

MASTERS OF IMMUNOLOGY

- 701 **Immunomodulatory Roles of Lymphatic Vessels in Cancer Progression**
Melody A. Swartz



CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 708 **Vaccines for Cancer Prevention: A Practical and Feasible Approach to the Cancer Epidemic**
Olivera J. Finn

MEETING REPORT

- 714 **Cancer Immunotherapy Highlights from the 2014 ASCO Meeting**
Lauren C. Harshman, Charles G. Drake, Jennifer A. Wargo, Padmanee Sharma, and Nina Bhardwaj

CANCER IMMUNOLOGY MINIATURES

- 720 **Therapeutic *In Situ* Autovaccination against Solid Cancers with Intratumoral Poly-ICLC: Case Report, Hypothesis, and Clinical Trial**
Andres M. Salazar, Rodrigo B. Erlich, Alexander Mark, Nina Bhardwaj, and Ronald B. Herberman
Synopsis: Salazar and colleagues describe an ongoing trial of sequential intratumoral and intramuscular poly-ICLC vaccination, partly based on results in a pilot volunteer patient with advanced rhabdomyosarcoma; the authors postulate conversion of tumor into a personalized vaccine, activating innate and adaptive immunity.

PRIORITY BRIEF

- 725 **Targeting Immune Suppression with PDE5 Inhibition in End-Stage Multiple Myeloma**
Kimberly A. Noonan, Nilanjan Ghosh, Lakshmi Rudraraju, Marilyn Bui, and Ivan Borrello
Synopsis: Noonan and colleagues report that addition of the phosphodiesterase-5 inhibitor, tadalafil, reduced the expression of immunosuppressive mediators in myeloid-derived suppressor cells, restored the patient's responsiveness to lenalidomide-based therapy, and elicited a durable antimyeloma clinical response.

RESEARCH ARTICLES

- 732 **CD1d-Restricted Antigen Presentation by V γ 9V δ 2-T Cells Requires Trogocytosis**
Famke L. Schneiders, Jan Prodöhl, Jurjen M. Ruben, Tom O'Toole, Rik J. Scheper, Marc Bonneville, Emmanuel Scotet, Henk M.W. Verheul, Tanja D. de Gruijl, and Hans J. van der Vliet
Synopsis: Schneiders and colleagues show that phosphoantigen (pAg)-activated V γ 9V δ 2-T cells were able to present glycolipid Ag α -galactosylceramide to iNKT cells not from *de novo* synthesis of antigen-presenting molecules but from trogocytosed CD1d-containing membrane fragments from pAg-expressing cells.

- 741 **Microtubule-Depolymerizing Agents Used in Antibody-Drug Conjugates Induce Antitumor Immunity by Stimulation of Dendritic Cells**



Philipp Müller, Kea Martin, Sebastian Theurich, Jens Schreiner, Spasenija Savic, Grzegorz Terszowski, Didier Lardinois, Viola A. Heinzelmann-Schwarz, Max Schlaak, Hans-Michael Kvasnicka, Giulio Spagnoli, Stephan Dirnhofer, Daniel E. Speiser, Michael von Bergwelt-Baildon, and Alfred Zippelius

Synopsis: Müller, Martin, von Bergwelt-Baildon, Zippelius, and colleagues show that the dolastatin family of microtubule inhibitors induced tumor-resident DC maturation and homing to draining lymph nodes to potentiate cellular antitumor immune responses, providing a rationale for combining dolastatin-based treatments with immunotherapy.

- 756 **Efficient Induction of Antitumor Immunity by Synthetic Toll-like Receptor Ligand-Peptide Conjugates**

Gijs G. Zom, Selina Khan, Cedrik M. Britten, Vinod Sommandas, Marcel G.M. Camps, Nikki M. Loof, Christina F. Budden, Nico J. Meeuwenoord, Dmitri V. Filippov, Gijsbert A. van der Marel, Hermen S. Overkleef, Cornelis J.M. Melief, and Ferry Ossendorp
Synopsis: Zom, Khan, Britten, and colleagues report that direct conjugation of lipopeptide Pam₃CSK₄ to synthetic long peptides enhanced *in vivo* targeting and maturation of the conjugate with superior priming of CD8⁺ and CD4⁺ T cells in two mouse tumor models.

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- 765** **The Promotion of Breast Cancer Metastasis Caused by Inhibition of CSF-1R/CSF-1 Signaling Is Blocked by Targeting the G-CSF Receptor**
Agnieszka Swierczak, Andrew D. Cook, Jason C. Lenzo, Christina M. Restall, Judy P. Doherty, Robin L. Anderson, and John A. Hamilton
Synopsis: Swierczak and colleagues show that blockade of CSF-1R signaling promoted metastasis in two mouse mammary tumor models, with increases in serum G-CSF and neutrophils, which can be overcome by anti-G-CSFR antibodies, raising concerns about targeting CSF-1R as breast cancer therapy.
- 777** **Whole-Body Irradiation Increases the Magnitude and Persistence of Adoptively Transferred T Cells Associated with Tumor Regression in a Mouse Model of Prostate Cancer**
Lindsay K. Ward-Kavanagh, Junjia Zhu, Timothy K. Cooper, and Todd D. Schell
Synopsis: Ward-Kavanagh and colleagues demonstrate in a mouse model of prostate cancer that radiation conditioning promoted accumulation of granzyme B-expressing donor T cells in lymphoid organs and prostates, altering the tumor microenvironment so that subsequent rounds of T-cell therapy can promote therapeutic benefit.
- 789** **Restoration of miR17/20a in Solid Tumor Cells Enhances the Natural Killer Cell Antitumor Activity by Targeting Mekk2**
Hong Jiang, Ping Wang, Xiaohua Li, Qilong Wang, Zhong-Bin Deng, Xiaoying Zhuang, Jingyao Mu, Lifeng Zhang, Baomei Wang, Jun Yan, Donald Miller, and Huang-Ge Zhang
Synopsis: The Zhang laboratory reports that restored miR-17/20a expression in murine breast and colon cancer cells reprogrammed tumor cells for NK cell-mediated cytotoxicity by inhibiting MHC class I via the Mekk2-Mek5-Erk5 pathway, indicating that miR-17/20a may be a tumor suppressor.
- 800** **Rescue of Notch-1 Signaling in Antigen-Specific CD8⁺ T Cells Overcomes Tumor-Induced T-cell Suppression and Enhances Immunotherapy in Cancer**
Rosa A. Sierra, Paul Thevenot, Patrick L. Raber, Yan Cui, Chris Parsons, Augusto C. Ochoa, Jimena Trillo-Tinoco, Luis Del Valle, and Paulo C. Rodriguez
Synopsis: Sierra and colleagues show that myeloid-derived suppressor cells (MDSC) blocked Notch expression in T cells via nitric oxide-dependent mechanisms, and overexpression of the Notch 1 intracellular active domain rendered the CD8⁺ T cells resistant to the MDSC-induced tolerogenic effect.
- 812** **Computational Algorithm-Driven Evaluation of Monocytic Myeloid-Derived Suppressor Cell Frequency for Prediction of Clinical Outcomes**
Shigehisa Kitano, Michael A. Postow, Carly G.K. Ziegler, Deborah Kuk, Katherine S. Panageas, Czrina Cortez, Teresa Rasalan, Mathew Adamow, Jianda Yuan, Philip Wong, Gregoire Altan-Bonnet, Jedd D. Wolchok, and Alexander M. Lesokhin
Synopsis: Kitano and colleagues developed an algorithm to determine the frequency of monocytic MDSC (m-MDSC), performed a retrospective analysis of samples from patients treated with ipilimumab, and found m-MDSC frequencies inversely correlated with clinical response and CD8⁺ T-cell expansion following treatment.

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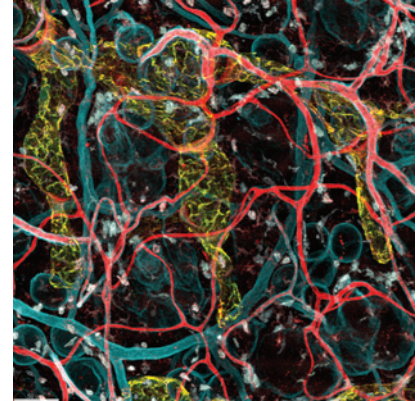
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ABOUT THE COVER

Lymphatic vessels are present throughout most organs, including the skin, as shown in the cover image, and have been considered primarily to provide transport functions for tissue fluid balance and cell exit from peripheral tissues. In addition to this classical role, however, emerging evidence implicates the lymphatic endothelium as an important regulator of adaptive immune responses, including dampening host immunity against tumors. The cover image is an immunofluorescence confocal microscopy image of an immunostained whole mount preparation of the dorsal mouse ear dermis, which shows lymphatic capillaries (Lyve-1, green), basement membrane (collagen IV, cyan), MHC class II cells (white), and blood vessels (CD31, red). CD31 is also present in cell-cell junctions of the lymphatic vessels (yellow). Scale bar, 50 microns. Tissue preparation, immunostaining, and confocal immunofluorescence imaging were performed by Witold Kilarski (EPFL, Lausanne, Switzerland.)



ABOUT THE MASTER

Melody A. Swartz, PhD, is the William B. Ogden Professor of Molecular Engineering at the University of Chicago and Professor of Bioengineering at the École Polytechnique Fédérale de Lausanne (EPFL) in the Institute for Bioengineering and the Swiss Institute for Experimental Cancer Research. Dr. Swartz was trained in chemical engineering; she earned a BS at The Johns Hopkins University in 1991 and a PhD at Massachusetts Institute of Technology in 1998. Her PhD thesis was completed in the laboratory of Dr. Rakesh Jain at the Massachusetts General Hospital, where she investigated how the transport functions of lymphatic vessels were coupled to the local tissue biomechanics and developed mathematical and experimental models to understand how the lymphatics respond to edema and how they restore homeostatic fluid balance. Dr. Swartz performed her postdoctoral studies in airway biomechanics at the Brigham and Women's Hospital and Harvard Medical School in the laboratory of Dr. Jeffrey Drazen, where she investigated how mechanical stresses are communicated between cells to instigate stress-dependent remodeling of the extracellular matrix. She was attracted to the discipline of engineering because of its quantitative and systems-level approaches to problem solving that can be used to address fundamental biological questions. After completing her training, Dr. Swartz joined the Department of Biomedical Engineering at Northwestern University as an assistant professor in 1999. She moved to the EPFL in 2003, where she was promoted to associate professor in 2006, and then full professor in 2010. After being away for over a decade, Dr. Swartz returned to her hometown, Chicago, in 2014, as she joined the newly founded Institute for Molecular Engineering at the University of Chicago.



With her training as a bioengineer, coupled with strong interests in cancer immunology, Dr. Swartz uses quantitative and multidisciplinary approaches to investigate the roles of the lymphatic system in immunophysiology and pathophysiology, focusing her efforts on the interface between vascular biology, transport biomechanics, and immunology. Her laboratory is currently exploring the function of lymphatic drainage in maintaining local immunologic tolerance and the roles of lymphangiogenesis in pathologic tolerance in diseases including cancer. These investigators are applying the cumulative knowledge of systems immunology of the lymphatic system to develop novel immunotherapeutic approaches in cancer, including lymph node-targeting vaccine approaches.

Dr. Swartz was elected as a fellow of the American Institute for Medical and Biological Engineering in 2007, and as a fellow of the Biomedical Engineering Society in 2012. She has received numerous awards, including the Arnold and Mabel Beckman Young Investigator Award in 2002, the Biomedical Engineering Society's Rita Schaffer Young Investigator Award in 2001, the European Research Council Investigator Awards in 2008 and in 2013, and the 2010 Robert Wenner Prize for Cancer Research from the Swiss Cancer League. In recognition of her creativity in research, she was named a MacArthur Foundation Fellow in 2012.

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