Medical Immunology Campus Erlangen

MICE Letter
Winter 2011/12

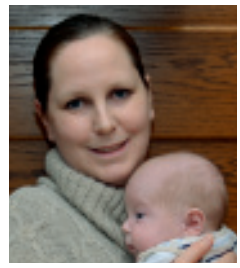
CONTENT

EDITORIAL

Dear colleagues and friends,

with this winter newsletter I would like to inform you about a number of notable events and changes that have taken place within the Medical Immunology Campus Erlangen during the past months.

In October 2011, I took over the position of chairman of the Immunology Campus from Prof. Bernhard Fleckenstein. Having the vision to form closer links between the numerous immunologists in Erlangen, Bernhard Fleckenstein initiated the foundation of this interdisciplinary research center at the Friedrich-Alexander Universität Erlangen-Nürnberg (FAU) more than three years ago. He was also the driving force of our participation in the Excellence Initiative of the German Federal Government. In addition, it was his idea to issue a regular newsletter, which presents scientific highlights within Erlangen´s community of immunologists. **In the name of all members of the Medical Immunology Campus Erlangen I wish to express my sincerest thanks to Bernhard Fleckenstein for his enthusiasm and commitment.**

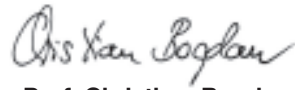


In November 2011, **Dr. Annette Grohmann**, who has been the Scientific Coordinator of the Campus for two and half years, went on maternity leave. She contributed a lot to the success of our guest semi-nar series and provided invaluable services to the Immunology Campus. We wish her much joy with her young family and hope to see her back at the FAU in the future.

Since February 1, 2012, **Dr. Sonja Pötzsch** is the new Scientific Coordinator of the Immunology Campus. Dr. Pötzsch was trained as a biologist in Erlangen and earned a PhD degree in immunology in 2010 in the group of Prof. Thomas Winkler, where she was already actively involved in scientific organizational work. She is therefore perfectly qualified for her new position. Welcome on board!

On December 21, 2011, Bernhard Fleckenstein, Andreas Mackensen and myself represented the Medical Immunology Campus Erlangen in Regensburg, where the Presidents and Deans of the Medical Faculties of the Universities of Erlangen, Würzburg and Regensburg met together with Dr. Wolfgang Heubisch, the Bavarian Minister for Science, Research and Arts. During this meeting the three universities officially inaugurated a Research Alliance in Immune Medicine, which is meant to promote life science research in the Northern part of Bavaria and to set the stage for the foundation of extrauniversity research institutes.

Finally, I would like to let you know that the 27th Annual Meeting of the European Macrophage and Dendritic Cell Society will take place in Erlangen in October 2013. More details on this exciting international event will follow in due time.



Prof. Christian Bogdan Coordinator

SCIENTIFIC HIGHLIGHTS

… over 90% of gB-specific antibodies are not neutralizing …

New Potential Targets for Immune Therapy on Human Cytomegalovirus Glycoprotein B

Repertoire Analysis of Human Memory B cells Identifies New Antigenic Domains on Glycoprotein B of Human Cytomegalovirus which are Target of Neutralizing Antibodies.

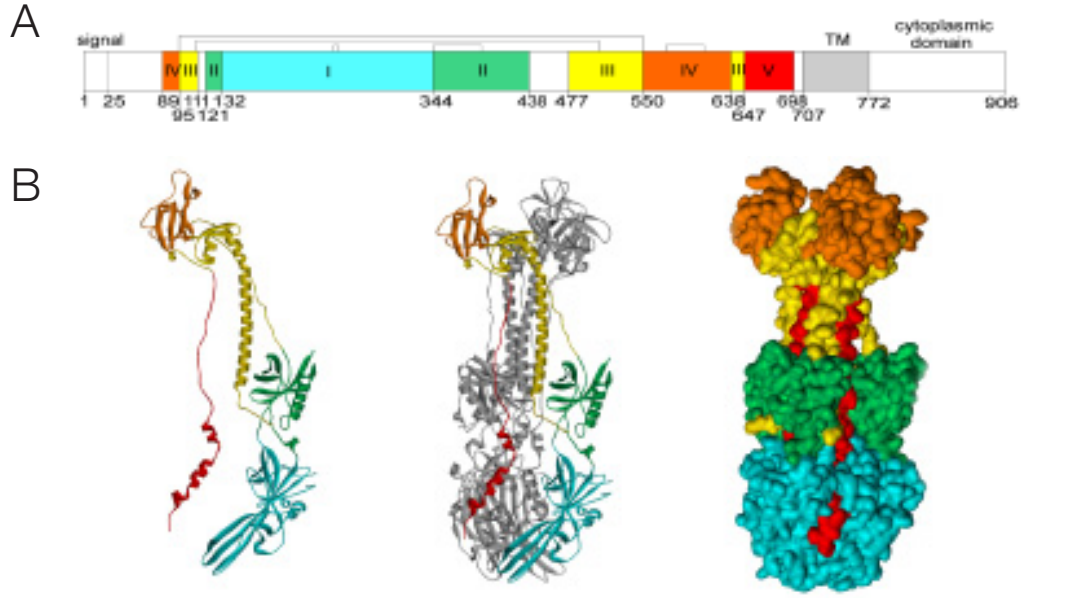
THOMAS WINKLER[1] · MICHAEL MACH[2]
SONJA PÖTZSCH[1] · NADJA SPINDLER[2]
1 CHAIR OF GENETICS, DEPARTMENT OF BIOLOGY
2 INSTITUTE OF CLINICAL AND MOLECULAR VIROLOGY

… two newly discovered domains on gB almost exclusively induce neutralizing antibodies …

… concentrating on these new domains should lead to improvement of future vaccine design and development of therapeutic antibodies …

Human cytomegalovirus (HCMV) is a widely circulating pathogen that causes severe disease in immunocompromised patients and infected foetuses. Glycoprotein (g)B is a major antigen for the induction of antiviral antibodies during infection and a constituent of experimental vaccines in humans. In order to design optimal antiviral biologicals for the prophylaxis and/or therapy of HCMV induced disease, it is crucial to understand the humoral immune response against gB. To this end, we comprehensively analyzed, for the first time, the human anti-gB memory B cell repertoire established by healthy, HCMV seropositive individuals in an unbiased fashion. To our surprise, the data revealed that the vast majority (>90%) of gB-specific antibodies are not neutralizing. Moreover, the target epitopes of the majority of neutralizing antibodies were not located within the previously characterized antigenic domains (AD) of gB. To map the target structures of these neutralizing antibodies, we generated a 3D model of HCMV gB. We discovered two protein domains targeted by the majority of neutralizing antibodies: Domain I, located between amino acids 132–343 of gB and domain II, a discontinuous domain, built from residues 121–131 and 344–437. These newly identified domains are recognized by serum antibodies of HCMV seropositive individuals (>50% of analyzed sera bind to domain I and >90% to domain II). Thus, in accordance with previous nomenclature, the domains were designated AD-4 (Dom II) and AD-5 (Dom I), respectively. Most interestingly, as opposed to the known AD of HCMV gB, both AD-4 and AD-5 almost exclusively induce antibodies capable of neutralizing free virus (>90%). Taken together, we propose that concentrating efforts on these two antigenic domains will improve future vaccine design as well as the development of effective therapeutic antibodies for passive immunization.

Pötzsch S., Spindler N., Wiegers A. K., Fisch T., Rücker P., Sticht H., Grieb N., Baroti T., Weisel F., Stamminger T. (2011)
B cell repertoire analysis identifies new antigenic domains on glycoprotein B of human cytomegalovirus which are target of neutralizing antibodies. PLoS Pathog 7, e1002172.



3D-model of Human Cytomegalovirus glycoprotein B (gB) and localization of structural antigenic domains I and II. The regions representing individual domains are displayed in different colors in analogy to the HSV gB structure by Heldwein et al. (2006) and the numbers of the starting residues are given. Brackets indicate disulfide bonds. Signal: signal sequence, TM: transmembrane helix. (B) Ribbon diagram of a gB monomer (left), trimer with two protomers shown in grey (middle) and accessible surface representation of the trimeric gB (right). Coloring scheme according to (A).

SCIENTIFIC HIGHLIGHTS

Herpes Simplex Virus type1 Infection Hampers Dendritic Cell Motility

Identification of a New Herpes Simplex Virus type1 Specific Immune Escape Mechanism: Interference with Adhesion and Migration of Dendritic Cells.

ALEXANDROS THEODORIDIS
ALEXANDER STEINKASSERER

DEPARTMENT OF IMMUNE MODULATION,
UNIVERSITY HOSPITAL ERLANGEN

HSV-1 is the prototypic member of the large and diverse family of herpesviridae, including several human pathogens. HSV-1 infections affect the majority of the adult population worldwide and are responsible for a variety of diseases, ranging from mild localized infections to life-threatening variants in newborns or immune-compromised persons. Moreover, HSV infections are related to HIV transmission, and coinfected patients have a higher plasma viral load. Thus, understanding the viral immune-evasion mechanisms is of great importance for the development of new therapies. Because dendritic cells (DCs) are the most important stimulators of antiviral immune responses by activating cytotoxic T lymphocytes, HSV-1 has evolved multiple strategies to inhibit normal DC function.

Immune responses require spatial and temporal coordinated interactions between different cell types within distinct microenvironments. This dynamic interplay depends amongst others on the ability of dendritic cells to actively migrate to defined sites of cellular encounters in various tissues. Therefore, pathogen-mediated interference with DC migration/ adhesion would be a very effective way of immune evasion.

CYTIP (cytohesin-interacting protein) is a key regulator of DC motility. It has previously been described to control LFA-1 deactivation and to regulate DC adherence. CYTIP expression is up-regulated during DC maturation, enabling their transition from the sessile to the motile state. Very recently, we could demonstrate that upon infection of human monocyte-derived DCs with HSV-1, CYTIP is rapidly degraded and as a consequence β-2 integrins, predominantly LFA-1, are activated (Theodoridis et al., 2011). Furthermore, we could show that the impairment of migration in HSV-1-infected DCs is in part the result of this increased integrin-mediated adhesion. This hijacking of the CD18 activation pathway interferes with central aspects of DC biology, such as homing to the T-cell areas of lymph nodes and T-cell priming. Understanding this new viral immune-evasion mechanism could help to develop new antiviral therapies in the future.

Theodoridis A. A., Eich C., Figdor C. G., Steinkasserer A. (2011).
Infection of dendritic cells with herpes simplex virus type 1 induces rapid degradation of CYTIP, thereby modulating adhesion and migration. Blood 118,107 – 115.

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 796, project B2).

… HSV-1 has evolved multiple strategies to inhibit normal DC function …

… infection of DCs with HSV-1 induces rapid degradation of CYTIP …

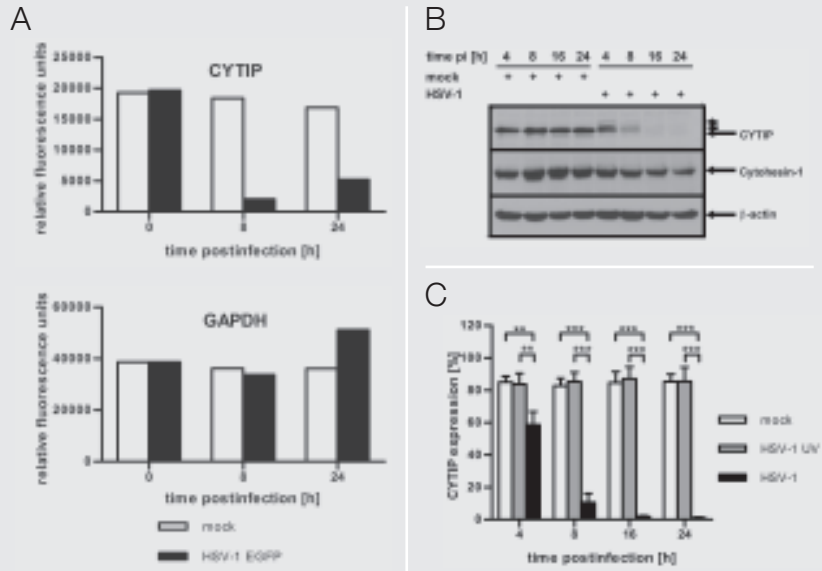


FIGURE 1 CYTIP is rapidly down-regulated in HSV-1-infected DCs. (A) Total mRNA was isolated from HSV-1 EGFP-infected and mock-infected DCs at the indicated time points, labeled and hybridized to Affymetrix Human Genome U133A arrays. (B) Western blot analyses of HSV-1 and mock infected DCs using antibodies against CYTIP, cytohesin-1, and ß-actin as loading control. (C) Quantification of CYTIP expression in mock-infected DCs, cells treated with UV-inactivated HSV-1 virions, and HSV-1-infected DCs by intracellular flow cytometry.

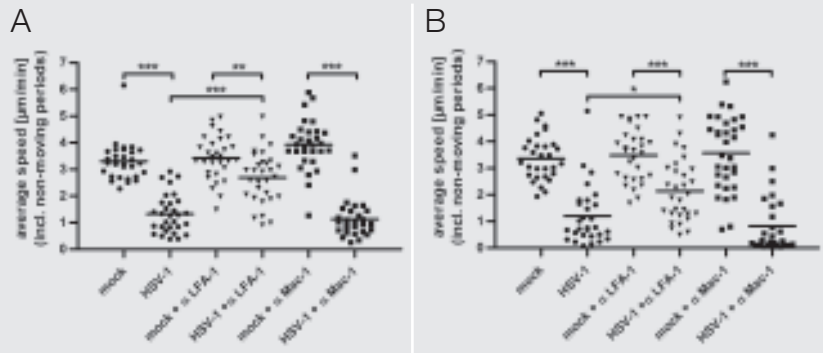


FIGURE 2 LFA-1 activation in HSV-1–infected DCs strongly reduces their chemotaxis. The specific influence of LFA-1 and Mac-1 on the adhesion of HSV-1–infected DCs was determined by adding anti-LFA-1 and anti-Mac-1 blocking antibodies in collagen matrices coated with fibronectin (A) or containing immobilized ICAM-1 Fc (B). In both conditions, the migration of mock-infected DCs was not significantly influenced. In contrast, the inhibition of LFA-1 significantly increased migration of infected DCs, whereas blocking of Mac-1 had no effect. Chemotaxis toward a CCL19 gradient was monitored by bright-field time-lapse video-microscopy.

SCIENTIFIC HIGHLIGHTS

Neuroimmunology of the Gut

Neuro-immune Vicious Cycle in the Gut

MATTHIAS ENGEL

INSTITUTE OF PHYSIOLOGY AND PATHOPHYSIOLOGY – DEPARTMENT OF MEDICINE

The human gut is richly innervated by axons of extrinsic sensory neurons that encode noxious chemical and mechanical stimuli and conduct the information to the central nervous system which finally leads to reflex responses and conscious sensation. The peptidergic subset of these nerve fibers release the neuropeptides CGRP (calcitonin gene-related peptide) and SP (substance P) upon activation. This quasi efferent neuropeptide release results in "neurogenic inflammation" which is characterized by vasodilatation and plasma extravasation through increased vessel permeability.

In the mouse, experimental colitis is induced by chemical enemas employing the hapten TNBS (2,4,6-trinitrobenzene-sulfonic-acid) or DSS (dextrane-sulfate-sodium-salt). In both cases the transient disruption of the epithelial barrier results in an overwhelming immune reaction, as colonic luminal or epithelial antigens overstimulate the mucosal immune system. In a recent study we investigated the role of the sensory nervous system in chemically-induced colitis mouse models using the above mentioned haptens.

The TNBS model was previously known to exert its colitogenic capacity through haptenization of colonic antigens, resulting in a Th1-dominated response. Surprisingly, we found TNBS to directly activate sensory neurons via the TRPA1 receptor-channel. Mass-spectrometry suggested an irreversible covalent binding of TNBS at intracellular cysteine residues of the N-terminus. TNBS-mediated activation of TRPA1 resulted in a huge efflux of colonic neuropeptides, SP being responsible for inducing and maintaining the colitis. TNBS colitis was abolished in TRPA1 knockout mice and wildtypes treated with a selective TRPA1 antagonist, either in a prophylactical or interventional manner. Chemically-induced sensory neuron depletion and nullmutation of the proinflammatory neuropeptide SP also prevented the TNBS colitis, suggesting that SP released from extrinsic sensory neurons was the phenomenological link between the nervous and immune systems.

Although the other colitis inductor DSS was not an activator of sensory neuronal receptor-channels, TRPA1-mediated SP release essentially contributed to colitis severity. In the manifest colitis, TRPA1 was found in a sensitized state and endogenous products of inflammatory lipid peroxidation (such as 4-HNE) induced increased TRPA1-dependent colonic neuropeptide release. Thus, we believe that pharmacological blockage of the TRPA1 receptor in sensory neurons of the colon will have therapeutic potential in human inflammatory bowel diseases as it may interrupt a proinflammatory neuro-immune vicious cycle.

… the role of the sensory nervous system in TNBS and DSS stimulated mice was investigated …

Engel M.A., Becker C., Reeh P.W., Neurath M.F. (2011a). Role of sensory neurons in colitis: increasing evidence for a neuroimmune link in the gut. Inflamm Bowel Dis *17*, 1030-1033.

Engel M. A., Khalil M., Mueller-Tribbensee S.M., Becker C., Neuhuber W. L., Neurath, M.F., Reeh, P. W. (2011b). The proximodistal aggravation of colitis depends on substance P released from TRPV1-expressing sensory neurons. J Gastroenterol.

Engel M.A., Khalil M., Siklosi N., Mueller-Tribbensee S.M., Neuhuber W. L., Neurath M.F., Becker C., Reeh P.W. (2012). Opposite effects of substance P and calcitonin gene-related peptide in oxazolone colitis. Dig Liver Dis *44*, 24-29.

Engel M.A., Leffler A., Niedermirtl F., Babes A., Zimmermann K., Filipovic M.R., Izydorczyk I., Eberhardt M., Kichko T.I., Mueller-Tribbensee S.M., *et al.* (2011c). TRPA1 and substance P mediate colitis in mice. Gastroenterology *141*, 1346-1358.

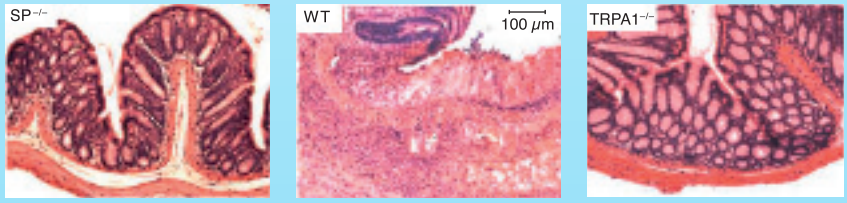


FIGURE 1 TNBS colitis. Wildtype mice show destruction of the mucosal architecture and accumulation of inflammatory cells. TRPA1-/- and mice lacking the proinflammatory neuropeptide SP (SP-/-) are protected.

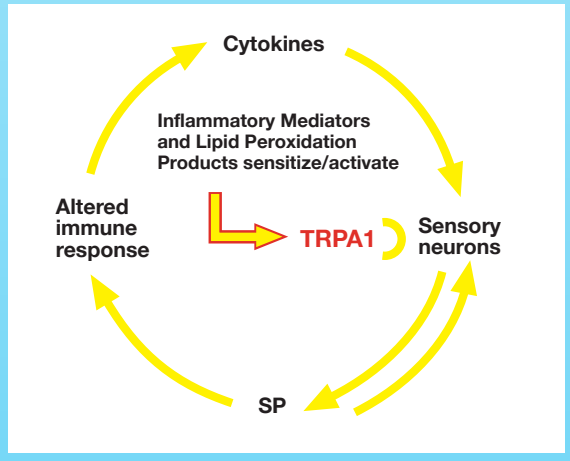
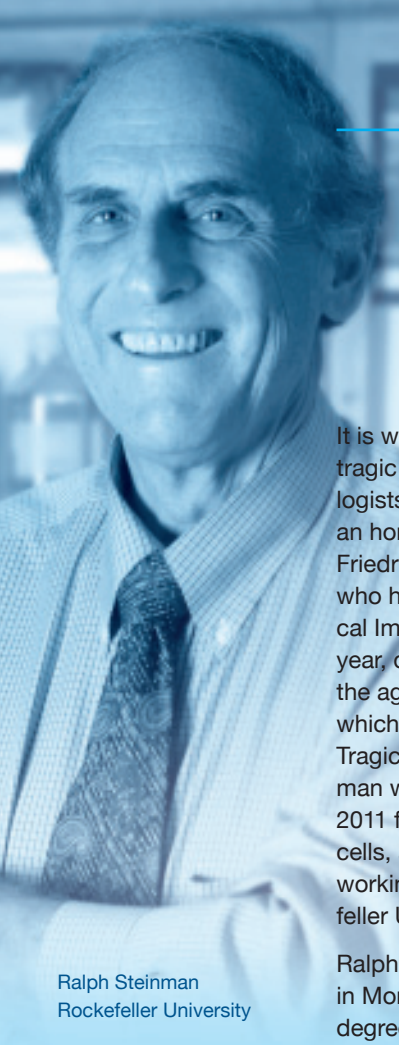


FIGURE 2 The vicious cycle of neuro-immune interaction (modified from Engel et al., Inflamm. Bowel Dis. 2011)

… TNBS-mediated activation of TRPA1 and SP mediate colitis in mice …



Ralph Steinman
Rockefeller University

OBITUARY

A bittersweet tragedy – Obituary for Professor Ralph M. Steinman

It is with our deepest regret that we learned of the tragic loss of one of the world´s leading immunologists, Professor Ralph Steinman. Ralph Steinman, an honorary doctor of the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg, who held the Joachim Kalden Lecture of the Medical Immunology Campus Erlangen on May 10 last year, died September 30, 2011 in New York City at the age of 68. He succumbed to pancreatic cancer which he had been battling for over four years. Tragically, only hours after his death, Ralph Steinman was awarded the Nobel Prize in Medicine 2011 for his fundamental research on dendritic cells, a cell type that he discovered in 1973 while working in the laboratory of Zanvil Cohn at Rockefeller University, New York.

Ralph Marvin Steinman was born January 14, 1943, in Montreal. He received a bachelor of science degree from McGill University in 1963 and a M.D. degree from Harvard Medical School in 1968. After completing an internship and residency at Massachusetts General Hospital, he joined Rockefeller University, in 1970 and eventually became the director of the Laboratory of Cellular Physiology and Immunology and a senior physician at the Rockefeller University Hospital. Ralph Steinman´s groundbreaking work has made possible the development of new methods for preventing and treating infectious, inflammatory and autoimmune disease and has been highly awarded on many occasions.

Ralph Steinman will be greatly missed!

Ralph Steinman was a frequent guest at our university and close friend of Gerold Schuler and other immunologists in Erlangen. He very much supported our endeavours in the field of immune intervention and strongly encouraged the translation of immunological research from mouse to man.

Our sincerest condolences go out to his family. Ralph Steinman will be greatly missed!

An appreciation of Ralph Steinman's achievements can be read in the November issue of the Journal of Experimental Medicine for which Ralph Steinman has served as an editor for several decades.

Moberg, C.L. (2011).
An appreciation of Ralph Marvin Steinman (1943–2011).
J Exp Med 208, 2337–2342.

PEOPLE

Langener Wissenschaftspreis for Prof. Dr. rer. nat. David Vöhringer

Prof. Dr. David Vöhringer, head of the Division of Infection Biology at the Universtätsklinikum Erlangen, has received the renowned Langener Wissenschaftspreis for his outstanding research on the function of eosinophilic and basophilic granulocytes during type-2 immune response. The prize endowed with 10,000 Euro is donated by the Paul Ehrlich Institute and the Stadtwerke Langen to young scientists every two years. The ceremony took place at the Paul Ehrlich Institute in Langen on November 11th, 2011.

From left to right: Dr. Erhard Schmidt, Prof. David Vöhringer, Prof. Klaus Cichutek, Manfred Pusdrowski, Frieder Gebhardt source: PEI

UPCOMING EVENTS

MICE Immunological Colloquium – Special Lectures 2012

Special Lecture
20.03.2012
PD Dr. Immo Prinz
Hannover
Is there a role for innate or adaptive gamma/delta T lymphocytes in the immune response to cytomegalovirus?

Special Lecture on Wednesday
28.03.2012
Prof. Jean-Laurent Casanova, M.D., Ph.D.
New York, USA
Toward a genetic theory of infectious diseases

Further Conferences of Interest

March 18 – 21, 2012
World Immune Regulation Meeting VI
Davos, Switzerland
www.wirm.ch

April 26 – 27, 2012
Immune Tolerance and Autoimmune Disease
Cambridge, UK
www.abcam.com/cambridge2012

May 04 – 8, 2012
Immunology 2012
Boston, USA
www.immunology2012.org

May 09 – 13, 2012
8th International Congress on Autoimmunity
Grenada, Spain
www.kenes.com/autoimmunity

September 01 – 03, 2012
The 26th Annual Meeting of the European Macrophage and Dendritic Cell Society (EMDS)
Debrecen, Hungary
www.emds2012.eu

September 05 – 08, 2012
Jahrestagung der Deutschen Gesellschaft für Immunologie (DGfI) – European Congress of Immunology (ECI)
Glasgow, Scotland
www.dgfi.org
www.eci-glasgow2012.com

September 22 – 25, 2012
The 4th EMBO meeting – advancing the life sciences
Nice, France
www.the-embo-meeting.org

October 03 – 06, 2012
15th Biennial Meeting of the European Society of Immunodeficiencies
Grenada, Spain
www.kenes.com/esid

October 07 – 11, 2012
12th International Symposium on Dendritic Cells – DC2012
Daegu, Korea
www.dc2012.kr

December 08 – 11, 2012
American Society of Hematology (ASH) 54th Annual Meeting and Exposition
Atlanta, USA
www.hematology.org/Meetings/Annual-Meeting

Medical Immunology Campus Erlangen

Publisher
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Dr. Sonja Pötzsch (Scientific Coordinator)

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Please note that the authors are responsible for the content of their contributions.

We are looking forward to suggestions for the next MICE letter.

Please send material to:
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