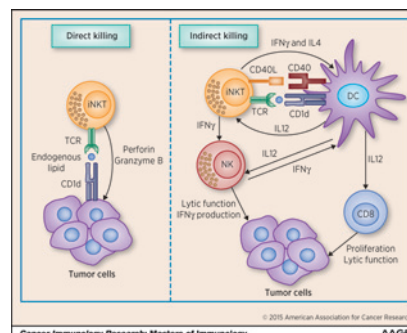
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ABOUT THE COVER

Invariant natural killer T (iNKT) cells are a unique population of T lymphocytes that lies at the interface between the innate and adaptive immune systems, and they are important mediators of immune responses and tumor surveillance. iNKT cells can recognize endogenous lipids presented by CD1d molecules on tumor cells and release Perforin and Granzyme B to lyse tumor cells directly. In the absence of CD1d expression on tumor cells, iNKT cells may become activated in response to CD1d-expressing or Toll-like receptor (TLR)-activated antigen-presenting cells (APC). The bidirectional activation of iNKT cells and APCs promotes the activation of NK-cell and tumor-specific T-cell responses, thereby mediating tumor-cell killing indirectly. This figure was created by Rosanna M. McEwen-Smith of the Weatherall Institute of Molecular Medicine and the University of Oxford. For details, see the Masters of Immunology article by Cerundolo and colleagues that begins on page 425 of this issue.



ABOUT THE MASTER

Vincenzo Cerundolo, MD, PhD, is the director of the United Kingdom Medical Research Council (MRC UK) Human Immunology Unit and professor of immunology at the Weatherall Institute of Molecular Medicine, University of Oxford, UK. In the early 1990s Dr. Cerundolo made key discoveries characterizing the cellular mechanisms involved in the presentation of intracellular peptides to MHC class I-restricted T lymphocytes, which have had a great impact on the field. In particular, he was instrumental in the identification of genes within the MHC locus that are critical for the generation of peptides presented by MHC class I molecules. Dr. Cerundolo described the first human antigen processing-deficient cells, leading to the cloning and characterization of the transporter associated with antigen-processing 1 and 2 (TAP1, TAP2) genes and the identification of several families of TAP1/2-deficient patients with necrotizing granulomatous skin lesions and small vessel vasculitis. He was the first to determine the relationship between the length of peptides and their binding affinity to MHC class I molecules, hence explaining the homogenous length of peptides isolated from MHC class I molecules. He showed the proteasome-dependent processing of defined melanoma antigenic proteins into epitopes for antitumor T cells and thus the direct role of immunoproteasomes in cross-presentation of exogenous proteins.

Dr. Cerundolo demonstrated how the length and saturation of lipid antigens contained within the CD1d binding site modulate their affinity of binding to invariant NKT cells (iNKT cells), hence explaining how lipid-specific lymphocytes are capable of recognizing both the group head and the length of lipid antigens, ensuring greater specificity of antigen recognition. His seminal findings on the processing and presentation of peptide and lipid antigens made fundamental advances to the field of antigen presentation to MHC class I-restricted T cells and CD1d-restricted iNKT cells. His demonstration that iNKT cells enhance both antigen-specific antibody and T-cell responses has had a major influence on the development of new vaccines and has opened up new therapeutic strategies to enhance immune responses against cancer and infectious pathogens.

Dr. Cerundolo was born in Lecce, Italy. He was a graduate in medicine and completed his PhD in immunology at the University of Padua, Italy, where he also received training in clinical and experimental oncology. He moved to the UK as an EMBO Fellow in 1988 to work with Professor Alain Townsend. Dr. Cerundolo was appointed professor of immunology at the University of Oxford in 2000, director of the MRC Human Immunology Unit in 2010, and head of the Investigative Medicine Division of the Radcliffe Department of Medicine in 2012. Dr. Cerundolo enjoys running and is a member of one of the Oxford Road Runner Clubs. He is a fellow of Merton College at the University of Oxford, the Academy of Medical Sciences, UK, and the Royal College of Pathologists, and is the Batsheva Fellow of the Israeli Academy of Medical Sciences. He serves on the scientific advisory boards of numerous institutions and charitable organizations, and on the editorial boards of leading peer-reviewed journals.

Current research in the Cerundolo laboratory focuses on gaining a better understanding of the mechanisms that control the cell-cell interplay required for optimal expansion and activation of tumor-specific T-cell populations, and to apply this knowledge to the development of better treatment strategies in cancer patients.



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