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MASTERS OF IMMUNOLOGY

- 969**  Neopeptides of Cancers: Looking Back, Looking Ahead
Pramod K. Srivastava

CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 978** Tumoral Immune Resistance Mediated by Enzymes That Degrade Tryptophan
Nicolas van Baren and Benoît J. Van den Eynde

PRIORITY BRIEFS

- 986** Single Institution Experience of Ipilimumab 3 mg/kg with Sargramostim (GM-CSF) in Metastatic Melanoma
Jason J. Luke, Hilary Donahue, Mizuki Nishino, Anita Giobbie-Hurder, Meredith Davis, Nancy Bailey, Patrick A. Ott, and F. Stephen Hodi
Synopsis: The FDA-approved dosage of anti-CTLA-4, with and without GM-CSF, was tested on patients with melanoma. Although the antitumor action was equivalent in all groups, the toxic side effects were reduced when GM-CSF was present.
- 992** Exome Sequencing to Predict Neoantigens in Melanoma
Antonia L. Pritchard, Julie G. Burel, Michelle A. Neller, Nicholas K. Hayward, J. Alejandro Lopez, Martina Fatho, Volker Lennerz, Thomas Wölfel, and Christopher W. Schmidt
Synopsis: Neopeptides produced by tumor cells may be key to personalized cancer therapies. Potential MHC-binding peptides were predicted from differential exome sequencing and immunogenic neopeptides rapidly identified through mixed lymphocyte-tumor cultures, a technique readily applicable to different tumor types.

RESEARCH ARTICLES


- 999**  The Coordinated Actions of TIM-3 on Cancer and Myeloid Cells in the Regulation of Tumorigenicity and Clinical Prognosis in Clear Cell Renal Cell Carcinomas
Yoshihiro Komohara, Tomoko Morita, Dorcas A. Annan, Hasita Horlad, Koji Ohnishi, Sohsuke Yamada, Toshiyuki Nakayama, Shohei Kitada, Shinya Suzu, Ichiro Kinoshita, Hirotoshi Dosaka-Akita, Koichi Akashi, Motohiro Takeya, and Masahisa Jinushi
Synopsis: TIM-3 interferes with tumor immunosurveillance. Expression of TIM-3 in patients, on both tumor and immune cells, was found to correlate with poorer outcomes. Mouse and in vitro studies showed that TIM-3 increases tumorigenic properties and treatment resistance.
- 1008** Preexisting Levels of CD4 T Cells Expressing PD-1 Are Related to Overall Survival in Prostate Cancer Patients Treated with Ipilimumab
Serena S. Kwek, Jera Lewis, Li Zhang, Vivian Weinberg, Samantha K. Greaney, Andrea L. Harzstark, Amy M. Lin, Charles J. Ryan, Eric J. Small, and Lawrence Fong
Synopsis: Retrospective analysis of blood from cancer patients receiving the combination of anti-CTLA-4 plus GM-CSF revealed no relation between survival and changes in immune cell subsets with treatment. However, short-term survivors had high preexisting PD-1⁺ CD4 T-cell counts.
- 1017** Resistance to Antiangiogenic Therapy Is Associated with an Immunosuppressive Tumor Microenvironment in Metastatic Renal Cell Carcinoma
Xian-De Liu, Anh Hoang, Lijun Zhou, Sarathi Kalra, Alper Yetil, Mianen Sun, Zhiyong Ding, Xuesong Zhang, Shanshan Bai, Peter German, Pheroze Tamboli, Priya Rao, Jose A. Karam, Christopher Wood, Surena Matin, Amado Zurita, Axel Bex, Arjan W. Griffioen, Jianjun Gao, Padmanee Sharma, Nizar Tannir, Kanishka Sircar, and Eric Jonasch
Synopsis: Therapeutic PD-1/PD-L1 blockade requires preexisting tumor-infiltrating T cells. In a subset of metastatic RCC patients, antiangiogenic therapy increased T-cell infiltration and PD-L1 upregulation, increasing the likelihood that they may uniquely benefit from combination checkpoint and antiangiogenic therapy.

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- 1030** **Decitabine Enhances Lymphocyte Migration and Function and Synergizes with CTLA-4 Blockade in a Murine Ovarian Cancer Model**
Lei Wang, Zohreh Amoozgar, Jing Huang, Mohammad H. Saleh, Deyin Xing, Sandra Orsulic, and Michael S. Goldberg
Synopsis: A mechanistic basis for the synergy between decitabine and anti-CTLA-4 was found. This provides a rationale for initiating trials of combination therapy in ovarian cancer, in which many patients do not benefit from immune checkpoint blockade alone.
- 1042** **Therapeutic Peptide Vaccine-Induced CD8 T Cells Strongly Modulate Intratumoral Macrophages Required for Tumor Regression**
Tetje C. van der Sluis, Marjolein Sluijter, Suzanne van Duikeren, Brian L. West, Cornelis J.M. Melief, Ramon Arens, Sjoerd H. van der Burg, and Thorbald van Hall
Synopsis: Intratumoral macrophages were found to be functionally malleable and can support, or be inhospitable to, tumors. Vaccine-induced cytokine-producing CD8 T cells modified intratumoral macrophage subsets, and both T cells and macrophages were indispensable for tumor regressions.
- 1052** **Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody**
Ross Stewart, Michelle Morrow, Scott A. Hammond, Kathy Mulgrew, Danielle Marcus, Edmund Poon, Amanda Watkins, Stefanie Mullins, Matthieu Chodorge, John Andrews, David Bannister, Emily Dick, Nicola Crawford, Julie Parmentier, Marat Alimzhanov, John S. Babcook, Ian N. Foltz, Andrew Buchanan, Vahe Bedian, Robert W. Wilkinson, and Matthew McCourt
Synopsis: A human antibody to PD-L1, engineered to eliminate Fc effector functions, which potently inhibits PD-L1 function, is in phase III clinical trials. Its characterization here provides clinicians and researchers with a basis for understanding and interpreting clinical trial results.
- 1063** **Survival Outcomes of Sipuleucel-T Phase III Studies: Impact of Control-Arm Cross-Over to Salvage Immunotherapy**
 Daniel J. George, Chadi Nabhan, Todd DeVries, James B. Whitmore, and Leonard G. Gomella
Synopsis: Control-arm patients from three prostate cancer clinical trials of sipuleucel-T (an autologous APC-based therapy) received APC therapy from their cryopreserved cells. Overall survival may have increased, which suggests that APC therapy may be more robust than estimated.
- 1070** **Optimization of T-cell Reactivity by Exploiting TCR Chain Centricity for the Purpose of Safe and Effective Antitumor TCR Gene Therapy**
Toshiki Ochi, Munehide Nakatsugawa, Kenji Chamoto, Shinya Tanaka, Yuki Yamashita, Tingxi Guo, Hiroshi Fujiwara, Masaki Yasukawa, Marcus O. Butler, and Naoto Hirano
Synopsis: Adoptive transfer of redirected antitumor T cells can have off-target toxicities. Peptide-MHC specificity can be focused on a single TCR chain, allowing the authors to separate antitumor-reactivity from cross-reactivity, while showing that monitoring for toxicities is still necessary.
- 1082** **Melanoma-Derived Wnt5a Promotes Local Dendritic-Cell Expression of IDO and Immunotolerance: Opportunities for Pharmacologic Enhancement of Immunotherapy**
 Alisha Holtzhausen, Fei Zhao, Kathy S. Evans, Masahito Tsutsui, Ciriana Orabona, Douglas S. Tyler, and Brent A. Hanks
Synopsis: Melanomas produce Wnt5a, which promotes the ability of local DCs to drive regulatory T-cell expansion and to generate an immunosuppressive tumor microenvironment. Targeting this system could lead to the development of novel immunotherapeutic strategies.
- 1096** **Salmonella-Based Therapy Targeting Indoleamine 2,3-Dioxygenase Coupled with Enzymatic Depletion of Tumor Hyaluronan Induces Complete Regression of Aggressive Pancreatic Tumors**
Edwin R. Manuel, Jeremy Chen, Massimo D'Apuzzo, Melanie G. Lampa, Teodora I. Kaltcheva, Curtis B. Thompson, Thomas Ludwig, Vincent Chung, and Don J. Diamond
Synopsis: Current treatments for late-stage pancreatic tumors provide small increases in survival with significant toxicity. The authors' combinatorial approach allows bacterial-based anti-immunosuppression therapy to penetrate the fibrotic capsule of aggressive tumors. The resulting tumor regression demonstrates potential for clinical application.

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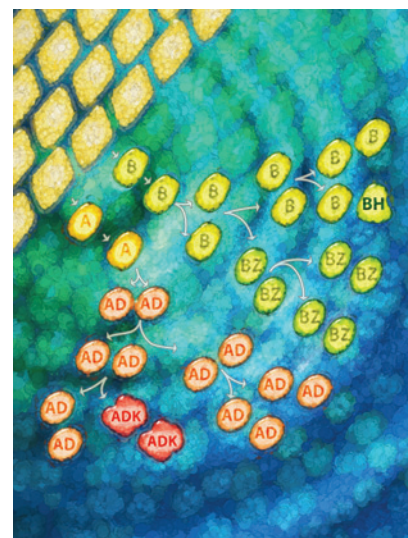
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ABOUT THE COVER

With normal cell division comes some genetic infidelity, and this is often exaggerated in cancer cells because of both error-prone replication and exposure to mutagens. Most mutations (represented by upper-case letters in the illustration) go unnoticed and are termed passenger mutations, but occasionally a slight growth or survival advantage is bestowed by the change. Mutations in exons can create neoepitopes, that is, new amino acids or protein conformations that may be visible to the immune system. As these accumulate, they are passed down the line. A tumor mass eventually comprises multiple neoepitope lineages, each expressing different accumulations of neoepitopes, diverging slightly from each other and from the original "mother" cell. Recognition of the role that these neoepitopes can play in cancer immunotherapy has engendered promising new insights and approaches to the treatment of tumors. See the Masters in Immunology article by Pramod K. Srivastava (pp. 969–977) in this issue.



ABOUT THE MASTER

Pramod Kumar Srivastava, PhD, MD, is the Northeast Utilities Chair Professor in Experimental Oncology, professor of immunology and medicine, and director of the Carole and Ray Neag Comprehensive Cancer Center at the University of Connecticut School of Medicine in Farmington, CT. Dr. Srivastava has championed the cause of personalized immunotherapy of human cancer for over 25 years. He was the first to demonstrate that immunization of mice with heat-shock proteins (HSP) hsp70 and hsp90 isolated from tumors elicited tumor-specific immunity, and that immunogenicity of tumor-derived HSPs comes from HSP-associated peptides, which include any antigenic peptides. He suggested and showed that hsp70 and hsp90 members play a critical role in antigen processing and presentation by MHC class I molecules. Dr. Srivastava showed that endogenous HSP-peptide complexes are the essential vehicles of antigen transfer from antigen-donor cells to antigen-presenting cells (APC) during cross-priming. To explain the powerful adjuvant-like properties of hsp70 and hsp90, he hypothesized and later showed that these HSPs interact with APCs through HSP receptors, such as CD91. Dr. Srivastava developed the HSP-peptide cancer vaccine vitespen or Oncophage, which was approved in Russia in 2008 for treatment of patients with nonmetastatic renal cell carcinoma. Oncophage is the first therapeutic cancer vaccine to be approved for clinical use in the world. An NIH/CTEP (Cancer Therapy Evaluation Program)–approved large randomized study testing Oncophage in patients with recurrent glioblastoma multiforme is ongoing at multiple U.S. centers.

Dr. Srivastava hypothesized in 1993 that cancers are individually antigenically distinct because of random passenger mutations, a proportion of which become immunogenic in any given patient. With the availability of high-throughput genomics and bioinformatics capabilities, he and others have demonstrated that this is indeed the case. Dr. Srivastava is now pursuing genomics-driven personalized immunotherapy for the treatment of human ovarian and other cancers.

Dr. Srivastava has had continuous research support from the NIH for 25 years. He was a member of the NIH Experimental Immunology Study Section and several study sections of the U.S. Department of Defense. He has been a member of the Scientific Advisory Council of the Cancer Research Institute since 1995. In 1997 he was inducted into the Roll of Honor of the Union Internationale Contre le Cancer and became a founding member of the Academy of Cancer Immunology. Dr. Srivastava is an inventor on over 200 awarded patents and has cofounded a number of biotechnology companies, including Antigenics (AGEN), Ikonisys, and Life Science Pharmaceuticals.

Dr. Srivastava obtained his bachelor's degree in biology and chemistry and a master's degree in botany (paleontology) from the University of Allahabad, India. He studied yeast genetics at Osaka University, Japan, and completed his PhD in biochemistry at the Center for Cellular and Molecular Biology, Hyderabad, India. He also trained at Yale University and Sloan Kettering Institute for Cancer Research. He obtained his MD degree from the University of Connecticut School of Medicine. He has previously held faculty positions at the Mount Sinai School of Medicine and Fordham University, both in New York City.



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