


## MASTERS OF IMMUNOLOGY

- 381 **Affinity Enhancement of Antibodies: How Low-Affinity Antibodies Produced Early in Immune Responses Are Followed by High-Affinity Antibodies Later and in Memory B-Cell Responses**  
 Herman N. Eisen

## CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 393 **Tim-3: An Emerging Target in the Cancer Immunotherapy Landscape**  
 Ana C. Anderson


## CANCER IMMUNOLOGY MINIATURES

- 399 **Sustained Complete Response to CTLA-4 Blockade in a Patient with Metastatic, Castration-Resistant Prostate Cancer**  
 Julie N. Graff, Sachin Puri, Carlo B. Bifulco, Bernard A. Fox, and Tomasz M. Beer  
**Synopsis:** Graff and colleagues analyzed sera and biopsies from a prostate cancer patient, which showed amplification of the 3-hydroxyisobutyryl-CoA hydrolase (HIBCH) gene with strong protein expression, suggesting that the augmented antibody response to HIBCH contributed to the durable immune response in prostate cancer.

## PRIORITY BRIEF

- 404 **Long-term Complete Remission Following Radiosurgery and Immunotherapy in a Melanoma Patient with Brain Metastasis: Immunologic Correlates**  
 Julia Karbach, Sacha Gnjatich, Melina Biskamp, Akin Atmaca, Eckhart Weidmann, Kathrin Brandt, Claudia Wahle, Helga Bernhard, Alexander Knuth, and Elke Jäger  
**Synopsis:** Karbach and colleagues identify the durable expansion of tumor-specific T cells as immune correlates induced by radiosurgery plus vaccination with tumor-lysate-loaded dendritic cells that protected against metastatic melanoma, indicating that combining radiotherapy with immunotherapy may improve cancer survival.

## RESEARCH ARTICLES

- 410 **Reversal of NK-Cell Exhaustion in Advanced Melanoma by Tim-3 Blockade**  
 Ines Pires da Silva, Anne Gallois, Sonia Jimenez-Baranda, Shaikat Khan, Ana C. Anderson, Vijay K. Kuchroo, Iman Osman, and Nina Bhardwaj  
**Synopsis:** Silva and colleagues show that Tim-3 expression in NK cells from melanoma patients correlates with poor prognosis; blockade of Tim-3 induces NK-cell proliferative and cytolytic capacity and responsiveness to growth factors, indicating that Tim-3 is a therapeutic target for patients with advanced melanoma.
- 423 **CD4<sup>+</sup> T Lymphocyte Ablation Prevents Pancreatic Carcinogenesis in Mice**  
 Yaqing Zhang, Wei Yan, Esha Mathew, Filip Bednar, Shanshan Wan, Meredith A. Collins, Rebecca A. Evans, Theodore H. Welling, Robert H. Vonderheide, and Marina Pasca di Magliano  
**Synopsis:** Zhang and colleagues show that Kras-expressing epithelial cells recruit CD4<sup>+</sup> T cells that repress the activity of CD8<sup>+</sup> T cells to establish the immunosuppressive microenvironment in the iKras\* mouse model of pancreatic cancer; elimination of CD4<sup>+</sup> T cells uncovers the antineoplastic function of CD8<sup>+</sup> T cells.
- 436 **Enhancing Efficacy of Anticancer Vaccines by Targeted Delivery to Tumor-Draining Lymph Nodes**  
 Laura Jeanbart, Marie Ballester, Alexandre de Titta, Patricia Corthésy, Pedro Romero, Jeffrey A. Hubbell, and Melody A. Swartz  
**Synopsis:** Jeanbart and colleagues show in two cancer models that targeting vaccines to the tumor-draining lymph node (tdLN) using nanoparticle carriers drives stronger effector immunity and better therapeutic outcomes, suggesting that the tumor-antigen experience of the tdLN outweighs the presence of tumor-derived immunosuppressive cytokines there.

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- 448**    **Combination of Alphavirus Replicon Particle–Based Vaccination with Immunomodulatory Antibodies: Therapeutic Activity in the B16 Melanoma Mouse Model and Immune Correlates**  
Francesca Avogadri, Roberta Zappasodi, Arvin Yang, Sadna Budhu, Nicole Malandro, Daniel Hirschhorn-Cymerman, Shakuntala Tiwari, Maureen F. Maughan, Robert Olmsted, Jedd D. Wolchok, and Taha Merghoub  
*Synopsis:* Avogadri and colleagues show that anti-CTLA-4 or anti-GITR immunomodulatory antibody improves the efficacy of a nonpathogenic viral vector–based vaccine (VRP-TRP-2) in the B16F10 melanoma mouse model. Superior antitumor protection conferred by anti-GITR was associated with enhanced humoral response and reduced CD4<sup>+</sup>PD-1<sup>+</sup> T-cell intratumoral accumulation.
- 459**    **Exposure to a Histone Deacetylase Inhibitor Has Detrimental Effects on Human Lymphocyte Viability and Function**  
Deborah J.L. Wong, Amol Rao, Earl Avramis, Douglas R. Matsunaga, Kimberly M. Komatsubara, Mohammad S. Atefi, Helena Escuin-Ordinas, Thilne Chodon, Richard C. Koya, Antoni Ribas, and Begoña Comin-Anduix  
*Synopsis:* Wong and colleagues show that human lymphocytes are highly susceptible to panobinostat, which alters their signaling pathways and is cytotoxic at a much lower dose than needed for antitumor activity. They caution against the combined use of panobinostat with immunotherapy for melanoma.
- 469**    **Streptavidin: A Novel Immunostimulant for the Selection and Delivery of Autologous and Syngeneic Tumor Vaccines**  
Chris Weir, Amanda L. Hudson, Elizabeth Moon, Angus Ross, Miles Alexander, Lyndsay Peters, Veronika Langova, Stephen J. Clarke, Nick Pavlakis, Ross Davey, and Viive M. Howell  
*Synopsis:* Weir and colleagues describe a novel method that uses streptavidin as an immune stimulant for autologous and syngeneic cancer vaccines. Streptavidin was an effective novel vaccine carrier for soluble tumor proteins that provided survival advantage in the syngeneic cancer model.
- 480**    **Cancer–Testis Antigen Expression in Digestive Tract Carcinomas: Frequent Expression in Esophageal Squamous Cell Carcinoma and Its Precursor Lesions**  
Yao-Tseng Chen, Nicole C. Panarelli, Kathryn C. Piotti, and Rhonda K. Yantiss  
*Synopsis:* Chen and colleagues studied the expression of 8 cancer–testis (CT) antigens in digestive tract cancers and found high-frequency CT expression in esophageal squamous tumors and in premalignant squamous dysplastic lesions, suggesting that these antigens might be useful as tumor markers in these lesions.
- 487**    **Reprogramming Tumor-Infiltrating Dendritic Cells for CD103<sup>+</sup>CD8<sup>+</sup> Mucosal T-cell Differentiation and Breast Cancer Rejection**  
Te-Chia Wu, Kangling Xu, Romain Banchereau, Florentina Marches, Chun I. Yu, Jan Martinek, Esperanza Anguiano, Alexander Pedroza-Gonzalez, G. Jackson Snipes, Joyce O’Shaughnessy, Stephen Nishimura, Yong-Jun Liu, Virginia Pascual, Jacques Banchereau, Sangkon Oh, and Karolina Palucka  
*Synopsis:* Wu and colleagues show that intratumoral delivery of dectin-1 ligand curdled in a humanized mouse model of breast cancer reprograms dendritic cells to induce Th1 cytokine production as well as expansion and accumulation of CD103<sup>+</sup>CD8<sup>+</sup> mucosal T cells in tumors, leading to cancer rejection.

## CORRECTION

- 501**    **Correction: Increased Frequency of ICOS<sup>+</sup> CD4 T Cells as a Pharmacodynamic Biomarker for Anti-CTLA-4 Therapy**

 AC icon indicates Author Choice

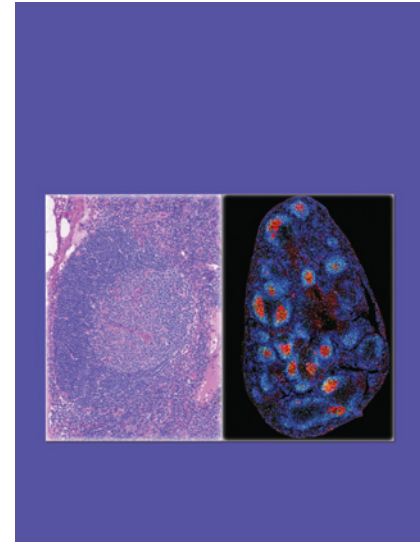
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## ABOUT THE COVER

Germinal centers (GC) are cellular factories in lymphoid tissues, where proliferating Ag-stimulated B cells expressing low-affinity IgM Abs are converted to cells that express high-affinity Abs of other classes, catalyzed by the Ag-induced cytidine deaminase (AID) that alters nucleotide sequences of transcribed Ig genes. GC comprise a dark zone with densely packed cells and a less densely packed light zone. The cells are embedded in a reticular network associated with specialized follicular dendritic cells and infiltrated by specialized follicular helper T cells. The cover image depicts GC in light and fluorescence microscopy. On the left is a human lymph node section stained with hematoxylin and eosin, showing a GC surrounded by the many small unstimulated B cells that make up most of a B-cell follicle (image courtesy of R.B. Colvin, Department of Pathology, Massachusetts General Hospital, Boston, MA). GC B cells are proliferating lymphoblasts undergoing Ig class-switching with rapid rates of mutation of Ig variable domains. Shown on the right are live cells in the spleen of an immunized mouse with GC cells expressing AID (red fluorescence) and antigen-specific helper T cells (green fluorescence). Blue patches are B-cell follicles stained for IgD (image generated by J. Tas, courtesy of G. Victora's laboratory, Whitehead Institute, Cambridge, MA). For details, see the Masters of Immunology primer by Herman N. Eisen on page 381 of this issue.

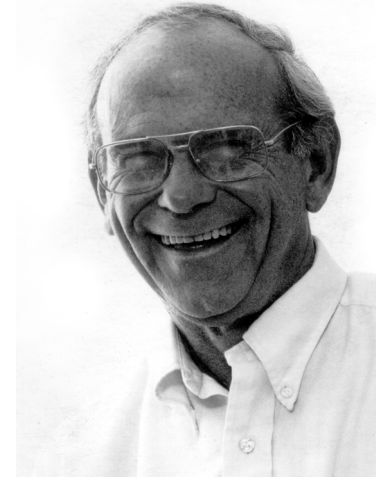


## ABOUT THE MASTER

Herman N. Eisen, MD, is a professor emeritus in the department of biology at the Massachusetts Institute of Technology (MIT). Dr. Eisen joined the faculty at MIT in 1973 as one of the founding members of the MIT Center of Cancer Research, later named the Koch Institute for Integrative Cancer Biology. He is also affiliated with the Ragon Institute of Massachusetts General Hospital (MGH), MIT, and Harvard University. His early interest was in chemistry. Inspired by the work of Karl Landsteiner, who generated antibodies from hapten-linked proteins, and a seminar by Fred Sanger, who described how he deduced the amino acid sequence of insulin, Dr. Eisen began his distinguished research career in immunology, focused on antibody development and antigen recognition. Benefiting from the post-World War II expansion of NIH-supported research, Dr. Eisen received one of the first physician-scientist awards to study sulfonamide-induced antibodies at New York University (NYU). Using equilibrium dialysis he and his bench-mate, Fred Karush, determined the number of antigen-binding sites on antibodies (Eisen and Karush, *J Am Chem Soc* 1949;71:363-4). At Washington University in St. Louis (WUSTL), Eisen and his colleagues discovered that the affinity of serum antibodies increases progressively with time after encountering antigen (later called affinity maturation of antibodies, and the subject of the Master primer in this issue). At MIT, the Eisen lab focused on CD8 T cells and their killing of cells that display peptide-MHC complexes recognized by the T cells' antigen-binding receptor.

Dr. Eisen was born in Brooklyn, New York, in 1918. He entered the NYU honors program in 1934 and was the free-swinging, left-handed first baseman for the college's baseball team until he developed tuberculosis and had to leave school for a year. He received his MD from NYU in 1943 and served residencies in pathology at the Columbia-Presbyterian Hospital and in medicine at the Bellevue Hospital. After brief stints at the Memorial Sloan-Kettering Institute and NYU Medical School, including part-time medical practice, he moved to WUSTL in 1955, first as professor of medicine and then as professor and chairman of the department of microbiology.

Dr. Eisen has received numerous honors, including a National Cancer Institute Outstanding Investigator award, the von Behring-Heidelberger Award, and the American Association of Immunologists (AAI) Lifetime Service/Achievement award. He has served on the scientific advisory boards of the Howard Hughes Medical Institute, Yale Medical School, Harvard School of Public Health, MGH, the Children's Hospital of Boston, the National Institute for Arthritis and Metabolic Diseases, the Roche Institute for Molecular Biology, and the Merck Institute. He was the vice president of the American Society for Clinical Investigation (1965) and the president of the AAI (1968). Dr. Eisen was elected to the American Academy of Arts and Sciences (1965), the U.S. National Academy of Sciences (1969), and the Institute of Medicine (1974).



# Cancer Immunology Research

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