

EDITORIAL

- 703** *Cancer Immunology Research: A Two-Year Anniversary*

MASTERS OF IMMUNOLOGY

- 704** Fc-Receptor Interactions Regulate Both Cytotoxic and Immunomodulatory Therapeutic Antibody Effector Functions



David J. DiLillo and Jeffrey V. Ravetch

CANCER IMMUNOLOGY AT THE CROSSROADS: FUNCTIONAL PROTEOMICS

- 714** Charting Immune Signaling Proteomes En Route to New Therapeutic Strategies
- Eric B. Haura, Amer A. Beg, Uwe Rix, and Scott Antonia

PRIORITY BRIEF

- 721** CARD9 Promotes Sex-Biased Colon Tumors in the APC^{min} Mouse Model



Vonny I. Leo, Sze Huey Tan, Hanna Bergmann, Peh Yean Cheah, Min Hoe Chew, Kiat Hon Lim, Jürgen Ruland, and Patrick T. Reilly

Synopsis: Leo and colleagues compared CARD9-competent and CARD9-deficient APC^{min} mice and show that CARD9 reduces viability in male mice and promotes tumorigenesis specifically in the large intestine, with a correlative disruption of plasma cytokine expression and immune infiltration of the tumors.

RESEARCH ARTICLES

- 727** SOCS3 Deficiency in Myeloid Cells Promotes Tumor Development: Involvement of STAT3 Activation and Myeloid-Derived Suppressor Cells

Hao Yu, Yudong Liu, Braden C. McFarland, Jessy S. Deshane, Douglas R. Hurst, Selvarangan Ponnazhagan, Etty N. Benveniste, and Hongwei Qin

Synopsis: Yu and colleagues show that the loss of SOCS3, a negative regulator of STAT3, in myeloid cells, leads to the development of MDSC and immunosuppressive activity within the tumor microenvironment via a G-CSF/STAT3 axis, and suggest targeting of SOCS3 in myeloid cells to regulate antitumor immunity.

- 741** Assessing the Effects of Concurrent versus Sequential Cisplatin/Radiotherapy on Immune Status in Lung Tumor-Bearing C57BL/6 Mice
- Chiao-Jung Kao, Gregory T. Wurz, Yi-Chen Lin, Daniel P. Vang, Stephen M. Griffey, Michael Wolf, and Michael W. DeGregorio

Synopsis: Kao and colleagues performed a comprehensive analysis in a lung cancer mouse model and show that sequential chemoradiotherapy had an equivalent amount of antitumor activity compared with concurrent therapy, but the two regimens elicited differences in immune response biomarkers, including Tregs, microRNA-29c, CD28, and serum IFN γ .

- 751** PolySia-Specific Retargeting of Oncolytic Viruses Triggers Tumor-Specific Immune Responses and Facilitates Therapy of Disseminated Lung Cancer

Arnold Kloos, Norman Woller, Engin Gürlevik, Cristina-Ileana Ureche, Julia Niemann, Nina Armbrecht, Nikolas T. Martin, Robert Geffers, Michael P. Manns, Rita Gerardy-Schahn, and Florian Kühnel

Synopsis: Kloos and colleagues show that polysialic acid-specific retargeting of systemically administered oncolytic viruses leads to effective tumor infection, CD8 T-cell responses for mutated tumor neopeptide Gsta2-Y9H, and improved survival in an immunocompetent mouse model of disseminated lung cancer.

- 764** Committing Cytomegalovirus-Specific CD8 T Cells to Eliminate Tumor Cells by Bifunctional Major Histocompatibility Class I Antibody Fusion Molecules



Martina Schmittnaegel, Victor Levitsky, Eike Hoffmann, Guy Georges, Olaf Mundigl, Christian Klein, and Hendrik Knoetgen

Synopsis: Schmittnaegel and colleagues describe the generation of a novel tumor-peptide-MHCI-antibody fusion protein that redirects a highly functional subset of CMV-specific T cells to eliminate tumor cells by engaging a naturally occurring T-cell population in humans that controls cytomegalovirus infection.

- 777** Induction of HER2 Immunity in Outbred Domestic Cats by DNA Electrovaccination
- Heather M. Gibson, Jesse J. Veenstra, Richard Jones, Ulka Vaishampayan, Michele Sauerbrey, Gerold Bepler, Lawrence Lum, Joyce Reyes, Amy Weise, and Wei-Zen Wei

Synopsis: Gibson and colleagues show that outbred domestic cats develop mammary tumors similar to those in humans. Electrovaccination of heterologous or point-mutated feline HER2 DNA overcomes T-cell immune tolerance in 40% of healthy cats and induces antibodies with distinct specificity.

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787 The Epstein–Barr Virus Lytic Protein BZLF1 as a Candidate Target Antigen for Vaccine Development

Alex S. Hartlage, Tom Liu, John T. Patton, Sabrina L. Garman, Xiaoli Zhang, Habibe Kurt, Gerard Lozanski, Mark E. Lustberg, Michael A. Caligiuri, and Robert A. Baiocchi

Synopsis: Hartlage, Liu, and colleagues show that vaccination of hu-PBL-SCID mice with EBV protein BZLF1-pulsed dendritic cells induced specific cellular immunity and prolonged survival from fatal EBV-driven lymphoproliferative disease, identifying BZLF1 as a prophylactic vaccine candidate for EBV-associated diseases.

795 IFN γ Induces DNA Methylation–Silenced GPR109A Expression via pSTAT1/p300 and H3K18 Acetylation in Colon Cancer

Kankana Bardhan, Amy V. Paschall, Dafeng Yang, May R. Chen, Priscilla S. Simon, Yangzom D. Bhutia, Pamela M. Martin, Muthusamy Thangaraju, Darren D. Browning, Vadivel Ganapathy, Christopher M. Heaton, Keni Gu, Jeffrey R. Lee, and Kebin Liu

Synopsis: Bardhan and colleagues show that short-chain fatty acid receptor GPR109A functions as a tumor suppressor that is silenced by DNA methylation in colon cancer, while host immune cytokine IFN γ upregulates GPR109A expression, via pSTAT1/p300 activation and H3K18 acetylation, to suppress tumor development.

806 T-cell Expression of IL10 Is Essential for Tumor Immune Surveillance in the Small Intestine



Kristen L. Dennis, Abdulrahman Saadalla, Nichole R. Blatner, Shuya Wang, Vysak Venkateswaran, Fotini Gounari, Hilde Cheroutre, Casey T. Weaver, Axel Roers, Nejat K. Egilmez, and Khashayarsha Khazaie

Synopsis: Dennis and colleagues show that in the small intestine CD4⁺ T cells are the major sources of IL10, and ablation of IL10 in CD4⁺ T cells leads to loss of IFN γ -dependent immune surveillance, resulting in inefficient Th1 commitment and carcinoma transition by slowing polyp growth and enhancing invasiveness.

815 Generation of Potent T-cell Immunotherapy for Cancer Using DAP12-Based, Multichain, Chimeric Immunoreceptors

Enxiu Wang, Liang-Chuan Wang, Ching-Yi Tsai, Vijay Bhoj, Zack Gershenson, Edmund Moon, Kheng Newick, Jing Sun, Albert Lo, Timothy Baradet, Michael D. Feldman, David Barrett, Ellen Puré, Steven Albelda, and Michael C. Milone

Synopsis: Wang and colleagues describe a new multichain, chimeric antigen receptor (CAR) that uses portions of KIR2DS2 to engage DAP12, mimicking natural NK- and T-cell signaling. This new CAR triggers potent T-cell antitumor responses in vivo due to improved retention of CAR surface expression and effector function.

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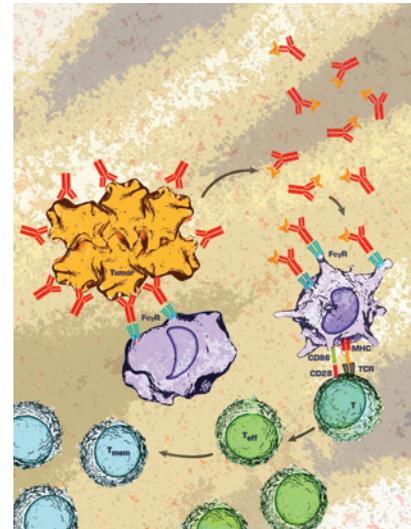
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ABOUT THE COVER

The cover image is an artistic rendition of the mechanism of antitumor vaccinal effect mediated by cytotoxic antibodies. Antitumor antibodies opsonize tumor cells and target them for killing by macrophages via FcγR-mediated antibody-dependent cellular cytotoxicity or phagocytosis (ADCC or ADCP), a process that generates antibody:tumor-associated antigen (TAA) immune complexes (IC). ICs engage activating FcγRs expressed by dendritic cells (DC), stimulating DC maturation and presentation of TAAs to T cells, thereby leading to the generation of antitumor effector T cells and long-term memory T cells. For details, see the Masters of Immunology article by DiLillo and Ravetch that begins on page 704 of this issue.



ABOUT THE MASTER

Jeffrey V. Ravetch, MD, PhD, is the Theresa and Eugene M. Lang Professor at The Rockefeller University and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology. Dr. Ravetch and his laboratory have made major discoveries contributing to our understanding of the biology of the Fc receptors (FcR) and their critical roles in inflammation and in shaping the immune response. Even though the existence of the FcRs was suggested decades earlier, the structures and functions of these receptors were not defined until Dr. Ravetch and his colleagues cloned and characterized two murine FcRs for the immunoglobulin G (IgG) isotype (FcγR) in 1986. In that seminal article they described the near homologous extracellular domains of these FcRs with distinct cytoplasmic tails, including the discovery of the immune-tyrosine inhibitory motif, thus providing the molecular basis for the functional heterogeneity of FcRs. Based on the cellular distribution and preferential expression patterns, they hypothesized that FcRs bind the same ligands but transmit different signals. Since then, using elegant biochemistry and mouse strains they generated with various components of the FcRs genetically modified, the Ravetch laboratory has defined mechanisms by which antibodies mediate their diverse biologic activities *in vivo*, establishing the preeminence of FcR pathways in host defense, inflammation, and tolerance. They have identified and described novel inhibitory signaling pathways to account for the paradoxical roles of antibodies as promoting and suppressing inflammation. The focus of the Ravetch laboratory is to continue to define the function and regulation of the IgG Fc domain and the diverse FcRs to which they bind. He has extended his studies into clinical applications for the treatment of neoplastic, inflammatory, and infectious diseases through collaborations with industry partners.

Dr. Ravetch has received numerous awards, including the Burroughs-Wellcome Scholar Award in molecular parasitology, the Pew Scholar Award, the Lee C. Howley Sr. Prize, the AAI-Huang Foundation Meritorious Career Award, the William B. Coley Award for distinguished research in basic and tumor immunology, the Sanofi-Institut Pasteur Award, the Canada Gairdner International Prize, and the Wolf Prize in Medicine. (Continued on the following page.)



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ABOUT THE MASTER

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He received an honorary doctorate from Freidrich-Alexander University, Nuremberg/Erlangen. Dr. Ravetch was elected as a member of the U.S. National Academy of Sciences and the Institute of Medicine, as a Fellow of the American Academy of Arts and Sciences, and of the American Association for the Advancement of Science. He serves as a consultant or a member on the scientific advisory boards of numerous organizations, including charitable foundations that support scientific research and training, such as the Cancer Research Institute, the Irvington Institute for Medical Research, and the Damon Runyon Foundation, and various biotechnology and pharmaceutical companies. He has published more than 200 research articles, book chapters, and reviews and serves on the editorial boards of leading peer-reviewed journals.

Dr. Ravetch is a native of New York City. He received his BS degree, *cum laude*, in molecular biophysics and biochemistry from Yale University, where he worked with Donald M. Crothers on the thermodynamic and kinetic properties of synthetic oligoribonucleotides. He earned his PhD in genetics from The Rockefeller University under the tutelage of Norton Zinder and Peter Model, investigating the genetics of viral replication and gene expression for the single-stranded DNA bacteriophage f1, and his MD from Cornell University Medical School. Dr. Ravetch pursued postdoctoral training with Philip Leder at the NIH, identifying and characterizing the genes encoding human antibodies and the DNA elements involved in switch recombination. He was a member of the faculty of Memorial Sloan Kettering Cancer Center and Cornell Medical College before joining The Rockefeller University. Dr. Ravetch is an avid fan of poetry, dating back to his undergraduate days at Yale, where he earned a BA in English literature simultaneously with his BS degree. He is a passionate collector of 20th century American poetry, focusing on the works of Wallace Stevens, Robert Penn Warren, and Mark Strand. He served on the board of the American Academy of Poets and is currently a board member of the National Poetry Series. When not in the lab or on the road, Dr. Ravetch can be found at the opera or tending to his gardens in the Hudson Valley.