

MASTERS OF IMMUNOLOGY

- 97** Modification of Cell Differentiation, One of the Mechanisms in the Surveillance of Malignancy



Eva Klein, Noemi Nagy, and Eahsan Rasul

CANCER IMMUNOLOGY AT THE CROSSROADS: MICROBIOLOGY

- 103** Microbiota Modulation of Myeloid Cells in Cancer Therapy
- Romina S. Goldszmid, Amiran Dzutsev, Sophie Viaud, Laurence Zitvogel, Nicholas P. Restifo, and Giorgio Trinchieri

CANCER IMMUNOLOGY MINIATURES

- 110** PD-L1 Expression in Melanocytic Lesions Does Not Correlate with the BRAF V600E Mutation
- Nemanja Rodić, Robert A. Anders, James R. Eshleman, Ming-Tseh Lin, Haiying Xu, Jung H. Kim, Katie Beierl, Shuming Chen, Brandon S. Lubber, Hao Wang, Suzanne L. Topalian, Drew M. Pardoll, and Janis M. Taube
- Synopsis:* Rodić and colleagues analyzed archival melanocytic lesions and cultured melanomas and found no correlation between melanocyte PD-L1 expression and BRAF V600E mutation, indicating that distinct biomarkers should be used to select patients for BRAF inhibitor and PD-1/PD-L1 checkpoint blockade therapies.

PRIORITY BRIEF

- 116** Checkpoint Blockade Immunotherapy Relies on T-bet but Not Eomes to Induce Effector Function in Tumor-Infiltrating CD8⁺ T Cells
- Melissa M. Berrien-Elliott, Jinyun Yuan, Lauryn E. Swier, Stephanie R. Jackson, Collin L. Chen, Maureen J. Donlin, and Ryan M. Teague
- Synopsis:* Berrien-Elliott and colleagues report that combination checkpoint blockade induced expression of T-bet and Eomes but only T-bet was required to restore CD8⁺ antitumor effector function, leading to a >95% cure rate in leukemia-bearing mice given this immunotherapy regimen.

RESEARCH ARTICLES

- 125** The Nonsignaling Extracellular Spacer Domain of Chimeric Antigen Receptors Is Decisive for *In Vivo* Antitumor Activity

Michael Hudecek, Daniel Sommermeyer, Paula L. Kosasih, Anne Silva-Benedict, Lingfeng Liu, Christoph Rader, Michael C. Jensen, and Stanley R. Riddell

Synopsis: Hudecek, Sommermeyer, and colleagues show that modifications of the length and composition of the extracellular spacer of a chimeric antigen receptor (CAR) that abrogate its binding to Fc receptors can prevent off-target activation of CAR T cells and enhance their antitumor efficacy.

- 136** Tasquinimod Modulates Suppressive Myeloid Cells and Enhances Cancer Immunotherapies in Murine Models



Li Shen, Anette Sundstedt, Michael Ciesielski, Kiersten Marie Miles, Mona Celander, Remi Adelaiye, Ashley Orillion, Eric Ciamporcerio, Swathi Ramakrishnan, Leigh Ellis, Robert Fenstermaker, Scott I. Abrams, Helena Eriksson, Tomas Leanderson, Anders Olsson, and Roberto Pili

Synopsis: Shen, Sundstedt, and colleagues show in murine models that tasquinimod enhanced the antitumor effects of SurVaxM tumor vaccine for prostate cancer and of 5T4Fab-SEA tumor-targeted superantigen for melanoma by inhibiting the accumulation and function of tumor-infiltrating suppressive myeloid cells.

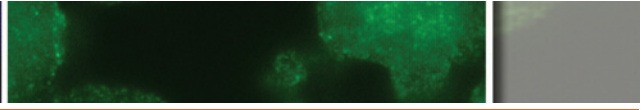
- 149** Combination of 4-1BB Agonist and PD-1 Antagonist Promotes Antitumor Effector/Memory CD8 T Cells in a Poorly Immunogenic Tumor Model



Shihao Chen, Li-Fen Lee, Timothy S. Fisher, Bart Jessen, Mark Elliott, Winston Eving, Kathryn Logronio, Guang Huan Tu, Konstantinos Tsaparikos, Xiaoi Li, Hui Wang, Chi Ying, Mengli Xiong, Todd VanArsdale, and John C. Lin

Synopsis: Chen, Lee, and colleagues compared the antitumor activity of anti-PD-1 in combination with anti-4-1BB versus with anti-LAG-3 and showed in syngeneic, poorly immunogenic mouse tumor models that the combination with anti-4-1BB elicited superior and well-tolerated tumor inhibition that did not require vaccine.

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161 Extensive Profiling of the Expression of the Indoleamine 2,3-Dioxygenase 1 Protein in Normal and Tumoral Human Tissues

Ivan Théate, Nicolas van Baren, Luc Pilotte, Pierre Moulin, Pierre Larrieu, Jean-Christophe Renaud, Caroline Hervé, Ilse Gutierrez-Roelens, Etienne Marbaix, Christine Sempoux, and Benoît J. Van den Eynde
Synopsis: Théate, van Baren, and colleagues used a highly specific antibody to characterize IDO1 expression in a large series of healthy and tumoral human tissues to facilitate the selection of appropriate tumor types for pharmacologic IDO1 inhibition and to anticipate possible side effects of this treatment.

173 Afucosylated Antibodies Increase Activation of FcγRIIIa-Dependent Signaling Components to Intensify Processes Promoting ADCC

Scot D. Liu, Cecile Chalouni, Judy C. Young, Teemu T. Junttila, Mark X. Sliwkowski, and John B. Lowe
Synopsis: Liu and colleagues show that afucosylated antibodies potentiate ADCC by increasing the cytotoxic rate and number of NK cells capable of killing multiple targets, which results from increased affinity between antibodies and FcγRIIIa to enhance activation of signaling molecules that promote cytoskeletal rearrangement and degranulation.

184 B7-H4 Expression by Nonhematopoietic Cells in the Tumor Microenvironment Promotes Antitumor Immunity



Ramtin Rahbar, Albert Lin, Magar Ghazarian, Helen-Loo Yau, Sangeetha Paramathas, Philipp A. Lang, Anita Schildknecht, Alisha R. Elford, Carlos Garcia-Batres, Bernard Martin, Hal K. Berman, Wey L. Leong, David R. McCready, Michael Reedijk, Susan J. Done, Naomi Miller, Bruce Youngson, Woong-Kyung Suh, Tak W. Mak, and Pamela S. Ohashi
Synopsis: Rahbar and colleagues show that B7-H4 promotes antitumor immunity against mouse mammary cancer and insulinomas and that its expression levels correlate with those of MHC class I in mouse and human tumors; high B7-H4 expression is associated with improved recurrence-free survival in breast cancer patients.

196 Cell-free Tumor Microparticle Vaccines Stimulate Dendritic Cells via cGAS/STING Signaling

Huafeng Zhang, Ke Tang, Yi Zhang, Ruihua Ma, Jingwei Ma, Yong Li, Shunqun Luo, Xiaoyu Liang, Tiantian Ji, Zhichao Gu, Jinzhi Lu, Wei He, Xuetao Cao, Yonghong Wan, and Bo Huang
Synopsis: Zhang, Tang, Zhang, and colleagues report that wide-spectrum antitumor immunity from vaccination with tumor microparticles (T-MP) or T-MP-loaded dendritic cells (DC) is mediated by the cGAS/STING DNA-sensing innate immune pathway and production of type I IFN, which promotes DC maturation and tumor-antigen presentation.

206 Safety of Targeting ROR1 in Primates with Chimeric Antigen Receptor-Modified T Cells

Carolina Berger, Daniel Sommermeyer, Michael Hudecek, Michael Berger, Ashwini Balakrishnan, Paulina J. Paszkiewicz, Paula L. Kosasih, Christoph Rader, and Stanley R. Riddell
Synopsis: Berger and colleagues adoptively transferred autologous ROR1 chimeric antigen receptor-modified T (CAR-T) cells into nonhuman primates to demonstrate the safety, persistence, and function of ROR1 CAR-T cells in vivo, and the utility of the model for preclinical testing of novel CARs.

CORRECTION

217 Correction: Mesothelin-Specific Chimeric Antigen Receptor mRNA-Engineered T Cells Induce Antitumor Activity in Solid Malignancies

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ABOUT THE COVER

Many cell types can be infected with Epstein–Barr virus (EBV), but only B lymphocytes express the set of EBV-encoded proteins that induce proliferation. Expression of these viral proteins is restricted to a defined B-cell differentiation stage. Emergence of EBV-induced B-cell malignancies is suppressed by highly efficient immunologic surveillance mechanisms. In addition to cytotoxic T cell-mediated elimination of infected cells, the regulatory circuit of the immune response also operates in surveillance, particularly in the early phase of infection. This mechanism involves T cell-mediated regulation of B-cell differentiation, a phenomenon that can be demonstrated *in vitro* with experimentally infected B cells.

The cover image (generated by Dr. Eahsan Rasul) comprises fluorescence micrographs of CBM1-Ral-STO cells treated with lymphokine IL21, a product of activated T cells. CBM1-Ral-STO is a lymphoblastoid cell line generated by *in vitro* infection of human cord blood mononuclear cells with EBV. IL21 pushes the cells to plasmacytoid differentiation as shown by the expression of Blimp-1, a plasma cell-specific marker. In these cells the EBV-encoded growth program is not expressed due to downregulation of EBNA-2, and consequently these EBV-infected cells cease to proliferate. Cells in the top two panels were stained with mouse anti-EBNA-2 mAb clone PE2 (green), and anti-LMP-1 mAb clone S-12 (red). Cells in the bottom two panels were stained with mouse anti-Blimp-1 mAb clone 3H2-E8 (green), and Dapi for nuclear DNA. For details, see the Masters of Immunology primer by Eva Klein and colleagues that begins on page 97 of this issue.

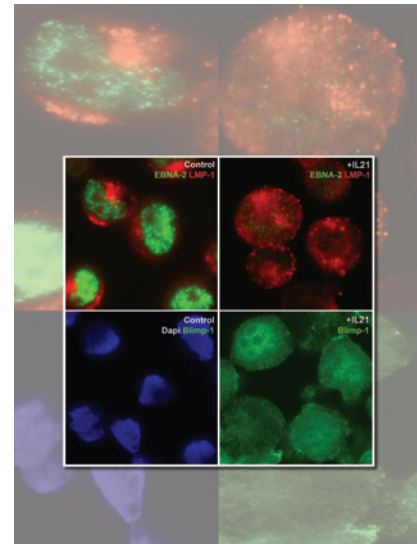
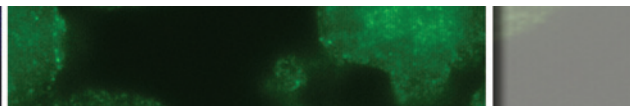


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ABOUT THE MASTER

Eva Fischer Klein, MD, PhD, is a professor emeritus and group leader in the Microbiology, Tumor and Cell Biology Center (MTC) of the Karolinska Institute, Stockholm, Sweden. Her pioneering contributions in experimental and clinical studies cover several aspects of malignancy including tumorigenesis, host immune responses, and the microenvironment. Guided by her work on virus-induced lymphomas in mice she began studies on Burkitt lymphoma in its initial stages when the Epstein–Bar virus (EBV) was discovered in Burkitt lymphoma tissues. EBV continues to be her main research focus. She has established a number of cell lines derived from African Burkitt lymphoma that are in use today.

Dr. Klein was born in Budapest, Hungary, in 1925. With the help of friends she survived the Holocaust (miraculously on a few occasions); immediately after the war she began medical studies at the University of Budapest, where she met Georg Klein, who became her husband. In the last days before the Iron Curtain descended on Hungary the couple moved to Stockholm. They both obtained positions as research students in the department of cell biology and genetics at the Karolinska Institute in 1948 under the tutelage of Professor Torbjörn Caspersson. The black and white photograph was taken in 1948 upon their arrival at the Karolinska. (For more details, see the article by G. Klein and E. Klein in *Ann Rev Immunol* 1989;7:1–33.)

Professor Klein received her MD in 1955 and her PhD in 1965. Her PhD thesis work was on the transformation of solid tumors into ascites tumors, focusing on the evolution of tumor cell populations based on variation and selection. This theme recurs in her present studies in chronic lymphocytic leukemia. Dr. Klein became a professor of tumor biology in 1979 and professor emeritus in 1993. She has mentored many students, some of whom have reached top positions in Sweden and internationally.

Dr. Klein has published over 500 papers. She has served as an editor for *Seminars in Cancer Biology*. She is a member of the Royal Swedish Academy of Sciences, a foreign member of the Hungarian Academy of Sciences and the Hungarian Immunological Society, the first honorary member of the Israel Immunological Society, and a fellow of the European Union Contra Cancer. She was elected as a fellow of the American Association for Cancer Research Academy in 2013.

Professor Eva Klein has received many awards and honors, including honorary doctorates from the University of Nebraska and the Ohio State University; the Bertha Goldblatt Teplitz Award from the Ann Langer Cancer Research Foundation; the inaugural William B. Coley Award in Tumor Immunology from the Cancer Research Institute; the Björken Prize from Uppsala University; the Nordic Prize of the Erik Fernström Foundation of Lund University; the Thomas P. Infusino Prize and Lectureship in Cancer Causation and Epidemiology from the Lautenberg Center for General and Tumor Immunology; the Orden Nacional al Mérito de la República de Colombia; and the Mendel Honorary Medal for Merit in the Biological Sciences from the Academy of Sciences of the Czech Republic. She was declared the 2006 MTC Scientist of the Year, and in 2010 she received the Karolinska Institute's 200-Year Anniversary Silver Medal for Medical Research. The Kleins have one son, who is a mathematician, and two daughters, one an MD and the other a playwright.



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