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MASTERS OF IMMUNOLOGY

- 1125** **Chemokines in Cancer**
 Melvyn T. Chow and Andrew D. Luster
 CME

CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

- 1132** **PD-1 Blockade in Renal Cell Carcinoma: To Equilibrium and Beyond**
 Lauren C. Harshman, Charles G. Drake, and Toni K. Choueiri

PRIORITY BRIEF

- 1142** **Quantitative Effect of Natural Killer–Cell Licensing on Hepatocellular Carcinoma Recurrence after Curative Hepatectomy**
 Naoki Tanimine, Yuka Tanaka, Tsuyoshi Kobayashi, Hiroataka Tashiro, Daiki Miki, Michio Imamura, Hiroshi Aikata, Junko Tanaka, Kazuaki Chayama, and Hideki Ohdan
Synopsis: Tanimine and colleagues report that multiplicity of compound KIR-HLA genotypes in blood cells of patients with hepatocellular carcinoma (HCC) correlate with HCC recurrence, supporting therapeutic manipulation of NK-cell activity to compensate for genetic susceptibility to HCC recurrence.



CANCER IMMUNOLOGY MINIATURES

- 1148** **Pulmonary Sarcoid–like Granulomatosis after Multiple Vaccinations of a Long-term Surviving Patient with Metastatic Melanoma**
 Natacha Bordry, Carla-Marisa Costa-Nunes, Laurène Cagnon, Philippe O. Gannon, Samia Abed-Maillard, Petra Baumgaertner, Timothy Murray, Igor Letovanec, Romain Lazor, Hasna Bouchaab, Nathalie Rufer, Emanuela Romano, Olivier Michielin, and Daniel E. Speiser
Synopsis: Bordry and colleagues report on a patient with metastatic melanoma, who received repetitive vaccinations with melanoma-associated antigen peptides augmented with CpG as adjuvant, developed autoimmunity without clinical complication, and experienced complete remission and long-term survival for more than 13 years.

RESEARCH ARTICLES

- 1154** **Phase II Study of Personalized Peptide Vaccination for Previously Treated Advanced Colorectal Cancer**
 Shiro Kibe, Shigeru Yutani, Satoru Motoyama, Takanobu Nomura, Natsuki Tanaka, Akihiko Kawahara, Tomohiko Yamaguchi, Satoko Matsueda, Nobukazu Komatsu, Masatomo Miura, Yudai Hinai, Satoshi Hattori, Akira Yamada, Masayoshi Kage, Kyogo Itoh, Yoshito Akagi, and Tetsuro Sasada
Synopsis: Kibe and colleagues report the safety and benefit in a phase II study of 60 pretreated, advanced colorectal cancer (CRC) patients of personalized vaccines comprising HLA-matched peptides selected from preexisting host immunity, providing a new approach of personalized immunotherapy for refractory CRC.
- 1163** **Intravenous Injection of MVA Virus Targets CD8⁺ Lymphocytes to Tumors to Control Tumor Growth upon Combinatorial Treatment with a TLR9 Agonist**
 Laetitia Fend, Tanja Gatard-Scheikl, Jacqueline Kintz, Murielle Gantzer, Emmanuelle Schaedler, Karola Rittner, Sandrine Cochin, Sylvie Fournel, and Xavier Préville
Synopsis: Fend and colleagues show in an orthotopic mouse model of renal carcinoma that intravenous and not subcutaneous injection of an MVA-MUC1 vaccine with TLR9 ligand (ODN1826) controls tumor growth by efficiently targeting tumor-specific effector/memory lymphocytes to the tumor.
- 1175** **Splenectomy Promotes Indirect Elimination of Intraocular Tumors by CD8⁺ T Cells That Is Associated with IFN γ - and Fas/FasL-Dependent Activation of Intratumoral Macrophages**
 Maxine R. Miller, Jonathan B. Mandell, Kelly M. Beatty, Stephen A.K. Harvey, Michael J. Rizzo, Dana M. Previte, Stephen H. Thorne, and Kyle C. McKenna
Synopsis: Miller and colleagues demonstrate a mechanism by which splenectomy promotes rejection of intraocular tumors, which involves an IFN γ -and-Fas/FasL-dependent interaction between CD8⁺ T cells and intratumoral macrophages eliciting severe ocular inflammation that indirectly eliminates intraocular tumors by inducing phthisis.

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- 1186** **c-Abl Modulates Tumor Cell Sensitivity to Antibody-Dependent Cellular Cytotoxicity**
Joseph C. Murray, Dalal Aldeghaither, Shangzi Wang, Rochelle E. Nasto, Sandra A. Jablonski, Yong Tang, and Louis M. Weiner
Synopsis: Murray and colleagues used RNAi functional genomics screening of 60 genes from an EGFR gene network and identified that inhibition of c-Abl activity in anti-EGFR-targeted cells can enhance the therapeutic efficacy of cetuximab, an ADCC-promoting anti-EGFR antibody, in colorectal and head and neck cancers.
- 1199** **STING Contributes to Antiglioma Immunity via Triggering Type I IFN Signals in the Tumor Microenvironment**
Takayuki Ohkuri, Arundhati Ghosh, Akemi Kosaka, Jianzhong Zhu, Maki Ikeura, Michael David, Simon C. Watkins, Saumendra N. Sarkar, and Hideho Okada
Synopsis: Ohkuri, Ghosh, Kosaka, and colleagues show that a STING-mediated DNA-sensor signaling is involved in IFN induction in the sterile microenvironment of brain tumor that enhances antitumor immunity, providing a proof-of-concept for developing STING agonists for cancer immunotherapy.
- 1209** **Granulin–Epithelin Precursor Renders Hepatocellular Carcinoma Cells Resistant to Natural Killer Cytotoxicity**
 Phyllis F.Y. Cheung, Chi Wai Yip, Nicholas C.L. Wong, Daniel Y.T. Fong, Linda W.C. Ng, Angus M.Y. Wan, Chun Kwok Wong, Tan To Cheung, Irene O.L. Ng, Ronnie T.P. Poon, Sheung Tat Fan, and Siu Tim Cheung
Synopsis: Cheung and colleagues show that hepatic oncofetal protein granulin–epithelin precursor (GEP) regulates HCC immunity by modulating MICA and HLA-E expression, which could be reversed by GEP blockade; serum GEP and MICA levels are prognostic and can be used to stratify patients for targeted therapy.
- 1220** **Prognostic Impact of Human Leukocyte Antigen Class I Expression and Association of Platinum Resistance with Immunologic Profiles in Epithelial Ovarian Cancer**
Tasuku Mariya, Yoshihiko Hirohashi, Toshihiko Torigoe, Takuya Asano, Takafumi Kuroda, Kazuyo Yasuda, Masahito Mizuuchi, Tomoko Sonoda, Tsuyoshi Saito, and Noriyuki Sato
Synopsis: Mariya and colleagues analyzed 122 cases of epithelial ovarian cancer (EOC) and identified low expression of HLA class I and low intraepithelial CTL infiltration as independent prognostic factors for poor overall survival for patients with advanced EOC; low HLA class I expression was correlated with platinum resistance.
- 1230** **Functional TCR Retrieval from Single Antigen-Specific Human T Cells Reveals Multiple Novel Epitopes**
 Petra Simon, Tana A. Omokoko, Andrea Breitreuz, Lisa Hebich, Sebastian Kreiter, Sebastian Attig, Abdo Konur, Cedrik M. Britten, Claudia Paret, Karl Dhaene, Özlem Türeci, and Ugur Sahin
Synopsis: Simon, Omokoko, and colleagues developed an integrated approach to retrieve and functionally characterize TCRs from single viral or tumor Ag-reactive T cells and isolated 56 unique Ag-specific TCRs against 39 different epitopes, supporting rational design of T cell-based immunotherapies using this approach.
- 1245** **Acknowledgment to Reviewers**

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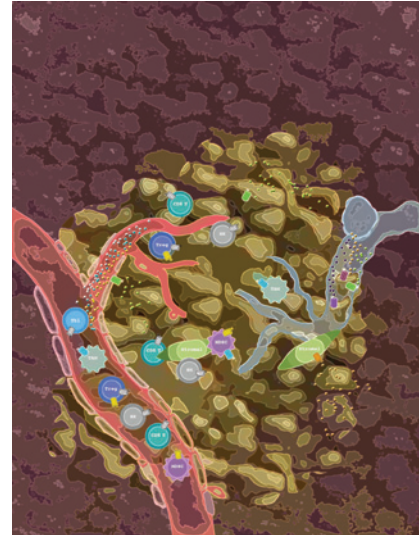
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ABOUT THE COVER

Chemokines are chemotactic cytokines with multifaceted roles in tumor development. The chemokine superfamily consists of approximately 50 endogenous chemokine ligands and 20 G-protein-coupled receptors, mediating the host response to cancer by directing the trafficking of leukocytes into the tumor microenvironment and inducing the development and maturation of lymphoid effector cells. Chemokines produced by tumor cells, intratumor stromal cells, and intratumor leukocytes can attract different immune cells into the tumor bed, and the composition of immune effector and suppressor cells in the tumor can affect the outcome of tumor development. Chemokines released by tumor cells, stromal cells, and leukocytes can directly affect the growth and survival of tumor cells by their angiogenic or angiostatic activity by inducing the release of tumor-promoting growth factors that can act in a paracrine fashion to promote tumor growth and by inducing the migration of tumor cells to distant sites for the development of metastasis. For details see the Masters of Immunology primer by Melvyn T. Chow and Andrew D. Luster on page 1125 of this issue.



ABOUT THE MASTER

Andrew D. Luster, MD, PhD, is the Persis, Cyrus, and Marlow B. Harrison Professor of Medicine at Harvard Medical School (HMS) and the E. Alexandria and Michael N. Altman Chair in Immunology at Massachusetts General Hospital (MGH). He received his BS in Biology *summa cum laude* from Duke University, his PhD in molecular genetics and immunology from the Rockefeller University, and his MD from Cornell University Medical College. Dr. Luster was a medical resident and infectious disease fellow in the Department of Medicine at MGH and a research fellow in the HMS Department of Genetics. In 1994, Dr. Luster established his independent laboratory at MGH. He was appointed chief of a new MGH division, the Division of Rheumatology, Allergy, and Immunology, and was named director of the new Research Center for Immunology and Inflammatory Diseases in 2000.

Dr. Luster is a quintessential medical scientist—a clinician with solid training in basic science. Over the past three decades, he has been intimately associated with the birth, growth, and development of the chemokine field. He performed his PhD research in the laboratories of Drs. Jeffrey Ravetch and Zev Cohn, identifying the interferon- γ inducible cytokine IP-10 and characterizing its molecular regulation. He continued his training in the fundamentals of basic science research as a postdoctoral fellow in Dr. Philip Leder's laboratory (HMS), studying the *in vivo* antitumor activity of the CXC chemokine IP-10 and defining the biologic activity of the CC chemokine eotaxin, an eosinophil chemoattractant. Dr. Luster has made multiple seminal contributions to our understanding of the roles of the chemokine family of immunoregulatory chemotactic cytokines in health and diseases since his initial discovery of the T-cell chemoattractant IP-10 (now also called CXCL10). His laboratory has helped define the chemokine family and its functions in immune-cell trafficking, which is necessary to generate innate and adaptive immune responses, and in the pathogenesis of immune and inflammatory diseases.

Dr. Luster is an outstanding teacher; he has taught many medical and immunology classes and has mentored over 60 clinical and basic science trainees from around the world. He is a reviewer for numerous peer-review journals and a member of various scientific advisory boards. Dr. Luster has received many awards and honors, including a Damon Runyon–Walter Winchell Postdoctoral Fellowship, a Cancer Research Institute Investigator Award, a Culpeper Medical Scientist Award, an NIH MERIT Award, and the 2011 Lee C. Howley Sr. Prize for Arthritis Research from the Arthritis Foundation. He is an elected member of the American Society for Clinical Investigation, the Interurban Clinical Club, and the American Association of Physicians.



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