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Cancer Immunology Research

Illuminating the Interplay of Cancer and the Immune System

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- 288 **Spontaneous Peripheral T-cell Responses toward the Tumor-Associated Antigen Cyclin D1 in Patients with Clear Cell Renal Cell Carcinoma**
Stefanie R. Dannenmann, Thomas Hermanns, Ali Bransi, Claudia Matter, Lotta von Boehmer, Stefan Stevanovic, Peter Schraml, Holger Moch, Alexander Knuth, and Maries van den Broek
Synopsis: Analyzing samples from patients with primary clear cell renal cell carcinoma (ccRCC), Dannenmann and colleagues identified naturally occurring, polyfunctional Cyclin D1-specific CD8⁺ T cells from patients with Cyclin-D1⁺ tumors, and they propose to develop Cyclin D1 as a target for immunotherapy in patients with ccRCC.

PRIORITY BRIEFS

- 296 **NY-ESO-1 Expression in Meningioma Suggests a Rationale for New Immunotherapeutic Approaches**
Gilson S. Baia, Otavia L. Caballero, Janelle S.Y. Ho, Qi Zhao, Tzeela Cohen, Zev A. Binder, Vafi Salmasi, Gary L. Gallia, Alfredo Quinones-Hinojosa, Alessandro Olivi, Henry Brem, Peter Burger, Robert L. Strausberg, Andrew J.G. Simpson, Charles G. Eberhart, and Gregory J. Riggins
Synopsis: Baia, Caballero, and colleagues found that NY-ESO-1 is the most frequently expressed cancer/testis antigen in meningioma tumors, and its expression positively correlates with higher-grade disease and worst prognosis. NY-ESO-1 proteins elicit spontaneous humoral immune responses; the authors propose that NY-ESO-1-based immunotherapy should be explored as a complement to standard therapy for patients with meningioma.

- 303 **CD4⁺ T Effectors Specific for the Tumor Antigen NY-ESO-1 Are Highly Enriched at Ovarian Cancer Sites and Coexist with, but Are Distinct from, Tumor-Associated Treg**
Maha Ayyoub, Pascale Pignon, Jean-Marc Classe, Kunle Odunsi, and Danila Valmori

Synopsis: CD4⁺ T effector cells specific for the tumor antigen NY-ESO-1 were found to accumulate at ovarian cancer tumor sites; they maintain an effector phenotype/function and remain distinct from Treg, even when Treg are present at high proportions. These findings encourage the use of combination therapies aiming at enhancing tumor antigen-specific immune responses and eliminating or inactivating Treg.

RESEARCH ARTICLES

- 309 **Combining Oncolytic HSV-1 with Immunogenic Cell Death-Inducing Drug Mitoxantrone Breaks Cancer Immune Tolerance and Improves Therapeutic Efficacy**
Samuel T. Workenhe, Jonathan G. Pol, Brian D. Lichty, Derek T. Cummings, and Karen L. Mossman
Synopsis: Workenhe and colleagues show that the combination regimen of oncolytic virus with mitoxantrone significantly increases the efficacy of either treatment alone by enhancing the immunogenicity of and breaking immune tolerance against tumor-associated antigens, an Achilles' heel of current cancer therapy.

GITR Pathway Activation Abrogates Tumor Immune Suppression through Loss of Regulatory T-cell Lineage Stability

David A. Schaer, Sadna Budhu, Cailian Liu, Campbell Bryson, Nicole Malandro, Adam Cohen, Hong Zhong, Xia Yang, Alan N. Houghton, Taha Merghoub, and Jedd D. Wolchok

Synopsis: Schaer and colleagues show that GITR ligation by agonist antibody DTA-1 inhibits intratumor immune suppression by inducing tumor-dependent loss of Foxp3 and altered expression of transcription factors and cytokines important for Treg function, resulting in impaired Treg lineage stability and enhanced killing of tumor cells by T effectors. These results will inform the effective use of GITR therapy in humans.

Peptide Vaccination in Montanide Adjuvant Induces and GM-CSF Increases CXCR3 and Cutaneous Lymphocyte Antigen Expression by Tumor Antigen-Specific CD8 T Cells

Eleanor Clancy-Thompson, Laura K. King, Lenora D. Nunnley, Irene M. Mullins, Craig L. Slingluff Jr, and David W. Mullins

Synopsis: A melanoma-specific peptide vaccine in Montanide ISA-51 induces tumor-infiltrating CD8⁺ T cells expressing CXCR3, with a subpopulation coexpressing CLA, both of which are associated with skin homing and are increased by GM-CSF. The authors hypothesize that specific modifications of the metastatic tumor microenvironment to elicit chemoattraction of vaccine-induced T cells would enhance vaccine efficacy for disseminated metastases.

Effect of Montanide and Poly-ICLC Adjuvant on Human Self/Tumor Antigen-Specific CD4⁺ T Cells in Phase I Overlapping Long Peptide Vaccine Trial

Takemasa Tsuji, Paul Sabbatini, Achim A. Jungbluth, Erika Ritter, Linda Pan, Gerd Ritter, Luis Ferran, David Spriggs, Andres M. Salazar, and Sacha Gnjatovic

Synopsis: In a comprehensive analysis of what contributes to the integrated immune responses elicited by the vaccination of ovarian cancer patients with OLP from tumor antigen NY-ESO-1, Tsuji and colleagues show that Montanide ISA-51 is critical for the expansion of high-avidity antigen-induced CD4⁺ T cells, and a TLR ligand poly-ICLC accelerates the induction and differentiation of vaccine-induced antigen-specific Th1 cells.

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ABOUT THE COVER

Paul Ehrlich shared the 1908 Nobel Prize with Elie Metchnikoff for their contributions to immunology. Ehrlich described and named mast cells (MC, or, in German *mastzellen* for "well-fed cells") in his doctoral thesis in 1878, identifying them in human connective tissue as cells containing abundant intracellular granules that stain purple with certain aniline dyes. Ehrlich noted that MCs were particularly abundant in some human tumors. MCs are long-lived secretory cells derived from hematopoietic precursors that are found in small numbers in the blood but complete their differentiation and maturation in the microenvironments of almost all vascularized tissues. In addition to their known function as effector cells in antigen-induced anaphylaxis and other acute IgE-dependent allergic reactions, MCs have been proposed to have diverse immunomodulatory and several other functions, spanning many aspects of health, host defense, and disease. In tumor biology, individual products of MCs have been shown to have the potential to negatively or positively regulate such processes as the proliferation and survival of tumor cells, tumor-associated angiogenesis and tissue remodeling, metastasis and distant growth of tumor cells, and the ability of tumors to modulate the immune system.

The cover image is a photograph of Paul Ehrlich superimposed on a high-power photomicrograph of a specimen of infiltrating ductal carcinoma of the breast stained by immunohistochemistry to detect tryptase, which identifies mast cells as cells with intensely brown-stained cytoplasm. (The photomicrograph was provided by Matt van de Rijn and Norm Cyr of Stanford University.) For details, see the "Masters of Immunology" article by Marichal, Tsai, and Galli starting on page 269 of this issue.

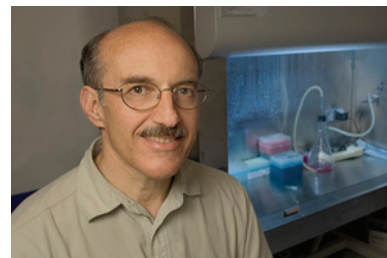


ABOUT THE MASTER

Stephen J. Galli, MD, has been chair of the Department of Pathology, the Mary Hewitt Loveless, MD Professor, and a professor of pathology and of microbiology and immunology at Stanford University School of Medicine since February 1999. He received his BA in biology in 1968 from Harvard College, a BMS in 1970 from Dartmouth Medical School (then a two-year school), and the MD in 1973 from Harvard Medical School (HMS) and completed a residency in Anatomic Pathology at Massachusetts General Hospital (MGH) in 1977. After postdoctoral training with Harold F. Dvorak at MGH, he joined the HMS faculty in 1979 as assistant professor of pathology, became professor of pathology in 1993, and, until moving to Stanford in 1999, served as director of the Division of Experimental Pathology at Beth Israel Deaconess Medical Center and a faculty member of the HMS Graduate Program in Immunology.

Steve Galli's research focuses on the development and function of mast cells and basophils (the major effector cells of asthma and anaphylaxis) and the development of new animal models for studying the roles of these cells in health and disease. These models include so-called "mast cell knock-in mice" (i.e., genetically mast cell-deficient mice, bearing mutations affecting *c-kit* structure or expression, which have been selectively engrafted with wild type or genetically altered mast cells generated *in vitro*) and, more recently, mice rendered genetically deficient in mast cells and basophils by a mechanism that does not involve mutations affecting *c-kit*. The Galli group has used these models extensively in efforts to elucidate the roles of mast cells in health and disease.

Dr. Galli was president of the American Society for Investigative Pathology (ASIP; 2005–2006) and has been elected to the Pluto Club (Association of University Pathologists), the Collegium Internationale Allergologicum (for which he serves as president from 2010–2014), the American Society for Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the U.S. National Academies. He is also a foreign member of the Accademia Nazionale dei Lincei (National Academy of the Lynxes) in Rome, regarded as the oldest secular scientific society in the Western World.



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