A collaboration of
University of Geneva Division of Rheumatology
Institute for Research in Biomedicine in Bellinzona
University of Lausanne Department of Biochemistry
University Hospital Zurich Center of Experimental Rheumatology

Institute for Arthritis Research

Scientific Report

2011-2013

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This Scientific Report covers the 2011 - 2013 Research Activities of the Institute for Arthritis Research (iAR)

The report can also be accessed at www.iar-suisse.ch

Foreword by Prof. Lars Klareskog

Member of Scientific Advisory Board

Science and care for common and yet chronic diseases like arthritis, provide a great challenge to the international community of scientists, and further progress towards better treatment and ultimately cure demands collaboration and contribution from scientists all over the world. The increasing complexity of methods and improved ways of communication means that science performed in one place will immediately have an international impact. This means increased demands for collaboration also on a national level in order to use the national expertise as efficiently as possible in the international context.

It was therefore a great thing for international research in arthritis when the iAR was founded as an initiative from the late Jurg Tschopp and with support from the Mäxi Foundation. This initiative managed to bring together some of the world´s leaders in immunology, inflammation and rheumatology research into a new joint research program for arthritis in Switzerland. Over the first years of research, supported by iAR, we have thus witnessed great progress in several important areas from the participating groups: Nicolas Fasel, having taken over from Jurg Tschopp, has continued to provide important results on innate immunity and stress responses. Cem Gabay´s group is performing pioneering work on the functions in arthritis of molecules belonging to the IL-1 family. Cem Gabay is one of the international pioneers of work on these molecules in different forms of arthritis. Steffen Gay is the international leaders in the field of epigenetics in arthritis and his laboratory produces a large number of original reports on epigenetics and its role in mediating effects of environment in inflammation. Antonio Lanzavecchia and Federica Sallusto are world leaders in the study of adaptive immunity in health and diseases, and have begun to use their cutting edge methods also on arthritis research. Taken together, the contributions from these groups, now working together in arthritis research, means an important Swiss contribution to international science in the area of arthritis.

Being very impressed with the rapid progress from the groups involved in the iAR effort, I am convinced that this progress will continue and hope that also the critical support from the Mäxi Foundation will continue to benefit research and care for patients with arthritis in the world.

Lars Klareskog, MD,PhD
Professor of Rheumatology and Director of the Center for Molecular Medicine
Karolinska Institutet, Stockholm, Sweden

Stockholm, November 2013

Foreword by Prof. Cem Gabay

Scientific Coordinator of the Institute for Arthritis Research

The term Arthritis comprises several pathological conditions of which certain have an extremely high incidence. The financial burden of these conditions for society led the World Health Organization to dedicate the 2000-2010 decade to these Bone and Joint diseases. Among the different forms of arthritis, the inflammatory diseases such as rheumatoid arthritis are considered as the most severe conditions leading to disability, unemployment, and reduced life expectancy. The effort to understand the pathogenesis of inflammatory disease has led to the development of novel therapies that have markedly changed their management and outcome. However, many patients do not respond to these treatments and none of these therapies is able to effect a cure. Hence there are unmet needs for patients emphasizing the importance of basic and translational research in the field of arthritis.

In 2009 the late Professor Jürg Tschopp had the idea of creating a network of leading Swiss laboratories with the objective to strengthen research in Arthritis. With the help of the Mäxi Foundation, the Institute of Arthritis Research (iAR) was established in Lausanne and included the laboratories of the Professors Jürg Tschopp (Lausanne), Steffen Gay (Zurich), Antonio Lanzavecchia (Bellinzona), and Cem Gabay (Geneva). The iAR international scientific advisory board included Professors Lars Klareskog (Stockholm) and Sir Marc Feldmann (London) who are well recognized for their major contributions to the field of arthritis research. After Professor Tschopp passed away in 2011, Professor Gabay became President of iAR and the laboratory of Professor Nicolas Fasel was included to represent Arthritis research in Lausanne.

Since 2009 the iAR achieved several important accomplishments. The iAR groups have published 88 scientific articles in leading journals. Moreover, two of these articles resulted from a close collaboration between two iAR research laboratories. The iAR supported the organization of an International Congress in Geneva (the 2012 Annual Joint Meeting of the International Cytokine Society and of the International Society for Interferon and Cytokine Research) and has funded a repository for transgenic mouse lines in Lausanne. The iAR provided a bursary for a PhD graduate student working on the pathogenesis of osteo-arthritis in the laboratory of Professor Alexander So (Lausanne).

More recently, the iAR funded a Professorial position for research in Rheumatology in Geneva, and Professor Monique Gannage was appointed as Assistant Professor in 2013. Her group will strengthen Arthritis research in Geneva and should also be considered as an important investment for future research in this field in Switzerland. In addition, exchange of students between the iAR laboratories and shared seminars are organized under the hospices of iAR.

In the future iAR has the objective to establish an Institute comprising several laboratories working in the field of Arthritis research in Geneva. This Institute will closely interact with the other laboratories of iAR located in Lausanne, Zurich and Bellinzona to develop common research projects. In addition, iAR will progressively identify and collaborate with other research groups as well as with companies working in drug development to further extend the network of collaboration with the ultimate aim to develop targeted therapies.

We would like to thank the Mäxi Foundation for its support.

Prof. Dr. Cem Gabay
Head of iAR

Geneva, November 2013

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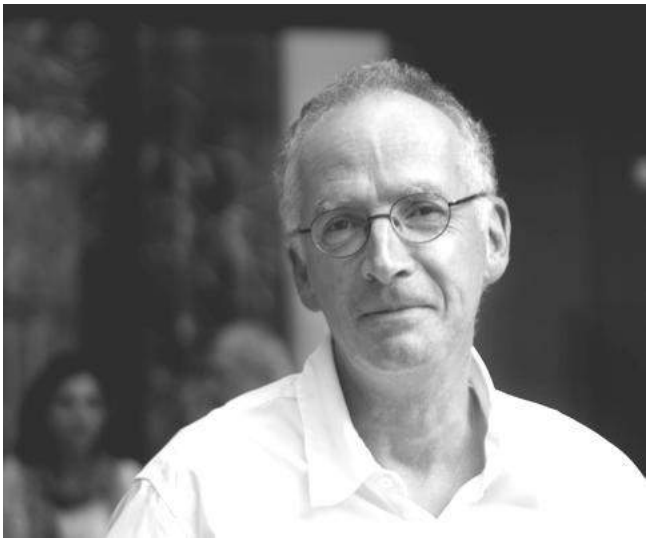
RESEARCH GROUPS

SECTION 1

UNIVERSITY of LAUSANNE

NICOLAS FASEL



Nicolas Fasel

Nicolas Fasel is full professor at the Faculty of Biology and Medicine of the University of Lausanne. After studying biology at the University of Fribourg (Switzerland) and obtaining a doctoral degree at the Swiss Institute for Experimental Cancer Research working on mouse mammary tumor virus, he took up a post-doctoral position at the University of California Los Angeles working on immunoglobulin gene regulation. On his return to Switzerland, he studied post-translational modifications of cell surface antigens. As an independent researcher of the Dr. Max Cloëtta Research Foundation, he had the opportunity to establish his own group investigating the molecular and cellular biology of pathogens and their impact on the host immune and metabolic response. Since September 2006, he is director of the Department of Biochemistry.

Research Focus

In the last years, our main interests have been centred around the innate immune and oxidative stress responses, two components important in chronic inflammatory pathologies. We focused mainly on Toll-like receptors (TLR) activation and detoxification metabolism as well as the spreading of the inflammation. As a model system, we used *Leishmania*, a human protozoan parasite. In some cases, this parasite carries a double-stranded RNA virus (LRV). Considering the high immunogenicity of these parasites and their LRV and their subsequent instigation of excessive local inflammation, they are surprisingly and notoriously evasive of immune-mediated killing. In the human host, *Leishmania* invade, reside and replicate in the oxidative phagolysosome of the macrophage (the very organelles designed to kill them). Understanding the immune responses to the parasites and its LRV may help us formulate appropriate immunotherapeutic strategies under oxidative pressure and could reveal novel and reliable drug targets, which could be used in chronic inflammatory pathologies.

As LRV's pathogenesis is immune mediated, we focused on the various components of its destructive TLR3-mediated inflammation. We found that IFN-beta and IL-17A induced chronic inflammation in response to LRV recognition. We further verified this pathogenesis to be exclusive to the TLR3 pathway, where the adaptor molecule, MyD88 (required in all other TLRs, excepting TLR3), as well as the MyD88-dependent TLR9 were not affected by LRV burden and dissimilarly, found to play a generalised protective role in *L. braziliensis* and *L. guyanensis* infections. We have reviewed all our experience of LRV in various publications, where we commented on the hidden influence of microbial viruses on disease and on the therapeutic potential of immune cross-talk in leishmaniasis.

Team

Group Leader: Nicolas Fasel, PhD > Nicolas.Fasel@unil.ch
Members: Castiglioni Patrik, PhD student; Desponds Chantal, Technician; Drexler Stefan, Postdoctoral fellow; Remzi Eren Onur, PhD student; Hartley Mary-Anne, PhD student; Kohl Kid, PhD student; Martin Ricardo, PhD student; Prevel Florence, Technician; Rodrigues Alessandro, Postdoctoral fellow; Ronet Catherine, Research associate; Rossi Matteo, PhD student; Zangger Haroun, Postdoctoral fellow.

Leishmania RNA Virus controls the severity of metastatic leishmaniasis

Catherine Ronet, Haroun Zangger, Stefan Drexler, Alessandro Rodrigues, Patrik Castiglioni, Mary-Anne Hartley, Remzi Onur Eren, Matteo Rossi, Chantal Desponds, Florence Prevel and Nicolas Fasel

Metastatic leishmaniases are caused by specific *Leishmania* species but species- and strains-specific factors inducing this exacerbation of disease have not yet been identified. Thus, our description of the viral endosymbiont, LRV, as an aggravating factor in metastatic forms of leishmaniasis was an exciting step towards understanding the devolution of this devastating and disfiguring disease. We found that *L. guyanensis* strains causing metastatic and disseminating leishmaniases contained an RNA virus in their cytoplasm, which induced a destructive hyper-inflammatory response after its dsRNA was recognised by host TLR3 (Figure 1). The innate response to LRV was characterised by the production of IFN-beta and we posited this to be the primary and essential effector molecule responsible for the early innate immune response to LRV, and that it was sufficient to induce inflammatory cytokines and chemokine (TNF-α, IL-6, CXCL-10 and CCL-5). We are currently dissecting the signalling pathway leading to IFN-beta expression.

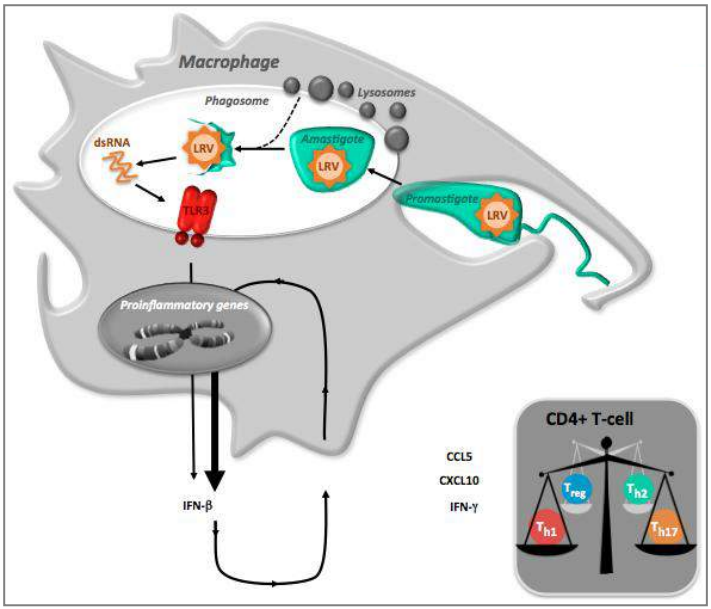


Figure 1
Impact of LRV on inflammation: metastatic leishmaniasis as an example.

This work is done in collaboration with Stephen M. Beverley, Washington University School of Medicine (USA)

Ives A et al. *Science. 2011, 331, 775-778, doi: 10.1126/science.1199326*
Fuertes-Marraco S et al. *PLoS ONE. 2011, 6(6): e20189. doi:10.1371/journal.pone.0020189*
Ronet C et al. *Virulence. 2011, 2(6), 547-52*
Hartley M.-A et al. *Current Opinion in Microbiology. 2012, doi.org/10.1016/j.mib.2012.05.011*
Hartley M.-A et al. *Front. Cell. Inf. Microbio. 2012, 2:99. doi: 10.3389/fcimb.2012.00099*
Zangger H et al. *PLoS Negl Trop Dis. 2013, doi: 10.1371/journal.pntd.0002006*
Hartley M.-A et al. *Clinical Microbiology and Infection. 2013, doi: 10.1111/1469-0691.12095*

TLR3, IFN-beta and inflammation

Matteo Rossi, Remzi Onur Eren, Catherine Ronet, Haroun Zangger

In the last years, we continuously examined the molecular pathways that can be modulated (up- or down-) by the LRV/TLR3 signaling pathway and could give a survival advantage to the parasite. Therefore, we performed several infection experiments of wild type (WT) and deficient mice to include/exclude other pathways, which could be activated by the viral dsRNA molecules or known to be relevant in the inflammasome formation. Thus, we infected mice deficient in IPAF, MAV5/CARDIF, NLRP3, ASC and conditional ASC, caspase 1, IL-1 beta and STAT-1. Deficiency in these genes did not change the outcome of the infection, confirming that the increase in severity is mainly due to the TLR3/TRIF/IFN-beta pathway and thus limiting the molecular mechanisms to be investigated.

To confirm the central role of IFN-beta, we have infected mice deficient in Type I IFN receptor (IFNAR-/-) with LRV+ *L. guyanensis* (LRV+Lg) and found that they developed smaller lesions and carried less parasites than their WT counterparts, where the infection rather resembled that of the LRV- Lg infected WT mice. Further, we found that supplementation with recombinant murine IFN-beta within the first hours of infection was sufficient to exacerbate lesional swelling and parasite load in WT mice infected with LRV- Lg *Leishmania*. These data suggest a critical role of IFN-beta in the early modulation of the immune response against LRV+ Lg parasites.

In addition, we recently had evidence that the supernatant of LRV+ Lg infected cells can induce inflammatory cytokines and chemokines in non infected cells after two hours of exposure and this induction is depending on the secretion of IFN-beta (Figure 2).

This result shows that IFN-beta acts not only in an autocrine loop but also in a paracrine manner. It could possibly explain why, in mucosal lesions, there is a high inflammatory and destructive response albeit parasites are detected only at very low level.

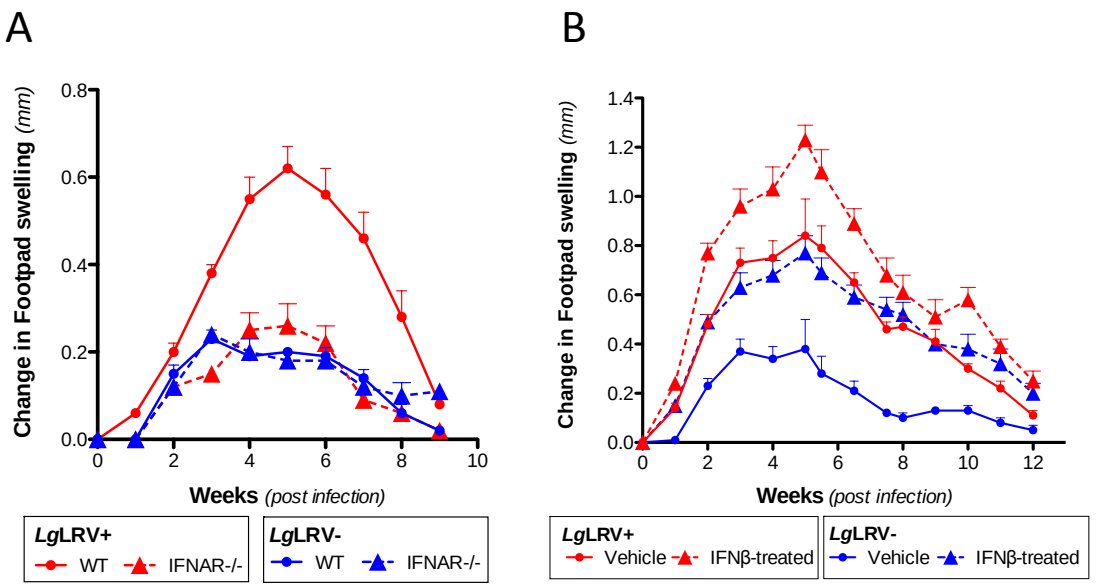


Figure 2
IFN-beta mediates LRV-dependent exacerbation of leishmaniasis in a murine model.

This work is done in collaboration with Stephen M. Beverley, Washington University School of Medicine (USA)

IL-17A mediates exacerbation and metastasis.

Mary-Anne Hartley, Stefan Drexler, Florence Prevel, Catherine Ronet

With the aim of elucidating the immunophenotype of LRV-associated metastatic leishmaniasis, we screened human biopsies and blood from patients infected by these parasites and found a potent up-regulation of the cytokine IL-17A. This phenotype was replicated in a murine model of *L. guyanensis* infection, which also showed an LRV-dependent up-regulation of IL-17A. This cytokine was also shown to contribute to LRV-dependent exacerbation of disease after we found IL-17A$^{-/-}$ mice infected with LRV+ parasites to have a significantly reduced disease severity and parasite burden as well as a greatly reduced production of tissue destructive proteases such as matrix metalloproteases. Understanding the immunophenotype in LRV-associated metastatic leishmaniasis could offer an immunotherapeutic alternative to this notoriously difficult to treat disease. Indeed, we show that antibodies against IL-17A are able to alleviate swelling that that a drug, recently described as an inhibitor of the IL-17A secretory pathway, has great therapeutic promise for chronic cutaneous leishmaniasis as both an anti inflammatory agent as well as an anti-parasitic agent. While some *L. guyanensis* strains have been associated to leishmanial metastasis in humans and hamsters, no secondary lesions occurred in conventional murine models. Here we describe the first murine model of LRV-mediated leishmanial metastasis occurring in the absence of IFN-gamma. We propose IFN-gamma as an essential cytokine not only for its expected role in parasite killing, but also as a key determinant of tissue protease activity, which precedes infectious metastasis. Finally, we also show that these mice have high concentrations of IL-17A, which we have previously linked to chronic inflammation.

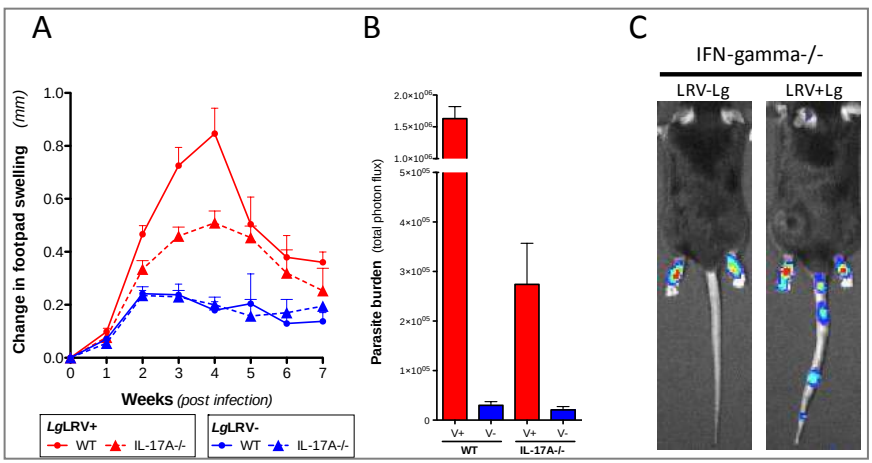


Figure 3
IL-17A contributes to LRV-mediated disease exacerbation and the first murine model of LRV-mediated metastatic leishmaniasis.

This work is done in collaboration with Stephen M. Beverley, Washington University School of Medicine (USA)

Identification of LRV in *L. aethiopica* and in HIV patient co-infected with a *L. braziliensis* and its endosymbiotic virus

Haroun Zangger, Patrik Castiglioni, Chantal Desponds, Mary-Anne Hartley, Florence Prevel, Catherine Ronet

Our seminal study on the role of LRV prompted us to develop simple tools to detect LRV in *Leishmania* species in culture or in lesions, such as an anti-dsRNA monoclonal antibody (J2), which specifically recognizes dsRNA in a quantitative and sequence-independent fashion to asses the LRV-related risk of complicated cutaneous leishmaniasis in the fields.

In Ethiopia, *L. aethiopica* infected patient can develop metastatic leishmaniases. Based on the tools we developed, we detected naturally occurring *Leishmania* RNA virus within *L. aethiopica* parasites isolated from patients. Three *Lae*-LRV genomes were sequenced from independent isolates confirming that LRV in *L. aethiopica* (*Lae*-LRV) belongs to the same *Totiviridae* family of LRVs found in South American species and present in a single isolate of *L. major*. Similarly to *L. guyanensis* LRV, the presence of *Lae*-LRV induced a TLR3 pro-inflammatory response in *L. aethiopica* infected murine bone marrow derived macrophages.

This work is done in collaboration with Stephen M. Beverley, Washington University School of Medicine (USA).

Zangger H et al. *PLoS Negl Trop Dis. 2013; doi: 10.1371/journal.pntd.0002006*

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2012-2014

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Swiss National Science Foundation
Role of human infection in domestic transmission of dermal leishmaniasis and drug resistance. Swiss Partner, Research partnerships with Developing Countries/FNS, grant No IZ70Z0_131421/2010-2013

Swiss National Science Foundation
Impact of *Leishmania* dsRNA virus on mucocutaneous leishmaniasis.
grant No 310030_135616/2011-2014

Swiss National Science Foundation
Leishmania genomics.
International Exploratory Workshop, grant IZ32Z0_137340/2011

Collaborations

Prof. Stephen M. Beverley, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, USA

UNIVERSITY of GENEVA

CEM GABAY

MONIQUE GANNAGE

Cem Gabay

Cem Gabay obtained his medical degree at the University of Geneva where he specialized in Internal Medicine and Rheumatology. He did also his clinical training in Claude Bernard-Bichat University Hospital in Paris and worked from 1995-1999 as research fellow and Assistant Professor at the University of Colorado in Denver (USA). In 1999 he returned to Geneva to open his research laboratory with a bursary from the Swiss National Science Foundation and was appointed as Head of the Division of Rheumatology and Associate Professor in 2001, Full Professor of Medicine in 2008, and Chairman of the Department of Internal Medicine Specialties at the University in Geneva in 2013. He was President of the Swiss Society of Rheumatology from 2008 to 2012 and Vice President of the Swiss Cohort of Rheumatic Diseases (SCQM) from 2006 to 2012. He received several Awards from the Swiss Society of Rheumatology, the European League Against Rheumatism, and the International Cytokine Society. Cem Gabay has published more than 150 articles. His research focuses on different aspects of cytokine biology and on clinical and translational aspects of Rheumatoid arthritis.

Research Focus

The aim of our current work is focused on better understanding the role of the interleukin-1 family of cytokines using experimental models of arthritis and other experimental models of inflammatory diseases. In particular we have generated several lines of transgenic mice to explore the role of interleukin-1 cytokines in vivo. In addition, we are currently examining the role of signaling pathways involved in the modulation of inflammatory responses in macrophages and other myeloid cells. Our research includes also translational aspects with the use of biological samples from patients with rheumatoid arthritis to identify biomarkers of disease severity and response to therapy, as well as to understand the pathogenic role of specific autoantibodies.

Team

Group Leader: Cem Gabay, MD > Cem.Gabay@hcuge.ch

Members: Gaby Palmer – PhD, Praxedis Martin, PhD – Solenne Vigne, PhD – Estelle Woldt, PhD – Maria Stella Lombardi, PhD – Sylvette Bas, PhD – Damien Dietrich, MD/PhD student – Dominique Talabot-Ayer, technician – Emiliana Rodriguez, technician – Isabelle Mean, technician

The role of cell-specific IL-1Ra production in inflammatory diseases

Céline Lamacchia, Gaby Palmer, Solenne Vigne, Cem Gabay

Interleukin (IL)-1 is a prototypic proinflammatory cytokine involved in several diseases. IL-1 receptor antagonist (IL-1Ra) is a natural inhibitor of IL-1 that is produced by different cell types in a constitutive manner or following stimulation. IL-1Ra deficiency is associated with excessive IL-1 signaling and exaggerated inflammation both in mice and humans. To analyze the role of different cell types as sources of IL-1Ra we have created conditional knockout mice in which IL-1Ra was specifically targeted in myeloid cells and in hepatocytes. We observed that myeloid cell-derived IL-1Ra deficient mice had increased lethality upon lipopolysaccharide-induced systemic inflammation and more severe arthritis in two experimental models, namely collagen-induced arthritis and K/BxN serum transfer-induced arthritis. Hepatocyte-derived IL-1Ra deficient mice had more severe inflammation in response to a model of systemic sterile inflammation induced by IL-1 and more severe and chronic concanavalin A-induced hepatitis. These results show the relative importance of different cellular source of IL-1Ra according to the type of disease models.

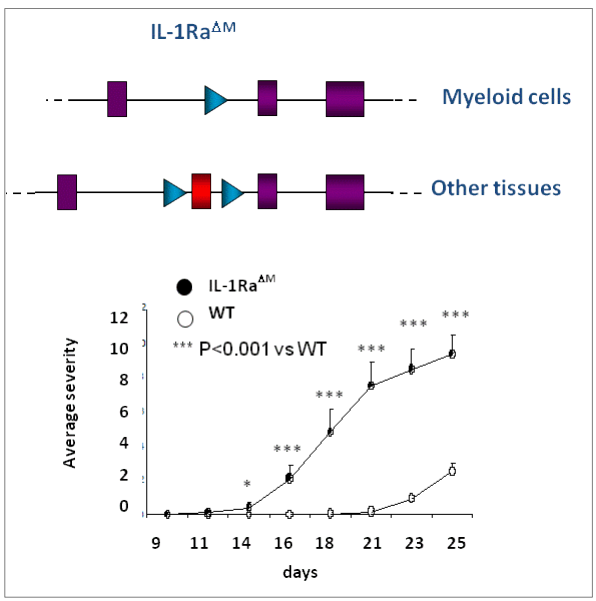

Figure 1
Conditional deletion of mouse *il-1rn* exon 2 in myeloid cells. Exons are depicted as purple boxes with the exception of exon 2 depicted as a red box. LoxP sites are shown as blue triangles. IL-1Ra$^{\Delta M}$ mice (black circles) exhibit milder arthritis as compared to wild-type mice (white circles) following immunization with type II collagen.

Lamacchia C. et al. J Immunol 2010 ; 185 : 2516-2524
Lamacchia C. et al. Arthritis Rheum 2010; 62: 452-462
Lamacchia C. et al. Eur J Immunol. 2012; 42: 1294-303
Lamacchia C. et al. Ann Rheum Dis 2012; 71: 281-287

The expression of IL-1R type 2 in physiological and pathological conditions

Praxedis Martin, Isabelle Mean, Gaby Palmer, Cem Gabay

IL-1 receptor type 2 (IL-1R2) belongs to the family of IL-1 receptor but has a short intracellular domain and does not transduce any intracellular signal upon IL-1 binding. In addition, IL-1R2 sequesters the co-receptor IL-1RAcP thus decreasing IL-1 signaling via IL-1R type 1 (IL-1R1). IL-1R2 is also cleaved from the cell surface and can bind IL-1 in the inflammatory milieu, thus interfering with its biological activities. All together IL-1R2 acts as a natural IL-1 inhibitor. However, the precise role of endogenous IL-1R2 is still unknown due to the lack of IL-1R2 knockout mice. We have observed that neutrophils are the major cellular source of IL-1R2 and that glucocorticoids markedly stimulate its production. IL-1β, but not IL-1Ra, binds to IL-1R2 present on neutrophils. The metalloproteinase ADAM17 is involved in the cleavage of IL-1R2 from neutrophils stimulated with lipopolysaccharide. Neutrophils expressing IL-1R2 are present during different types of inflammatory responses, including arthritis. We have recently created IL-1R2 deficient mice, thus allowing us to determine the relative role of IL-1R2 in the regulation of IL-1 activities in different models of inflammation.

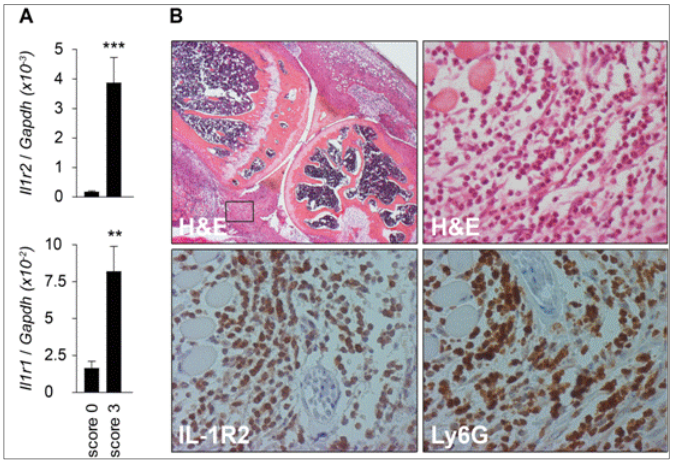

Figure 2

(A) Determination of *Il1r2* (upper panel) and *Il1r1* (lower panel) mRNA levels in ankles during K/BxN serum-induced arthritis **p<0.01, ***p<0.001 versus non arthritic samples as analyzed by unpaired two-tailed Student's t-test. (B) Representative H&E-stained paraffin sections (upper panels) and immunohistochemical localization of IL-1R2 and Ly6G on paraffin sections of knees of arthritic mice.

Martin P. et al. J Leukoc Biol 2013 (in press)

The role of IL-36 in innate and adaptive immune responses and in Th1 polarization

Solenne Vigne, Céline Lamacchia, Praxedis Martin, Estelle Woldt, Emiliana Rodriguez, Isabelle Mean, Gaby Palmer, Cem Gabay

IL-36 is a member of the IL-1 family of cytokines. IL-36 cytokines include three agonists, namely IL-36α, IL-36β, and IL-36γ, and one antagonist IL-36Ra. The three agonists bind to IL-36R and IL-1RAcP. IL-36Ra and IL-1Ra share a common mechanism of inhibition. We observed that bone marrow-derived dendritic cells (BMDC) express IL-36R and respond to IL-36 agonists by the production of several cytokines and the enhanced expression of MHC class 2 and co-stimulatory molecules. CD4 positive T cells express also IL-36R. In particular, IL-36 stimulates the production of IL-2 and the proliferation of CD4 positive naïve T cells. Using in vitro and in vivo experimental systems we were able to show that IL-36 stimulate the polarization of Th0 cells into interferon-γ producing Th1 cells. This was the first demonstration of the role of IL-36 in innate and adaptive immunity. Recently we have examined the role of IL-36R signaling in different models of arthritis using anti-IL-36R antibodies and IL-36R deficient mice. We have observed that arthritis development and severity were independent of IL-36R severity. Future experiments will be performed to understand the role of endogenous IL-36 in inflammatory diseases and host defense.

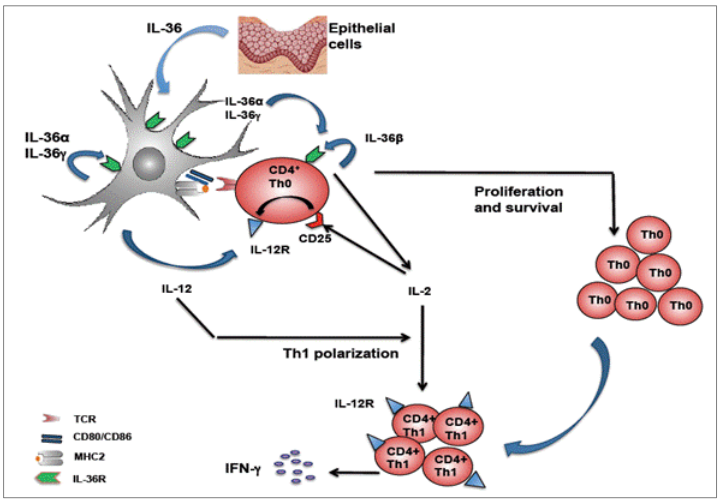

Figure 3
IL-36 produced by epithelial cells and DCs activates DCs to secrete IL-12. IL-36 activates Th0 cells, resulting in cell proliferation, survival of naïve T cells and IL-2 secretion. By a synergistic effect, IL-36 and IL-12 induce Th1-polarization in an IL-2-dependent manner through the induction of IL-12Rβ2 expression, leading to IFN-γ secretion. The formation of a positive feedback loop created by IL-36/IL-36R leads to sustained IFN-γ-mediated immune responses.

Vigne S. et al. Blood 2012; 120: 3478-87
Vigne S. et al. Blood. 2011; 118: 5813-23
Lamacchia C. et al. Arthritis Res Ther 2013; 15: R38

The expression and biological function of IL-33 in arthritis

Praxedis Martin, Dominique Talabot-Ayer, Solenne Vigne, Céline Lamacchia, Emiliana Rodriguez, Cem Gabay and Gaby Palmer

Interleukin (IL)-33 is a cytokine of the IL-1 family, which signals through the ST2 receptor. Previous work suggested implication of the IL-33/ST2 axis in the pathogenesis of human and mouse arthritis. We quantified IL-33 levels in serum and synovial fluid (SF), and assessed synovial IL-33 expression in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or osteoarthritis (OA). Circulating IL-33 levels tended to be elevated in RA, as compared to OA patients, while IL-33 was undetectable in the serum or SF of PsA patients (Figure xy-1). Local expression of IL-33 in the synovium was observed at similar variable levels in RA, PsA and OA patients, suggesting that inflamed joints are not the primary source of elevated IL-33 in RA. We also investigated the role of IL-33 in experimental arthritis, using the K/BxN serum transfer-induced arthritis model. Our results show that, although IL-33 is expressed in the arthritic synovium, IL-33-deficient mice display similar arthritis incidence and severity as compared to WT controls, indicating that endogenous IL-33 is not required for the development of joint inflammation in this model.

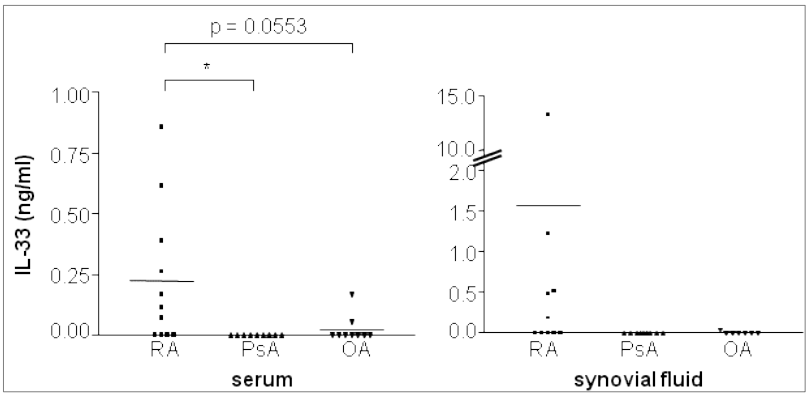

Figure 4

IL-33 levels were assessed by ELISA in the serum (left panel) and SF (right panel) of patients with RA (squares; serum, n=11; SF, n=10), PsA (triangles; serum, n=9; SF, n=9) or OA (inverted triangles; serum, n=9; SF, n=7). Results are shown as individual values (symbols) and means (lines) for each group of patients. *$p<0.05$ as assessed by ANOVA or Kruskal-Wallis test, as appropriate.

Talabot-Ayer D. et al. *Joint Bone Spine 2012; 79:32-37*
Martin P. et al. *Art. Res. Ther. 2013 ; 15:R13*

The regulation of IL-33 production

Dominique Talabot-Ayer, Nicolas Calo, Solenne Vigne, Céline Lamacchia, Cem Gabay, Gaby Palmer

Regulated expression of IL-33 has been reported in different mouse and human cell types, but little information is available concerning the regulation of IL33 gene transcription. GenBank entries for mouse Il33 reveal the existence of two transcripts, Il33a and Il33b. We investigated expression of these transcripts in different mouse organs and cell types in basal and inflammatory conditions. Constitutive Il33a mRNA expression was detected in mouse stomach, lung, spleen, and brain, whereas basal Il33b mRNA expression was observed only in the stomach. Expression of both transcripts increased after systemic LPS administration. In vitro, constitutive Il33a mRNA expression was observed in bone marrow-derived dendritic cells, where it was preferentially increased in response to poly(I:C), whereas LPS increased levels of both Il33a and Il33b mRNA (Figure x2). In contrast, bone marrow-derived macrophages and Raw 264.7 cells did not express Il33 mRNA constitutively, and LPS stimulation selectively induced expression of Il33b mRNA in these cells. Our data indicate that the Il33 gene is expressed from two alternative promoters in the mouse and that the relative expression of Il33a and Il33b transcripts is cell type- and stimulus-dependent.

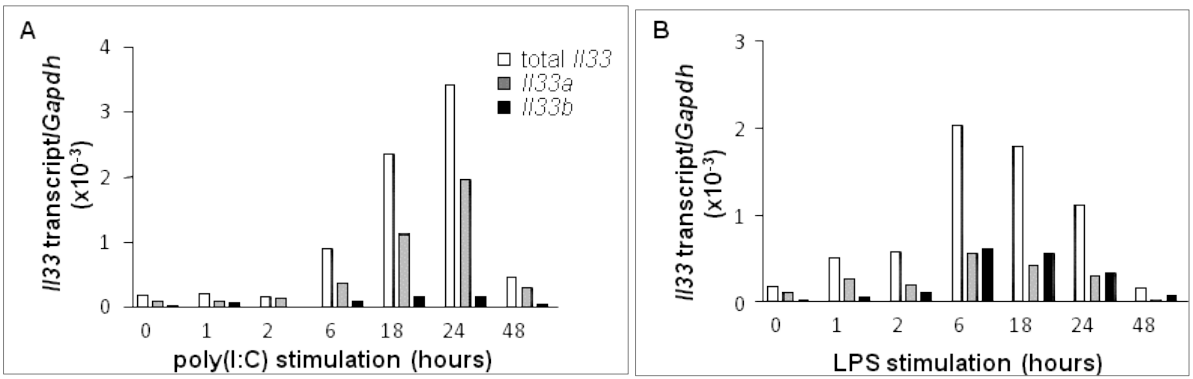

Figure 5

Expression levels of total *Il33* (white columns), *Il33a* (grey columns) and *Il33b* (black columns) mRNA, normalized to *Gapdh* mRNA levels are shown for mouse primary bone marrow-derived dendritic cells stimulated or not for indicated times with poly(I:C) (50 µg/ml) **(A)** or LPS (100 ng/ml) **(B)**. Data shown are representative of 3 independent experiments.

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Fundings

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2005, 2007, 2011

Geneva Academic Society
2005

Institute for Arthritis Research (iAR)
2009-2014

Swiss National Science Foundation
From 1998-2014 to Cem Gabay
From 2008-2014 to Gaby Palmer

Collaborations

Federica Sallusto
Institute of Research in Biomedicine, Bellinzona

Bernhard Ryffel
CNRS, Orleans (FR)

Jennifer Towne, Dirk Smith
Amgen Inc., Seattle, WA (USA)

Visiting Scientists

John Sims
Visiting Professor (2012)
Amgen Inc., Seattle, WA (USA)

Monique Gannagé

Monique Gannagé earned a degree in Medicine at the University of Paris V, at the faculty of Necker, where she specialized in medical biology with a special focus on immunobiology. She is holding a PhD in Immunology from the University of Paris V. Her PhD project focused on characterizing anti- viral and anti-tumoral CD8 T cell response in two models: chronic myeloid leukemia (CML) and Kaposi sarcoma.
Her postdoctoral training in the laboratory of Christian Munz started in 2006 at the Rockefeller University (New York), and took place since 2009 at the Institute of Experimental Immunology (Zurich). During that time her work focused on macroautophagy and its role in the adaptive immune response with a special focus on Influenza A virus. Since October 2013 she joined the department of Pathology and Immunology in Geneva University, as an assistant professor, to establish a junior group funded by the IAR. She will work in close contact with the department of Rheumatology, and her research will be focused on the contribution of macroautophagy to the immune response during rheumatological diseases.

Research Focus

Macroautophagy is a major biological pathway, implicated in cellular homeostasis. The involvement of this process in controlling multiple aspects of the immune response has recently emerged. Our Group will be involved in studying how macroautophagy can influence the initiation and outcome of the immune response during autoimmune diseases with a focus on rheumatoid arthritis.

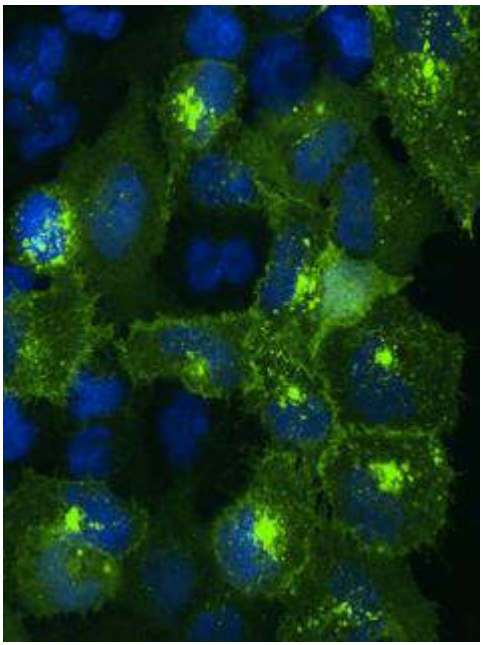

Figure 1
Influenza A virus has evolved strategies to induce apoptosis of its host cells. The matrix protein 2 of Influenza A virus compromises cell survival by blocking autophagosome degradation, thereby inhibiting the pro-survival pathway of macroautophagy. The figure represent an immunofluorescence image of lung epithelial cells infected with Influenza A virus. Autophagosomes accumulation is shown in green fluorecence (autophagosome marker GFP-Atg8/LC3).

Using both mice models and clinical samples we aim to analyse macroautophagy contribution to the deregulated immune response during this disease. The aim of our research is to find which steps of the immune response are controlled by autophagy and if manipulating the pathway can influence the course of the disease.

Team *(starting October 2013)*
Group Leader: Monique Gannagé, MD, PhD Assistent Professor > Monique.Gannage@hcuge.ch
Members: Pascale Sattonnet, Research Assistant

UNIVERSITY of ZURICH

STEFFEN GAY

Steffen Gay

Professor Steffen Gay has graduated from the Medical School at the University in Leipzig. Holding office from 1976-1996 at the Department of Medicine at the University of Alabama in Birmingham AL, he served there as Professor of Medicine from 1984-1996. Since 1996 he is Professor of Experimental Rheumatology at the University Hospital of Zurich. The center has been recognized as a EULAR Center of Excellence in Rheumatology from 2005-2015.

Steffen Gay has published largely related to the molecular and cellular basis of rheumatic diseases, including 64 book chapters and over 350 peer-reviewed scientific papers. He is among the most cited scientists in Clinical Medicine (ISI) with over 18,000 citations and a h-index of 75. He is a Honorary Member of the American Association of Physicians (AAP) and the Alpha Omega Alpha Honor Medical Society. He became the Spinoza Professor for 2002 at University of Amsterdam and a member of the Deutsche Akademie der Naturforscher Leopoldina in 2004. In 2008 he received the Kussmaul-Medal from the German Society of Rheumatology and in 2011 he became Honorary Member of EULAR.

Current interest focuses on the epigenetic regulation of gene expression by acetylation, methylation, sumoylation and microRNAs in health and diseases.

Research Focus

Epigenetic modifications in rheumatic and cardiovascular diseases including methylation, acetylation, sumoylation and microRNA, represent the major focus of our current research.

The molecular and cellular basis of joint destruction in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, involves especially the search for novel genes and their signaling pathways ("Functional Genomics"). The laboratory explores the molecular and cellular mechanisms by studying the processes of synovial adhesion to cartilage and bone, the activation of synovial cells to invade and the cellular interactions with cells of the immune system.

Suppressive subtractive hybridization and micro-arrays are used to establish cDNA libraries of genes which are induced by various stimuli, including signaling via cytokine receptors and TOLL-like receptors. Somatic gene transfer is applied to inhibit synovial cell-mediated cartilage destruction in the SCID mouse model engrafted with normal human cartilage and rheumatoid synovial tissues or isolated cells. Anti-sense constructs, ribozymes, siRNA and antagomirs are used to identify specific targets for future therapeutical interventions. The model is further used to explore the effect of novel drugs from the pharmaceutical industry.

Molecular mechanisms of fibrosis are investigated in progressive systemic sclerosis (scleroderma) and in pulmonary hypertension in another focus of our research. Specifically, hypoxia –induced pathways, expression of chemokines and growth factors are explored with regard to impaired angiogenesis and the excessive production of extracellular matrix.

In close cooperation with the Department of Cardiology at the University Hospital of Zürich, we are studying the endothelial function in both rheumatic and cardiovascular patients. Novel investigations on fresh thrombi retrieved from myocardial infarcted patients explore the role of inflammation in the acute coronary syndrome.

A new clinical Research Program has been developed within our EC IMI BTCURE grant entitled "Molecular Analysis of Gene Expression modulated by Novel Drug Therapies" to study the molecular effects of drugs on individual cells. By evaluating most comprehensively these changes, novel modes of action as well as unwanted side effects can be discovered to develop safer therapeutics.

We have established a molecular biology training course, twice a year, to train new international research fellows in cloning, sequencing, cell-culture, cell-sorting (FACS), TaqMan Real Time PCR, primer design, in situ PCR, in situ hybridization , analysis of acetylation, methylation and miRNAs and immunohistology.

Team

Group Leader: Steffen Gay, MD > steffen.gay@usz.ch

Members: Aradi Borbola, MD, PhD student – Engler Anna, PhD student – Frank Mojca, MD, PhD – Gaur Niharika, Master student – Jüngel Astrid, PhD, PD – Karouzakis Emmanuel, PhD – Kato Masaru, MD, PhD – Klein Kerstin, PhD – Neidhart Michel, PhD – Ospelt Caroline, MD, PhD – Plestilova Lenka, MD, PhD student – Umekita Kunihiko, MD

Epigenome analysis reveals TBX-5 as a novel transcription factor involved in the activation of rheumatoid arthritis synovial fibroblasts

Emmanuel Karouzakis, Michelle Trenkmann, Renate E. Gay, Beat A. Michel, Steffen Gay, Michel Neidhart

DNA methylation and histone modifications marks are imprinted in the chromatin and constitute the epigenetic code. In this study, we analyzed the methylation status of human promoters in rheumatoid arthritis synovial fibroblasts. Differentially methylated genes between RASF versus OASF were identified by methylation immunoprecipitation and hybridization of human promoter tiling arrays. In RA synovium and RASF, TBX5 was found to be less methylated than in OASF. The demethylation of TBX5 promoter in RASF and RA synovium induced higher TBX5 expression than in OASF and OA synovium. In RA synovium, TBX5 was mostly localized in the synovial lining. In addition, the TBX5 locus was found to be enriched in RASF with open chromatin marks such as H3K4 trimethylation and histone acetylation. Microarray analysis revealed that the molecular targets of TBX5 to be the proinflammatory chemokines IL8, CXCL2 and CCL20. TBX5 may be a novel regulator of chemotaxis thereby associated with the ability of RASF to attract inflammatory cells to the synovium.

Increased recycling of polyamines in rheumatoid arthritis synovial fibroblasts causes global DNA hypomethylation

Emmanuel Karouzakis, Renate E. Gay, Steffen Gay, Michel Neidhart

Our previous in vitro studies suggested that the aggressive phenotype of RASFs is associated with global genomic hypomethylation. Therefore, we investigated whether increased polyamine metabolism is associated with a decreased level of S-adenosylmethionine (SAM), causing global DNA hypomethylation. *S*-adenosyl methionine (SAM) is produced from the essential amino acid methionine. It is needed by DNA methyltransferase 1 (DNMT-1) in somatic cells to add methyl (M) marks on the DNA during replication. Putrescine is produced from ornithine upon activation of ornithine decarboxylase (ODC) and is further processed into spermidine and spermine by spermidine synthase (SdS) and spermine synthase (SmS), respectively. This process requires decarboxy-SAM (dSAM), which is produce from SAM by *S*-adenosyl methionine decarboxylase (AMD). Putrescine enhances the activity of AMD. Finally, spermidine and spermine can be back-converted into putrescine through the action of the enzymes spermidine/spermine N1-acetyltransferase (SSAT1) and polyamine oxidase. Increased spermine expression indirectly stimulates the expression of SSAT1 through activation of the transcription factor polyamine-modulated factor 1–binding protein 1 (PMFBP1). Diacetylpolyamines can be excreted through the transporter system solute carrier family 3 member 2 (SLC3A2). Interestingly, the expression of SSAT1, AMD and PMFBP1 was significantly increased in RASF, compared to OASF. The expression

of DASp in cell culture supernatants and the expression of SC3A2 were significantly elevated in RASF. The levels of SAM in cell culture extracts, as well as of Dnmt1 protein and 5-MeC were significantly reduced in RASF. Parameters of the polyamines metabolism negatively correlated with SAM, Dnmt1 and 5-MeC. In conclusion, the above results show that the increased expression of PMFBP1 and SSAT1 enhance the catabolism and recycling of polyamines in RASF and suggest that a high consumption of SAM via this pathway is an important factor contributing to the global DNA hypomethylation in these cells.

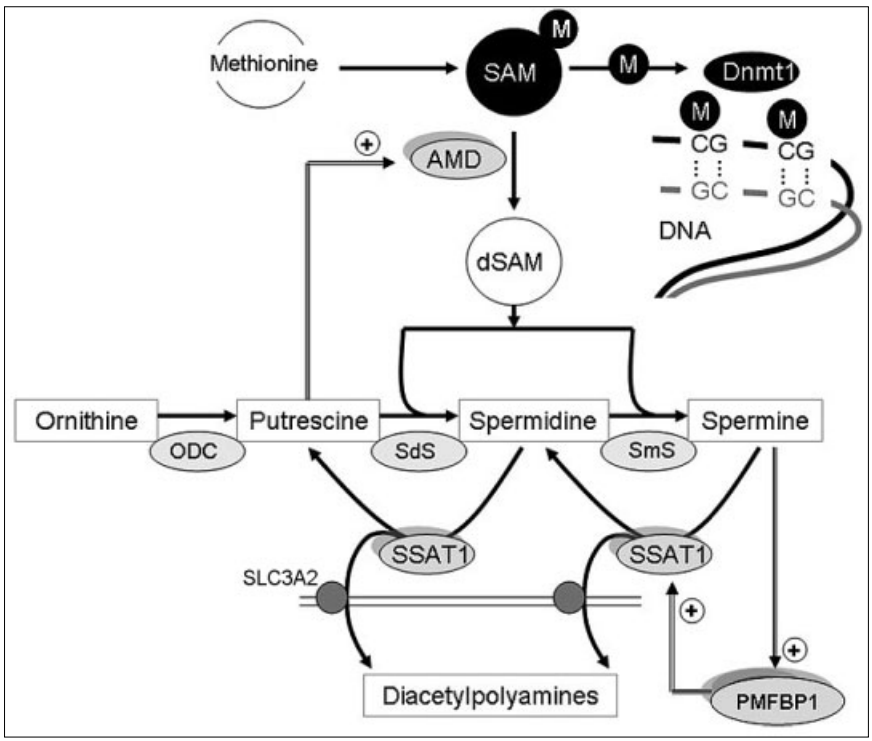

Figure 1
Activation of polyamines pathway causes DNA hypomethylation through S-adenosylmethione (SAM) reduction.

Inhibition of spermidine/spermine N1-acetyltransferase (SSAT1) activity – a new therapeutical concept in rheumatoid arthritis

Michel Neidhart, Emmanuel Karouzakis, Astrid Jüngel, Renate E. Gay, Steffen Gay

Previously, we found that spermine/spermidine N1-acetyltransferase (SSAT1) is increased and S-adenosylmethionine (SAM) levels are reduced in rheumatoid arthritis synovial fibroblasts (RASF). Therefore, we wanted to inhibit the activity of SSAT1 and to evaluate the effect of this treatment - alone or in combination with SAM supplementation - on DNA methylation and behavior of RASF. Diminazene aceturate (DA) decreased the expression of S-adenosyl methionine decarboxylase (AMD) in RASF. DA increased 5-methylocytosine, increased the expression of DNMT-1, reduced intracellular putrescine, decreased the expression of activation markers such as CXCL12, integrin β1, MMP1 and altered the adhesion of RASF to fibronectin. The combination of DA plus SAM increased most efficiently DNMT-1, than DA or SAM alone. In addition, it further decreased CXCL12 and integrin β1 expression, as well as MMP-1 levels, but not of MMP-3. Most interestingly, the combination DA and SAM reduced the invasiveness of RASF in the SCID mouse model of RA by 70%. The use of DA alone or in combination with SAM might introduce a new therapeutic concept in RA. This is the first therapy that would directly target RASF and thereby inhibit the ongoing joint destruction.

Levels of circulating microRNAs are associated with disease activity in patients with early rheumatoid arthritis

Maria Filkova, Borbala Aradi, Caroline Ospelt, Renate E. Gay, Beat A. Michel, Steffen Gay

Our group and others reported recently characteristic changes of microRNA expression levels in cells of patients with rheumatoid arthritis (RA).Since miRNAs are stably present in cell free form in body fluids they are becoming new candidate biomarkers for diagnosis and prognosis in different diseases.
From all analyzed RA-relevant miRNAs (miR-146a, miR-155, miR-223, miR-16, miR-203, miR-132 and miR-124a) levels of miR-146a, miR-155 and miR-16 were decreased in the sera of ERA patients in comparison with established RA.
Furthermore, we could show that the levels of circulating miR-16 and miR-223 are changed upon therapy with DMARDs such as methotrexate combined with glucocorticoids in patients with early RA. Changed levels of miR-16 in the first 3 months of therapy were associated with a decrease in DAS28 and levels of circulating miR-223 in treatment naïve ERA correlated with C reactive protein, DAS28 and change in DAS28. We are currently using the samples for a screening approach using miRNA- arrays to identify novel treatment responsive circulating miRNAs.
In addition we are analyzing miRNA profiles of sera from patients with resolving arthritis such as reactive arthritis and from patients with RA at a very early stage of the disease (< 3 months since onset of symptoms) to compare cellular and circulating miRNA profiles at the very early stage of the disease.

This work is done in collaboration with Andrew Filer, Karim Raza and Christopher Buckley Rheumatology Research Group, School of Immunity and Infection, Birmingham (UK) and Ladislav Šenolt, Jiří Vencovský and Karel Pavelka from the Department of Clinical and Experimental Rheumatology of the 1st Faculty of Medicine, Institute of Rheumatology, Charles University in Prague, Czech Republic

TNFα-induced Protein Tyrosine Phosphatase Non-receptor Type 2 (PTPN2) counter regulates inflammation in rheumatoid arthritis

Borbála Aradi, Masaru Kato, Kerstin Klein, Renate E Gay, Steffen Gay, Astrid Jüngel

PTPN2 has been shown to be associated with the development of autoimmune diseases in GWA studies however; the function of PTPN2 has not been extensively studied in rheumatoid arthritis (RA). We analyzed what role PTPN2 plays in RA synovial fibroblasts (RASF).
We could show that the expression of PTPN2 was higher in synovial tissues from RA patients compared to osteoarthritis (OA) patients. Most interestingly, in anti-TNF treated patients PTPN2 expression was 30% lower than in patients who were not treated with anti-TNFs. PTPN2 mRNA expression was increased in synovial tissues and synovial fibroblasts from RA compared to OA patients. This could also be confirmed on protein level. PTPN2 expression was upregulated after stimulation with inflammatory cytokines such as TNFα, IL1β, LPS and hypoxia. Chronic stimulation with TNFα to mimics the conditions in the joint of an RA patient further upregulated PTPN2 protein expression. We used silencing RNAs to study the function of PTPN2 in RASF. PTPN2 silenced cells produced more IL-6 compared to scrambled control cells, whereas levels of IL-8 did not change suggesting that PTPN2 plays a counter regulatory role in inflammation. PTPN2 also plays a role in the regulation of apoptosis and autophagy. More apoptosis and less autophagy can be induced in cells transfected with siPTPN2. As a next step, we are studying the epigenetic regulation of PTPN2 in RASF.

This work is done in collaboration with Michael Scharl, Division Gastroenterology at the University Hospital of Zurich

Dual Role of Autophagy in Stress-Induced Cell Death in Rheumatoid Arthritis Synovial Fibroblasts

Masaru Kato, Caroline Ospelt, Renate E Gay, Steffen Gay, Kerstin Klein

The induction of autophagy was described to be activated by several cellular stress conditions such as ER stress, starvation, hypoxia but also by pro-inflammatory cytokines and Toll-like receptor ligands in different cell types. These factors were also described to play a role in the pathogenesis of rheumatoid arthritis (RA). Continued removal of unfolded and misfolded proteins by the proteasome pathway and by autophagy are essential survival pathways for cells. We analyzed the role of autophagy in the regulation of cell death pathways in rheumatoid arthritis synovial fibroblasts (RASF), which are key effector cells in the pathogenesis of RA. Our data provides the first evidence on a dual role of autophagy in the regulation of death pathways in RASF. Synovial fibroblasts (SF) derived from RA and osteoarthritis (OA) patients show different susceptibilities to reagents inducing autophagy. Consistent with previous data we showed that autophagy induction by proteasome inhibition or ER stress is more pronounced in RASF than in OASF. We showed that OASF are more susceptible to apoptosis induced by proteasome inhibition, a pathway that is dependent on caspase-3 activation. In RASF, increased autophagy activity partially compensates for an impaired proteasome function. Interestingly, we showed that RASF are hypersensitive to an autophagy-associated cell death pathway induced by severe ER stress. We identified a deregulated pattern of autophagy-related proteins (p62, ALFY) involved in the clearance of poly-ubiquitinated protein aggregates in RASF during ER stress leading to the formation of poly-ubiquitinated protein aggregates and non-apoptotic cell death.

This work is done in collaboration with Annette van der Helm-van Mil, Department of Rheumatology, Leiden University Medical Center, Leiden (NL).

The expression and regulatory role of long noncoding RNAs in gene regulation and function of rheumatoid arthritis synovial fibroblasts

Mojca Frank Bertoncelj, Kunihiko Umekita, Michelle Trenkmann, Christoph Kolling, Beat A Michel Renate E Gay, Steffen Gay

Long noncoding RNAs (lncRNAs) have emerged as key regulators of gene expression at almost every level from affecting epigenetic modifications to influencing stability and translation of mRNA. RA synovial fibroblasts (RASF), key effector cells of joint destruction in RA, exhibit profound alterations in epigenetic landscape and gene regulation leading to their stable activation and aggressiveness. Recently, several new susceptibility loci have been identified for rheumatoid arthritis (RA), mapping to noncoding genomic regions. The aim of our work is to elucidate the functional role of lncRNAs in gene regulation and stable activation of RASF.

The role of long-noncoding RNA NRON (Noncoding Repressor of Nuclear factor of activated T cells (NFAT)) is investigated in the regulation of NFAT5 transcription factor, which is increased in RA synovial tissues and in RASF, influencing their migration and proliferation. We have found NRON to be significantly up-regulated in RASF compared to control osteoarthritis SF (OASF). Down regulation of NRON in RASF – after silencing or TNFα stimulation – is accompanied by the cytoplasmic-nuclear translocation of NFAT5 and by up-regulation of NFAT5 target genes, including IL-6 and MMP-13. The formation of stress fibers, the migratory and proliferative abilities of RASF are increased after silencing of NRON. This indicates that the lncRNA NRON regulates gene expression profiles and function of RASF in a NFAT5-dependent manner and can significantly contribute to the pathogenic characteristics of RASF.
Additionally, we have analyzed the global lncRNA expression profile of RASF using human LncRNA Array v3.0 (Arraystar) that detects more than 30.000 lncRNA transcripts. The primary analysis, comparing the lncRNA profiles of 3 RASF and 3 OASF identified 100 lncRNAs being differentially expressed (DE) in RASF vs. OASF. To date we have analyzed 14 of the identified DE lncRNAs in a larger cohort of SF using real time PCR. Among them, small nucleolar RNA host gene 1 (SNHG1) and RP11-39708.4 were confirmed to be DE in RASF. Their function is not known. It is of interest, however, that RP11-39708.4 is a natural antisense transcript in the locus of fibroblast growth factor 14 and SNHG1 is a host gene for several small nucleolar RNAs, including SNORD22 and SNORD25-31. The validation of the remaining identified DE lncRNAs is planned. The gene regulatory and functional roles of validated DE lncRNAs in RASF will be studied in-depth to elucidate their contribution to the pathogenesis of RA.

Smoking induces a stress response in synovial fibroblast and tissues

Caroline Ospelt, Renate E. Gay, Beat A. Michel, Steffen Gay

Smoking is a major risk factor for the development of anti-citrullinated protein antibodies positive rheumatoid arthritis (RA) in individuals who carry shared epitope alleles. The molecular mechanisms that confer this risk are however not clarified up to now. We analyze synovial tissues of human smokers and of mice exposed to cigarette smoke as well as synovial fibroblasts (SF) that are *in vitro* stimulated with cigarette smoke extract (CSE) to find effects of smoking on joint physiology.
Gene expression analysis and functional classification showed that CSE treatment in vitro leads to a broad activation of the chaperone and heat shock protein system. This finding could be confirmed in vivo, where we found a significant increase in the expression of the HSP40 family members, DnaJB4 and DnaJC6 in synovial tissues of human smokers as well as in mice exposed to cigarette smoke. Furthermore, in human synovial tissues, but not in mice, smokers had higher levels of Hsp70 and of HspB8 similar to what was seen in vitro stimulations.
In addition we found that expression levels of the stress-induced ligands of the innate immune receptor NKG2D MICA and MICB were significantly higher in synovial tissues of smokers than of non-smokers.

Accordingly, RASFs stimulated with CSE in vitro produced significantly more MICA and MICB compared to unstimulated cells. To test whether the increased production of MICA and MICB by SFs after CSE stimulation was relevant for the activation of the NKG2D pathway on PBMCs, we performed co-culture experiments and measured internalization of the receptor on PBMCs after ligand binding. In co-cultures of PBMCs and osteoarthritis (OA) SFs stimulated with CSE, NKG2D was internalized and significantly less surface NKG2D was measureable on PBMCs after 72h compared to co-cultures without CSE. In co-cultures with PBMCs and RASFs however, no change in surface NKG2D was seen with addition of CSE even though RASFs produced similar amounts of MICA and MICB after CSE stimulation than OASFs. We are currently analyzing why PBMCs co-cultured with RASFs react differently and whether differences in the cytokine profile of RASFs and OASFs might influence the expression of NKG2D in PBMCs.

This work is done in collaboration with Giovanni G. Camici, Institute of Physiology, University of Zürich; Anca Catrina and Lars Klareskog, Karolinska Institute, Stockholm (S).

Smoking increases levels of citrullinated proteins in the joints

Caroline Ospelt, Renate E. Gay, Beat A. Michel, Steffen Gay

Since it was reported that smoking induces citrullination and peptidyl arginine diminase (PAD) enzymes in the lungs of human smokers, we measured levels of PAD2 and citrullinated proteins in the joints of smoke-exposed mice. While mRNA levels of PAD2 were not changed by smoke exposure, PAD2 protein levels and the total amount of citrullinated proteins were increased in ankle and elbow joints of mice after smoke exposure. Also, in muscle samples of smoke exposed mice citrullination was increased. In contrast, no changes in citrullination after smoke exposure occurred in the skin.
Smoking OA patients had a marked increase in citrullination as well as PAD2 levels in their synovial tissues as seen on immunoblots. An increase in citrullination in OA smokers could also be confirmed with antibodies against mutated citrullinated vimentin. In RA patients, as expected due to the inflammation, levels of citrullinated proteins and PAD2 were very high and equally high in smokers as well as non-smokers. As in mice also in human synovial tissues mRNA of PAD2 was not changed in smokers.
Currently, we are analyzing the serum of smoke –exposed mice to see whether also the development of auto-antibodies against citrullinated peptides (ACPAs) is promoted by smoking. We also measure levels of microRNAs in smokers and non-smokers to see whether the downregulation of microRNAs might be responsible for the post-transcriptional regulation of PAD2.

This work is done in collaboration with Giovanni G. Camici, Institute of Physiology, University of Zürich; Anca Catrina and Lars Klareskog, Karolinska Institute, Stockholm (S) and Holger Bang, Orgentec Diagnostik, Mainz (D).

Sirtuins modify cigarette smoke induced expression of MMP1 and IL-8 in rheumatoid arthritis synovial fibroblasts

Anna Engler, Renate E. Gay, Beat A. Michel, Steffen Gay, Caroline Ospelt

Sirtuins (SIRTs) are recently discovered regulators of inflammation. The aim of the current study was to investigate the impact of cigarette smoke extract (CSE) on the expression of interleukins (ILs) and matrix metalloproteinases (MMPs), and the possible function of SIRTs in the cigarette smoke induced inflammatory response in RASF.

Analysing the expression of SIRTs 1-7 revealed that CSE significantly increases the expression of SIRT1 and SIRT6. Furthermore, stimulation of RASF with CSE increased the secretion of the pro-inflammatory cytokine IL8. Since overexpression of SIRT1 further increased the release of IL8 in CSE stimulated RASF, we conclude that SIRT1 promotes IL8 secretion under CSE stimulation. Production of IL8 was also increased in unstimulated cells after overexpression of SIRT1, pointing to a pro-inflammatory function of SIRT1 in RASF.

In contrast, basal production of MMP1 was significantly higher after silencing of SIRT6. Also after stimulation with CSE, silencing of SIRT6 lead to increased levels of MMP1 protein. Therefore, we conclude that SIRT6 acts as a protective regulator attenuating CSE induced MMP1 production in RASF.

Changes in microRNAs in RA synovial fibroblasts

Caroline Ospelt, Renate E. Gay, Beat A. Michel, Steffen Gay

MicroRNAs are small non-coding RNAs that can inhibit gene translation by sequence-specific binding to target mRNAs. Previously, we and others showed that specific microRNAs (miR-155, miR-146a, miR-203) are differentially expressed between RA and OA synovial fibroblasts and that they can modulate the expression of matrix-metalloproteinases (MMPs) and interleukin (IL) 6 in these cells.

We now found that also the expression of miR-323 is increased in synovial fibroblasts from RA patients. Inhibition and over-expression experiments showed that this microRNA strongly influences expression of MMPs and the tissue inhibitor of metalloproteinases TIMP-3, a natural inhibitor of MMPs could be identified as a direct target of miR-323. Experiments to test a potential therapeutic use of anti-miR-323 in a mouse model of arthritis are under way.

In addition we are analyzing the microRNA profile of synovial fibroblasts from patients with resolving arthritis such as reactive arthritis and from patients with RA at a very early stage of the disease (< 3 months since onset of symptoms). MicroRNAs that are deregulated at this early stage of the disease do not only give interesting insights into pathogenetic mechanisms operative in RA, but could be of potential use as biomarkers, since early diagnosis and treatment of RA is crucial to prevent joint damage, but early markers of disease are scarce.

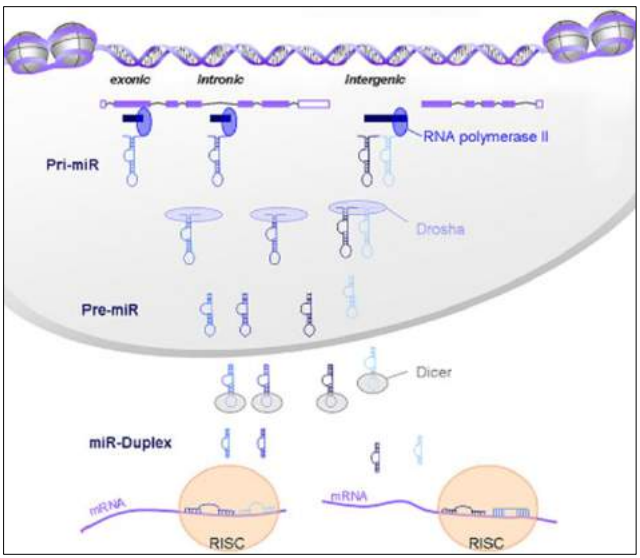

Figure 2
MicroRNA biogenesis. MicroRNAs are transcribed as primary transcripts (pri-miR), which are further processed by the RNase III enzymes Drosha and Dicer. The resulting miR-Duplex is loaded onto the RNA induced silencing complex (RISC) where the separated strands bind their target mRNA and induce its degradation or inhibit its translation.

This work is done in collaboration with Mary Connolly, University College Dublin, Dublin (IRE); Christopher Buckley and Andrew Filer, Rheumatology Research Group, School of Immunity and Infection, Birmingham (UK).

The direct effect of antibodies against citrullinated peptides (ACPAs) on synovial fibroblasts

Caroline Ospelt, Renate E. Gay, Beat A. Michel, Steffen Gay

Auto-antibodies that are directed against the post-translational modification citrulline, so-called anti-citrullinated peptide antibodies (ACPAs) are highly specific for RA, their role in the pathogenesis of RA is however unclear. Recently, it was shown that ACPAs can promote osteoclastogenesis and bone destruction. The aim of this project is to find out whether ACPAs can directly stimulate synovial fibroblasts and via this way influence disease outcome and progression.
ACPAs are isolated from patient's serum or synovial fluid by our collaborators from Karolinska and Orgentec. Our preliminary data show that RA but not OASF produce IL-6 after incubation with ACPAs. On the other hand, miR-146a is upregulated in OASF but not in RASF in response to ACPAs. Since higher increase of miR-146a correlates with lower levels of IL-6, and miR-146a has previously been described to dampen IL-6 production, we assume that also in the ACPA response, miR-146a restrains production of IL-6.

This work is done in collaboration with Heidi Wähämaa and Anca Catrina, Karolinska Institute, Stockholm (S) and Holger Bang, Orgentec Diagnostik, Mainz (D).

Epigenetic modulation of TLR-mediated tolerance in synovial fibroblasts

Kerstin Klein, Renate E. Gay, Beat A. Michel, Steffen Gay, Caroline Ospelt

It is well-known that in macrophages, genes are either silenced (tolerizable) or sustained (non-tolerizable) after repeated TLR4 stimulation. Tolerizable genes are mainly pro-inflammatory mediators such as IL-6, which get transiently silenced via epigenetic mechanisms to protect inflamed tissues form inflammation induced damage. We found that synovial fibroblasts maintain their IL-6 production after repeated LPS stimulation. Furthermore also matrix-metalloproteinases and certain chemokines (CCL5) are non-tolerizable in synovial fibroblasts in contrast to macrophages. On the other hand a subset of genes (CXCL10, OAS1, MDA5, RIG1) which are dependent on the transcription factor CREB (cAMP response element-binding protein) is also tolerizable in synovial fibroblasts. Interestingly, some non-tolerizable genes become tolerizable by inhibition of bromodomain proteins (I-BET 151). Since bromodomain proteins are readers of histone acetylation marks, we assume that histone acetylation plays a role in the maintained expression of non-tolerizable genes in synovial fibroblasts.
This lack of tolerization in stromal cells might significantly contribute to maintained inflammation and tissue damage in chronic inflammatory diseases.

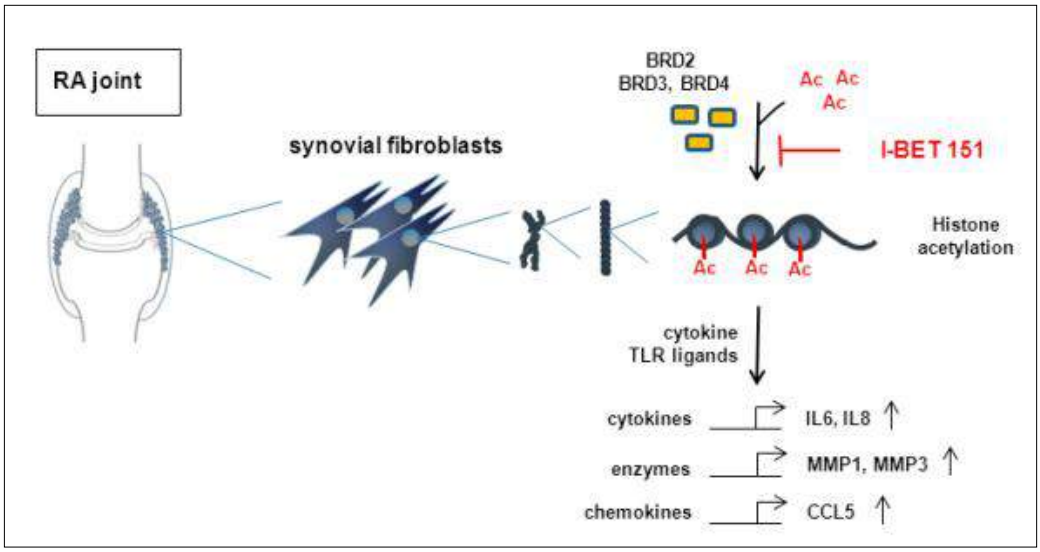

Figure 3
Bromodomain proteins (BRD2, BRD3, BRD4) can modulate cytokine- and TLR ligand- induced expression of cytokines, chemokines and matrix-degrading enzymes.

This work is done in collaboration with Pfizer.

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European Union
Seventh Framework Programme
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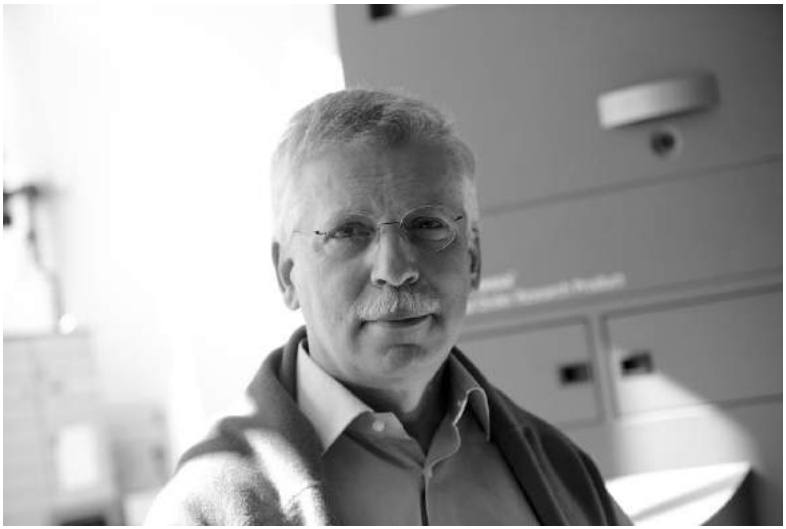

Antonio Lanzavecchia

Antonio Lanzavecchia earned a degree in Medicine at the University of Pavia where he specialized in Pediatrics and in Infectious Diseases. From 1983 to 1999, he worked at the Basel Institute for Immunology and since 1999 he is the founding Director of the Institute for Research in Biomedicine in Bellinzona. He taught immunology at the Universities of Genova and Siena and since 2009 is Professor of Human Immunology at the Swiss Federal Institute of Technology ETH Zurich. He is Member of the EMBO and Fellow of the Royal College of Physicians. Awarded the EMBO medal in 1988 and the Cloëtta prize in 1999, Antonio Lanzavecchia published more than 250 papers. His research has covered several aspects of human immunology: from antigen processing and presentation to dendritic cell biology, from lymphocyte activation and trafficking to T and B cell memory.

Research Focus

The aim of the current work is to unravel the basis of host resistance to infectious diseases to create a new generation of passive antibody therapies and novel vaccines. The human monoclonal antibodies that we isolate from memory B cells and plasma cells can be used not only as drugs for prophylaxis and treatment of infectious diseases, but also as tools to identify vaccine candidates. Besides these translational studies we address fundamental issues with regard to the cellular basis of immunological memory, the role of somatic mutations in the generation of broadly neutralizing antibodies. In particular we are interested to understand the relationship between infection and autoimmunity and the role that somatic mutations play in the generation of autoantibodies.

Team

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The role of somatic mutations in the generation of autoantibodies

Davide Corti and Antonio Lanzavecchia

The mechanism of somatic mutation is responsible for the diversification of the antibodies in germinal centers leading to affinity maturation through the generation of variants that are selected for their fitness for the antigen. Our recent studies on influenza- and HRSV/HMPV-neutralizing have clearly shown that somatic mutations offer also the possibility of broadening the antibody specificity thus anticipating viral evolution. While somatic mutation can provide useful mechanisms such as affinity maturation and repertoire broadening it also poses some risks such as the somatic generation of antibodies that react against self-antigens. Based on our recent results obtained in the study autoantibodies found in pemphigus, PAP and rheumatoid arthritis patients and on a previous report on a lupus autoantibodies (Wellmann, PNAS 2005), we suggest that these newly generated autoreactive B cells that fail to be tolerized in germinal centers may enter the memory pool and be stimulated by self antigens found in peripheral tissues. Environmental and genetic factors may contribute to the expansion and differentiation of these autoreactive B cells. These factors may range from the release of self-antigens following necrotic or infectious events to genetic polymorphisms that facilitate the activation of memory B cells.

Autoantibodies to GM-CSF in patients with pulmonary alveolar proteinosis and in healthy individuals: mechanisms of neutralization and role of somatic mutations

Luca Piccoli, Blanca Fernandez-Rodriguez, Laurent Perez, Davide Corti and Antonio Lanzavecchia

Pulmonary alveolar proteinosis (PAP) is a rare severe autoimmune disease caused by autoantibodies that neutralize GM-CSF causing the loss of alveolar macrophages and the accumulation of lipoproteinaceous material within the alveoli. By immortalizing memory B cells from several PAP patients we isolated more that 50 monoclonal antibodies that bind to human GM-CSF with high affinity. Surprisingly, in spite of high neutralizing activity of the patient's serum, none of these antibodies showed GM-CSF neutralizing activity. By cross-competition experiments using surface plasmon resonance we established a map of the antigenic sites of GM-CSF and showed that 3 antibodies can bind simultaneously to a single GM-CSF molecule. Strikingly, while single antibodies were ineffective, a combination of 3 antibodies targeting non-overlapping sites was capable of completely and potently neutralizing the biological activity of GM-CSF. These findings indicate that in PAP the neutralization of GM-CSF is dependent on synergistic antibody combinations. We therefore investigated whether anti-GM-CSF antibodies could be found also in healthy individuals. Using a site-specific serological assays we identified healthy blood donors with low levels on non-neutralizing GM-CSF antibodies. Remarkably, the serum of these donors synergized with some non-neutralizing monoclonal antibodies directed against complementary sites leading to full GM-CSF neutralization. Taken together these results indicate that otherwise healthy individuals can

generate autoantibodies to GM-CSF and that in vivo neutralization of GM-CSF observed in PAP patients requires the presence of synergizing antibodies directed against complementary sites.

This work was done in collaboration with Federica Sallusto and Luca Varani, IRB and Ilaria Campo and Maurizio Luisetti, Fondazione IRCCS Policlinico San Matteo, Pavia (IT).

Pemphigus autoantibodies are generated through somatic mutations and target the desmoglein-3 cis-interface

Giulia Di Lullo, Davide Corti and Antonio Lanzavecchia

Pemphigus vulgaris is an autoimmune blistering disease of skin and mucous membranes caused by autoantibodies to the desmoglein (DSG) family proteins DSG3 and DSG1, leading to loss of keratinocyte cell adhesion (Figure 1). To learn more about pathogenic pemphigus autoantibodies, we isolated 15 IgG antibodies specific for DSG3 from 2 PV patients. Three antibodies disrupted keratinocyte monolayers in vitro, and 2 were pathogenic in a passive transfer model in neonatal mice. The epitopes recognized by the pathogenic antibodies were mapped to the DSG3 extracellular 1 (EC1) and EC2 subdomains, regions involved in cis-adhesive interactions. Using a site-specific serological assay, we found that the cis-adhesive interface on EC1 recognized by the pathogenic antibody PVA224 is the primary target of the autoantibodies present in the serum of PV patients. In contrast, autoantibodies that target the trans-adhesive interface appear to be less frequent in PV patients. The autoantibodies isolated used different heavy- and light-chain variable region genes and carried high levels of somatic mutations in complementary-determining regions, consistent with antigenic selection. Remarkably, binding to DSG3 was lost when somatic mutations were reverted to the germline sequence. These findings identify the cis-adhesive interface of DSG3 as the immunodominant region targeted by pathogenic antibodies in PV and indicate that autoreactivity relies on somatic mutations generated in the response to an antigen unrelated to DSG3.

This work is done in collaboration with Giovanna Zambruno and Giovanni Di Zenzo, IDI-IRCCS, Rome (IT) and with Fabrizia Vanzetta and Gloria Agatic, Humabs BioMed, Bellinzona (CH).

Di Zenzo, G et al.
J Clin Invest 2012, 122, 3781–3790.

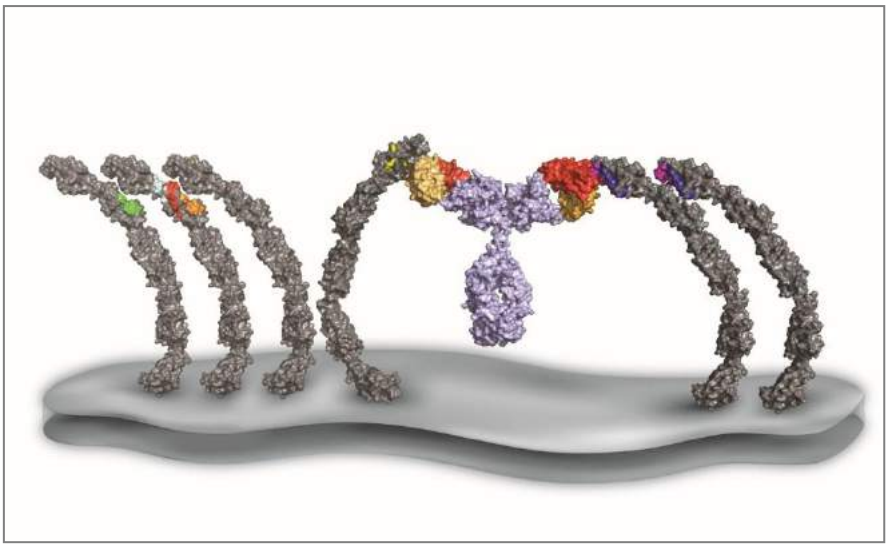

Figure 1
The study demonstrates how the autoantibodies (in purple) can destroy the net of desmoglein (in grey), which is necessary to maintain the adhesion between the epidermal cells

AncesTree: an algorithm to draw the genealogy tree of clonally related antibodies

Mathilde Perez, Leontios Pappas, Davide Corti and Antonio Lanzavecchia

B cell affinity maturation occurs in germinal centers and is based on the introduction of somatic mutation in immunoglobulin genes followed by selection of the fittest mutants. Analysis of sister clones and the reconstruction of their ancestral relationships allows the reconstruction of genealogical trees illustrating the developmental pathway for the generation of high affinity antibodies and the identification of the key somatic mutations required to achieve high affinity binding. We have developed a novel algorithm to generate genealogy trees from mutated V-gene sequences and their germline unmutated sequences. Original sequences found in experiments are assigned to either terminal or internal nodes of the tree and the branching nodes represents hypotetical developmental clones which are reconstructed by gene synthesis and tested in vitro. An example of a family of antibodies specific for influenza hemagglutinin is shown in figure 2.

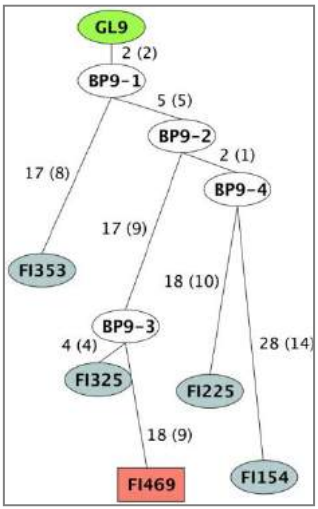

Figure 2
Genealogy tree of an antibody family reconstructed using AncesTree. Shown are the number of nucleotide mutations and amino acid substitutions (in brackets). Empty symbols indicate hypothetical branchpoints.

Long-term culture of normal and malignant plasma cells

Dora Pinto, David Jarrossay and Antonio Lanzavecchia

Plasma cells do not survive in conventional cell cultures a fact that has prevented the in vitro analysis of this cell type. However plasma cells survive in the bone marrow niches organized by mesenchymal stromal cells. We found that bone marrow mesenchymal stromal cells (MSC) are suitable feeder cells to support the survival of human plasma cell in vitro. $CD138^{+}$ plasma cells isolated from peripheral blood or bone marrow were seeded as single cells on MSC monolayers and IgG production was monitored over several weeks. We found that over this period, Ig accumulated in the culture supernatants at a constant rate (70-140 pg/cell/day). IgG and IgA secreting plasma cells were maintained in culture with a plating efficiency ranging from 65% to 100%, while the plating efficiency of IgM plasma cells was lower. Ig production was unaffected by hydroxyurea and

irradiation, as expected for terminally differentiated non-dividing cells. We have adapted the single cell culture method to interrogate circulating plasma cells isolated seven days after infection or vaccination. The culture supernatants were screened for the presence of specific antibodies using parallel ELISA and from selected cultures the Ig genes were rescued by RT-PCR. We are currently using this method to study myeloma cells in cultures. Our findings indicate that the rate of Ig secretion is lower in myeloma cells as compared to normal plasma cells and that drugs that target autophagy and proteasome function can synergistically inhibit survival of malignant plasma cells.
This work is done in collaboration with Francesca Fontana and Roberto Sitia, HSR, Milano (IT).

A dynamic model of serological memory

Dora Pinto, Leon Pappas, Silvia Preite, and Antonio Lanzavecchia

To understand the mechanisms that maintain serological memory we have systematically interrogated the repertoire of recently generate plasma cells ($CD138^+$ DR^+ $CD62L^+$) that are found in peripheral blood. We found that seven days following vaccination with influenza virus most of the recently generated plasma cells produce antibodies specific for the vaccine. However, a sizeable fraction of these recently generated plasma cells produced antibodies of other specificities, including antibodies specific for irrelevant recall antigens. We also found that that in the steady state recently generated plasma cells produced antibodies to vaccines or viruses that the donor had encountered years and even decades before. Representative monoclonal antibodies were isolated from plasma cells to formally demonstrate that in the absence of specific antigenic stimulation there is a continuous generation of plasma cells making memory antibodies. To investigate the mechanism that underpins this polyclonal B cell activation we immunized mice with influenza virus and transferred the memory cells, alone or with memory or naïve T cells, into immunodeficient mice. We found that in the absence of antigenic stimulation serum antibodies to influenza virus slowly but steadily increased over a period of 6 weeks. Interestingly, this increase was observed only in mice transferred with memory B cells and either naïve or memory T cells, but not in mice transferred only with B cells alone. Taken together, these findings support a dynamic model of serological memory where activated T cells drive, in an antigen-independent fashion, the polyclonal stimulation of memory B cells that contributes to maintaining constant levels of plasma cells and consequently lasting levels of protective serum antibodies.

A functional B cell receptor on human IgA and IgM plasma cells

Dora Pinto, Antonio Lanzavecchia and David Jarrossay

Plasma cells are terminally differentiated cells of the B cell lineage that secrete antibodies at high rate and are thought to lack the expression of the B cell receptor (BCR). Clear differences between the IgG and the IgA humoral systems in terms of dynamics have recently emerged. We found that human IgA and IgM unlike IgG plasma cells express a membrane functional BCR associated with the Igα/Igβ heterodimer. BCR crosslinking on IgA and IgM plasma cells led to Ca2+ mobilization, ERK1/2 and AKT phosphorylation and impacted survival of IgA plasma cells. These findings demonstrate fundamentally distinct biology between IgG, IgM and IgA plasma cells and suggest that the IgA plasma cell repertoire may be modulated by the presence of specific antigens.

This work was done in collaboration with Martin Bolli and Guido Garavaglia, Ospedale San Giovanni, Bellinzona (CH).

The human antibody response to gut commensals, pathogens and food antigens

Costanza Casiraghi, Andrea Minola, and Antonio Lanzavecchia

Our immune system is continuously exposed to a plethora of antigens derived from commensals, pathogens and food antigens that are supposed to sustain the strong antibody response observed in the gut and other mucosal sites, in particular but not exclusively secretory IgA. However, little is known on the specificity, kinetics and memory of the secretory immune system in humans. Using a variety of approaches we investigate the response to aerobic and anaerobic commensals, pathogens and food antigens in the tissues that are accessible to this analysis. In particular we interrogate memory B cells as well as recently activated B cells and plasma cells that circulate in peripheral blood on their way to mucosal tissues. By determining the frequency of specific cells and characterizing the antibodies produced we expect to gain insight into the normal activity of the immune system and address issues such as the duration of immune responses and immunological memory in the secretory system.

The repertoire of recently activated B cells

Alexander Fruehwirth, Davide Corti and Antonio Lanzavecchia

We are interested to find a method to discriminate recently activated B cells from the bulk of memory B cells. This will offer the possibility of investigating the ongoing activity of the immune system in the steady state and in the course of the response to pathogens. In addition this approach would be extremely valuable to analyse disease activity in autoimmune diseases to identify the factors that elicit and maintain the production of autoantibodies. To identify surface markers of recently activated B cells we used polychromatic flow cytometry and an unbiased analysis program to identify subsets that increase following vaccination or infection. This approach was combined with the immortalization and analysis of the specificity of the specific cells and the isolation of monoclonal antibodies and the analysis of Ki67. Using this approach we were able to identify in peripheral blood a small subset of Ki-67+memory-type B cells that increase 2-4 weeks after vaccination and are highly enriched in vaccine-specific memory cells. After validation of these findings in vaccinated individuals we will start to analyse the repertoire of these cells as compared to bona fide memory cells in healthy individuals and in patients with chronic infections and autoimmune disorders.

Funding

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Tuning of immune homeostasis and immune response by persistent viral infections
CRSII3-147662 / 2013-2016

Swiss National Science Foundation
Human B cells and plasma cells in health and diseases
310030-141254 / 2012-2015

Swiss National Science Foundation
Role of innate receptors in dendritic cell and lymphocyte activation
31003A-126027/1 / 2009-2012

European Union - ERC
IMMUNExplore: New approaches to analyze and exploit the human B and T cell response against viruses
ERC-2009-AdG-20090506-250348 / 2010-2015

European Union
ADITEC: Advanced Immunization Technologies
FP7-HEALTH-2011-280873 / 2011-2016

European Union
Innovative Medicines Initiative (IMI) Joint Undertaking (JU)
ABIRISK: Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk
IMI-2010- Call3- 115303 / 2012-2017

European Union
IDAMS: International Research Consortium on Dengue Risk Assessment, Management and Surveillance
FP7-HEALTH-F3-2011-281803 / 2011-2016

National Institute of Health (USA)
Vaccine-induced immunity in the young and aged
U19 AI057266-06 / 2009-2014

National Institute of Health (USA)
Susceptibility and protective immunity to Noroviruses
2R01AI056351-06A1-#5-30027 / 2009-2014

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Federica Sallusto

Federica Sallusto received the degree of Doctor in Biology from the University of Rome and performed postdoctoral training at the Istituto Superiore di Sanità in Rome working on T cell response to allergens and at the Basel Institute for Immunology in the laboratory of Antonio Lanzavecchia on human monocyte-derived dendritic cells. In 1997 she became member of the Basel Institute and since 2000 she is group leader at the IRB. Her studies in the human system revealed a differential expression of chemokine receptors in Th1 and Th2 cells and led to the characterization of "central memory" and "effector memory" T cells as memory subsets with distinct migratory capacity and effector function. Among her recent contributions are the discovery of Th22 cells, the identification of markers to identify human Th17 cells and the characterization of two distinct types of Th17 cells that produce IFN-γ or IL-10. Studies in the mouse model challenged current dogmas as to the mechanisms that control lymphocyte migration in lymph nodes and in the central nervous system; more recently her lab showed that persistent antigen and germinal centre B cells sustain Tfh cell responses and phenotype. For her scientific achievements, she received the Pharmacia Allergy Research Foundation Award in 1999, the Behring Lecture Prize in 2009 and the Science Award from the Foundation for Studies of Neurodegenerative Diseases in 2010. She was elected member of the German Academy of Science Leopoldina in 2009 and member of EMBO in 2011. She is President of the Swiss Society for Allergology and Immunology for the period 2013-2015.

Research Focus

Our work is focused on the understanding of the mechanisms that control T cell priming and regulate cytokine production and homing capacities in humans. We combine *ex vivo* analysis of memory T cell subsets with *in vitro* priming of naive T cells. This approach has led to the identification of chemokine receptors expressed in human Th17 and Th22 cells, and to the dissection of the cytokines that drive naive T cell polarization and modulate T cell effector functions. In parallel, we have used the mouse system to address fundamental questions on the regulation of lymphocyte trafficking during inflammation and in autoimmunity. We also developed a method for the analysis of human naive and memory CD4 and CD8 T cell repertoires based on high throughput cellular screenings of human T cell libraries. This method is currently used to dissect the human T cell response to pathogens, allergens, and self-antigens.

Team

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Two types of human Th17 cells producing IFN-γ or IL-10 and regulated by IL-1β

Christina E. Zielinski, Federico Mele, Dominik Aschenbrenner, David Jarrossay, Francesca Ronchi, and Federica Sallusto

IL-17-producing $CD4^+$ T helper cells (Th17) have been extensively investigated in mouse models of autoimmunity. However, the requirements for differentiation and the properties of human Th17 cells remain poorly defined. Using an approach that combines the *in vitro* priming of naive T cells with the *ex vivo* analysis of memory T cells, we describe here two types of human Th17 cells with distinct effector function and differentiation requirements. *Candida albicans* (*C.a.*)-specific Th17 cells produced IL-17 and IFN-γ, but no IL-10, while *Staphylococcus aureus* (*S.a.*)-specific Th17 cells produced IL-17 and could produce IL-10 upon restimulation. IL-6, IL-23, and IL-1β contributed to Th17 differentiation induced by both pathogens, but IL-1β was essential in *C.a.*-induced Th17 differentiation to counteract the inhibitory activity of IL-12 and to prime IL-17/IFN-γ double producing cells. In addition, IL-1β inhibited IL-10 production in differentiating and in memory Th17 cells, while blockade of IL-1β *in vivo* led to increased IL-10 production by memory Th17 cells. We also show that following restimulation, Th17 cells transiently downregulated IL-17 production through a mechanism that involved IL-2-induced activation of STAT5 and decreased expression of RORγt. Taken together these findings demonstrate that by eliciting different cytokines *C.a.* and *S.a.* prime Th17 cells that produce either IFN-γ or IL-10, and identify IL-1β and IL-2 as pro- and anti-inflammatory regulators of Th17 cells both at priming and in the effector phase.

This work was done in collaboration with Silvia Monticelli, IRB, and Marco Gattorno, Istituto Gaslini, Genova (IT).

Zielinski, C.E., et al.
Nature. 2012; 484:514-518.

Human Th17 subsets.
Sallusto, F., et al.
Eur J Immunol. 2012; 42:2215-2220.

Unravelling the transcriptional circuit regulating IL-10 production in human Th17 cells

Samuele Notarbartolo, Dominik Aschenbrenner and Federica Sallusto

IL-17 producing CD4+ cells (Th17) are a subset of effector T helper cells known to play an important role in host defense against fungi and extracellular bacteria but also involved in tissue inflammation and autoimmune diseases, such as multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis. The function of Th17 cells depends critically on the range of cytokines produced and on the balance between pro- and anti-inflammatory cytokines. Autoreactive Th17 cells producing IFN-γ and GM-CSF are pathogenic in a mouse model of EAE, while Th17 cells producing IL-10 are not. We have recently shown that *C. albicans*-specific human Th17 cells produce IL-17 and IFN-γ, while *S. aureus*-specific human Th17 cells produce IL-17 and, after restimulation, IL-10. While the ontology of the two different Th17 subsets has been clarified, it still remains elusive what is the transcriptional circuit that regulates the expression of the immunoregulatory molecule IL-10. Using a combination of transcriptional profiling and epigenetic approach, we identified the transcription factor c-MAF as a candidate for the regulation of IL-10 production in human Th17 cells, thus potentially representing a discriminant factor between pathogenic and non pathogenic Th17 cells.

Specificity and distribution of self-reactive T cells in health and disease

Daniela Impellizzieri, Daniela Latorre and Federica Sallusto

Our aim is to develop sensitive methods to study self-reactive T cells in healthy donors and in patients with autoimmune diseases. Since self-reactive T cells may have low avidity and may be present at low frequencies we will combine cell sorting strategies to enrich specific populations, with the T cell library method that allows detection of even low avidity cells. The feasibility of this approach is illustrated by the analysis of T cells from multiple sclerosis (MS) patients that shows that MOG-specific T cells are detectable in most patients and are virtually all present in the CCR6+ memory subset. These findings are consistent with our previous demonstration that CCR6 is required to drive migration of pathogenic T cells in the CNS of mice developing autoimmune encephalomyelitis. We are extending the analysis to other organ-specific autoimmune diseases, in particular pemphigus, for which autoantigens are well characterized, and to other conditions of aberrant responses to self antigens such as Pulmonary alveolar proteinosis, a rare disease characterized by autoantibodies against GM-CSF, and Factor VIII-treated hemofilia in which anti-Factor VIII antibodies develop in response to the therapy.

These studies are done in collaboration with Antonio Uccelli, University of Genova (IT) and Gianna Zambruno, IDI, Rome (IT).

Sallusto, F., Impellizzieri, D., et al.
Immunol. Rev. 2012; 248:216-227.

T follicular helper cell response and phenotype are sustained by persistent antigen and germinal center B cells

Dirk Baumjohann, Silvia Preite, Andrea Reboldi, Francesca Ronchi, and Federica Sallusto

T follicular helper (Tfh) cells provide help to B cells and are crucial for the establishment of the germinal center (GC) reaction, including the production of high-affinity antibodies and the generation of memory B cells and long-lived plasma cells. Here we report that the magnitude of the Tfh cell response was dictated by the amount of antigen and directly correlated with the magnitude of the GC B cell response. In addition, maintenance of the Tfh cell phenotype required sustained antigenic stimulation by GC B cells. In lymphopenic conditions, a strong and prolonged Tfh cell response led to bystander B cell activation, hypergammaglobulinemia, and production of poly- and self-reactive antibodies (Figure 1). These data demonstrate that antigen dose determines the size and duration of the Tfh cell response and GC reaction, highlight the transient nature of the Tfh cell phenotype, and suggest a link between overstimulation of Tfh cells and the development of dysregulated humoral immune responses.

This work is done in collaboration with Antonio Lanzavecchia, IRB, and K. Mark Ansel, UCSF, CA (US).

Baumjohann D. Preite S, et al.
Immunity 2013, 38:596-605.

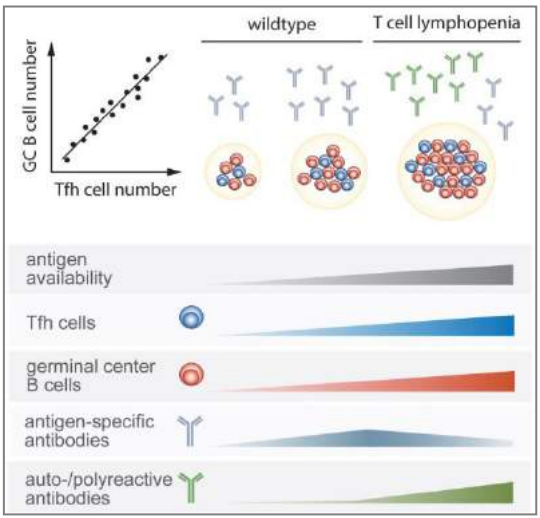

Figure 1
Graphical representation of the results

T follicular helper cell response in lymphopenic mice

Silvia Preite, Luana Perlini and Federica Sallusto

In the previous study, we showed that T cells in lymphopenic mice preferentially differentiate into Tfh cells which are however impaired in their ability to induce antibody affinity-maturation and to help generate long-lived plasma cells. Also we showed that in lymphopenic mice a large number of monoclonal OVA-specific Tfh cells can induce activation of "bystander" B cells and production of isotype switched antibodies of unrelated specificities. To understand the basis of this phenomena, we are performing several experiments. First, we have cloned and sequenced Ig genes from NP-specific B cells 21 days following immunization of OT-II-transferred CD3$\varepsilon^{-/-}$ mice with NP-OVA. We found that two point mutations in the VH186.2 sequences, which are known to confer high affinity to anti-NP antibodies, were only present in wild type mice but not in CD3$\varepsilon^{-/-}$ mice, consistent with low serum antibody titers found in CD3$\varepsilon^{-/-}$ mice as measured by ELISA. Additional experiments are being performed to obtain sequences and identify somatic mutations that will be used to draw phylogenetic trees and define branch points. Based on a in house developed algorithm we hope to gain a better understanding on how and when antibody sequences differed in wild type and CD3$\varepsilon^{-/-}$ mice. Second, we are defining the requirements to induce the "bystander" B cell activation which is observed as a consequence of the strong and prolonged Tfh cell response in lymphopenic mice. Ongoing experiments are addressing the role of cognate interaction, for instance using B cells of unrelated specificities lacking MHC class II molecules. Finally, we are investigating the role of Tregs in controlling Tfh responses, in light of the recent findings of specialized Treg cells (Tfr) residing in the B cell follicle and regulating GC reactions. We found that Treg cells co-transferred with OT-II into CD3$\varepsilon^{-/-}$ mice immunized with OVA in alum become dysfunctional and lose the ability to suppress naïve CD4 T cells in vitro when isolated from CD3$\varepsilon^{-/-}$ hosts 22 days after transfer. Since some cytokines, for example IL-21 and IL-15, are known to drastically reduce the suppressive activity of Treg cells, we are planning to perform adoptive transfer experiments using Treg cells from mice deficient in different cytokine receptors. Experiments using Treg from DEREG-IL-21R$^{-/-}$ mice (kindly provided by Manfred Kopf, ETH Zurich) are ongoing.

Cervical lymph nodes and the pivotal role in the CCR6$^+$ T helper cell priming

Camilla Basso, Luana Perlini and Federica Sallusto

To perform their function, effector and memory T cells have to migrate to sites of antigen challenge. Previous studies have shown that CCR9 is expressed by T cells that migrate to the gut, while CCR10 is expressed on T cells that migrate to the skin. These receptors are induced by dendritic cells (DCs) that process gut derived vitamin A and skin derived vitamin D into active metabolites (retinoic acid and 1,25-dihydroxy-vitamin D3) that elicit CCR9 and CCR10 expression in activated T cells. Using the experimental autoimmune encephalomyelitis (EAE) model, we have recently shown that pathogenic Th17 cells upregulate expression of CCR6 and use this receptor to enter into the CNS by crossing the epithelium of the choroid plexus, which constitutively express the CCR6 ligand CCL20. Based on these findings we hypothesized that CCR6 regulates constitutive migration of lymphocytes in the CNS and that this receptor may be selectively induced in the local microenvironment of the cervical lymph nodes (CLNs). Consistent with this hypothesis, we found that naive CD4$^+$ T cells primed by antigens draining in the CLNs selectively upregulate CCR6 expression. Moreover, *in vitro* experiments showed that CD4$^+$ T cells cultured with cells isolated from CLNs also upregulate CCR6 expression. Migratory DCs seem to be responsible for CCR6 upregulation on T cells, since CCR6 was not induced in CLNs of CCR7 deficient animals which lack this DC subset. We are currently performing experiments to understand what are the signals required for induction of CCR6 expression in T cells primed in the CLNs and to define their cytokine profile.

Pertussis toxin-driven IL-1β production is required for priming of highly encephalitogenic GM-CSF$^+$ T cells and for EAE pathogenesis

Francesca Ronchi, Camilla Basso, Luana Perlini and Federica Sallusto

IL-1β is a pleiotropic cytokine that plays a role in several inflammatory disorders in humans and in animal models, including mouse experimental autoimmune encephalomyelitis (EAE). It is produced after cleavage of pro-IL-1β by IL-1 converting enzyme (caspase-1), which in turn is activated by a complex of proteins called inflammasome. IL-1β has been shown to be required for differentiation of human and mouse inflammatory Th17 cells characterized by co-expression of IL-17 and IFN-γ. We found that mice deficient for IL-1β or for a component of the inflammasome (the apoptosis-associated speck-like protein containing a caspase recruitment domain, ASC) did not develop EAE following immunization with myelin oligodendrocyte glycoprotein (MOG) in complete Freund's adjuvant (CFA) and pertussis toxin (PT). Autoreactive T cells were primed in wild-type (wt), IL-1β$^{-/-}$ and ASC$^{-/-}$ mice. However, while in wt mice T cells proliferated extensively and acquired the capacity to produce inflammatory cytokines, such

as IL-17, IL-22, IFN-γ, and GM-CSF, in IL-1β$^{-/-}$ and ASC$^{-/-}$ mice, cells expanded poorly and showed reduced capacity to produce simultaneously inflammatory cytokines, in particular GM-CSF. Interestingly, induction of polyfunctional (IL-17^{+} IL-22^{+} IFNγ^{+} GM-CSF^{+}) T cells in wt mice was dependent on the presence of PT at the time of immunization. PT was found to rapidly induce IL-1β secretion by CD11c^{+} and Gr1^{+} myeloid cells, which are highly recruited in secondary lymphoid organs after *in vivo* PT treatment. Moreover, in mice depleted of Gr1^{+} myeloid cells, IL-1β production was not induced by PT and priming of polyfunctional T cells was impaired. Taking together, these data support the notion that the disease-inducing effect of PT is due to its ability to induce recruitment of Gr1^{+} myeloid cells, production of IL-1β, and differentiation of pathogenic polyfunctional T cells.

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Institute of Arthritis Research
The role of T and B cells in arthritis / 2009-2011

European Union
NEWTBVAC: Discovery and Pre-Clinical Development of New Generation Tuberculosis Vaccines 241745 / 2010-2013

Swiss National Science Foundation
Effector and memory T cell subsets in man and mouse
3100A0_131092 / 2010-2013

Swiss National Science Foundation
Studies on T cell activation, differentiation and plasticity in humans
310030_149475 / 2013-2016

European Union
IDAMS: International Research Consortium on Dengue Risk Assessment, Management, and Surveillance
281803 / 2011-2016

Swiss National Science Foundation
ProDoc Cell Migration
PDFMP3_137127 / 2011 – 2014

European Union
ABIRISK: Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk
IMI-2010- Call3- 115303 / 2012 – 2017

Swiss MS-Society
Investigating the cellular and molecular mechanisms involved in the migration of human CD4+ effector/memory T cell subsets across novel human in vitro models of the blood-brain barrier and the blood-cerebrospinal fluid barrier
2013

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Mariagrazia Uguccioni

Mariagrazia Uguccioni received a degree in Medicine from the University of Bologna (IT) where she specialized in Haematology in 1994. From 1993 to 2000 she was a member of the Theodor Kocher Institute, University of Bern (CH), and since 2000 she is group leader at the IRB, and vice-director since 2010. She is member of the Bologna Academy of Science since 2009. Mariagrazia Uguccioni's research has covered aspects of human haematology and immunology: chemokine expression and activities in normal and pathological conditions, leukocyte activation and traffic, natural chemokine antagonists and synergy-inducing chemokines. Recently, her group is focusing on chemokine activities in human inflammatory diseases, tumours, and infections and has identified a novel regulatory mechanism of leukocyte trafficking induced by synergy-inducing chemokines.

Research Focus

Our research interest remains focused on CHEMOKINE activities in physiology and pathology, with an emphasis on the mechanisms governing fine-tuning modulation of their expression and activity. Chemokines are secreted proteins and have emerged as key controllers of integrin function and cell locomotion. The effects of chemokines are mediated by seven transmembrane domain receptors coupled to GTP-binding proteins, which are differentially expressed in a wide range of cell types. The resulting combinatorial diversity in responsiveness to chemokines guarantees the proper tissue distribution of distinct leukocyte subsets under normal and inflammatory/pathological conditions. A vast range of *in situ* experiments, aimed at understanding which chemokines are produced in specific circumstances, has revealed that a variety of chemokines can be concomitantly produced at target sites of leukocyte trafficking and homing. This renders the chemokine system a good target for therapy, and has increased the search also by pharmaceutical companies for small molecule chemokine antagonists. While we understand the effects of different chemokines individually, much less is known about the potential consequences of the expression of multiple chemokines, cytokines, toll-like receptor ligands or other inflammatory molecules on leukocyte migration and function. Our group discovered the existence of additional features of chemokines: their ability to antagonize or enhance, as synergy-inducing chemokines, the activity of other chemokines. We have been the first to discover that the alarmin HMGB1 can enhance chemokine activities and contribute to the first phase of cell influx in injured tissues. Moreover, HMGB1 orchestrates cell migration and cytokine production by switching among mutually exclusive redox states. Reduced cysteines make HMGB1 a chemoattractant, whereas a disulfide bond makes it a proinflammatory cytokine and further cysteine oxidation to sulfonates by reactive oxygen species abrogates both activities.

Team

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Members: Denise Bottinelli, PhD student – Valentina Cecchinato, PhD – Maria Gabriela Danelon, Technician – Camilla Marini, MSc – Lorenzo Raeli, PhD – Karolin Rommel, PhD student

Chemokines: Structure/Function Studies

Milena Schiraldi, Lorenzo Raeli, Camilla Marini, Gabriela Danelon and Mariagrazia Uguccioni

Chemokine structure/function studies led us to identify chemokines that can act as natural antagonists by preventing natural agonist binding and the subsequent activation of the receptor. Recently, we have described chemokines that can act in synergism with chemokine receptor agonists, forming heterocomplexes able to induce functional responses at lower agonist concentration. Several mechanisms have been proposed by us and other groups to provide an explanation for the synergy between chemokines: Dual receptor-mediated chemokine synergy and chemokine heterocomplexes (Figure 1).

After tissue damage, inflammatory cells infiltrate the tissue and release pro-inflammatory cytokines. HMGB1, a nuclear protein released by necrotic and severely stressed cells, promotes cytokine release via its interaction with the TLR4 receptor, and cell migration via an unknown mechanism. HMGB1-induced recruitment of inflammatory cells depends on CXCL12. HMGB1 and CXCL12 form a heterocomplex, which we characterized by nuclear magnetic resonance and surface plasmon resonance, that acts exclusively through CXCR4 and not through other HMGB1 receptors. FRET data show that the HMGB1/CXCL12 heterocomplex promotes different conformational rearrangements of CXCR4 from that of CXCL12 alone. Mononuclear cell recruitment *in vivo* into airpouches and injured muscles depends on the heterocomplex and is inhibited by AMD3100 and glycyrrhizin. Moreover, HMGB1 orchestrates cell migration and cytokine production by switching among mutually exclusive redox states. Reduced cysteines make HMGB1 a chemoattractant, whereas a disulfide bond makes it a proinflammatory cytokine and further cysteine oxidation to sulfonates by reactive oxygen species abrogates both activities. Studies are on-going on the activities of synergy-inducing molecules as biomarkers in Rheumatoid Arthritis.

Schiraldi M. et al.
J Exp Med. 2012, 209: 551-563.
- Highlights, *Nat. Rev. Immunol.* 2012, 12: 232.

J Exp Med. 2012, 209: 1519-1528.

Gouwy M. et al.
Immunol Lett. 2012, 145:10-14.

Venereau E. et al.
Mol Immunol. 2013, 55:76– 82.

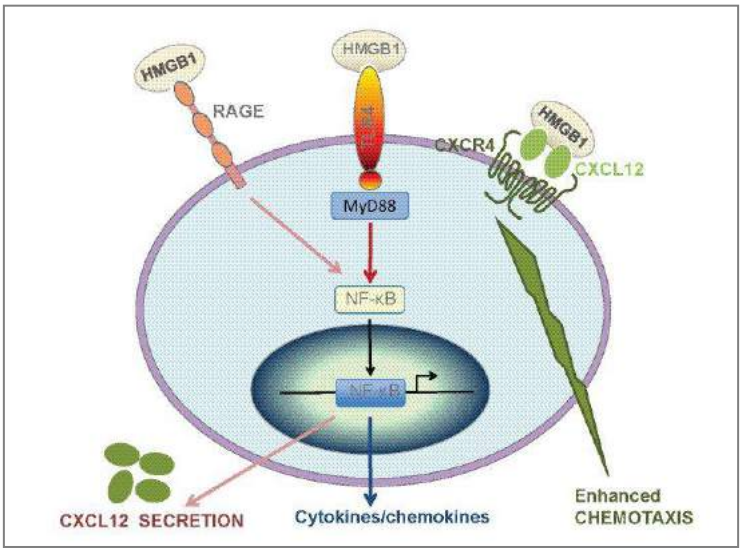

Figure 1
Model of action of HMGB1/CXCL12 synergism in leukocytes response. HMGB1 binds CXCL12 and the heterocomplex activates CXCR4 and induces enhanced cell migration. HMGB1 binding to TLR4 and RAGE leads to the activation of NF-κB and the transcription of cytokine and chemokine genes. In particular, RAGE activation induces CXCL12 secretion.

Responses to chemokines in HIV/SIV infection

Valentina Cecchinato, Denise Bottinelli, Gabriela Danelon, and Mariagrazia Uguccioni

More than 25 years after the discovery of human immunodeficiency virus (HIV) as the causative agent of AIDS, the mechanisms governing pathogenesis and disease progression are still not fully understood. Indeed, a progressive impairment of the immune system, with alterations that affect both innate and adaptive immunity, characterizes the infection with HIV-1 in humans and with simian immunodeficiency virus (SIV) in macaques. It has been proposed that a state of chronic immune activation contributes to the loss of $CD4^+$ T cells and to alterations of immune responses, ultimately leading to disease progression.

The loss of $CD4^+CCR5^+$ T cells in the gut associated lymphoid tissue (GALT) has been well documented both in the natural host and in pathogenic models of SIV infection. A decrease in the frequency of Th17 cells, a subset of effector T cells involved in the immune response against extracellular bacteria, has been described by Dr. Cecchinato in the mucosa of SIV infected animals. Nevertheless, the migratory capacity of this T cell subpopulation has not been investigated so far.

Chemokines are important mediators of leukocyte trafficking and function, and deregulation of their expression might contribute in part to the pathogenesis of HIV-1/SIV infection. In the frame of a projects funded by the European Community and by the Swiss HIV Cohort Study, we are investigating the

mechanisms that mediate CCR6^{+}/Th17 cells trafficking and activities at mucosal sites together with their decrease in frequency during HIV/SIV infection in order to better understand the pathogenesis of AIDS and in view of generating efficient vaccines (Figure 2).

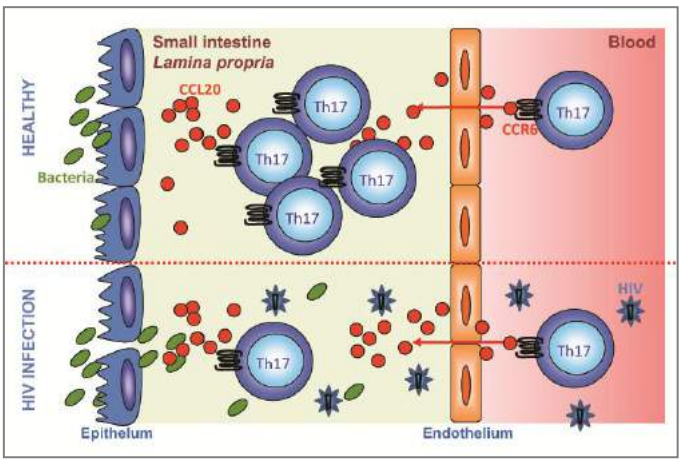

Figure 2
We study the impact of chemokines and chemokine receptor expression on the migratory capacity of CCR6+ cells.

Modulation of chemokine activity in spontaneous and therapy-induced breast cancer metastasis

Karolin Rommel and Mariagrazia Uguccioni

The chemokine receptor CXCR4 and its ligand CXCL12 are the most abundant receptor/ligand expressed in cancer. In a model of breast cancer, CXCR4 and CXCL12 were shown to be crucial for tumour cells migration and metastasis, and their blockade impairs metastasis formation. Physiologically, CXCL12 is one of the most abundant homeostatic chemokines, important for organogenesis, cell trafficking and bone marrow niches formation. CXCL12-induced migration has been broadly studied at molecular and cellular level in all cells bearing CXCR4. It has been demonstrated that high CXCL12 concentrations exert a repulsive effect on T cells. Following this study, it was discovered that repulsion of tumour Ag-specific T cells from a tumour expressing high levels of CXCL12 allows the tumour to evade immune control. Only recently, our laboratory and other colleagues discovered that chemokine activities can be modulated by non-ligand chemokines, concomitant activation of several chemokine receptors, or dimerization of chemokine receptors leading to synergism.

Chemotaxis of tumour and stromal cells in the tumour microenvironment is an essential component of tumour dissemination toward metastasis. Human and murine cancers possess a complex chemokine

network that influences tumour cell behaviour, leukocyte infiltrate, and angiogenesis. The role of chemokines in cancer is modified in time and space by additional factors of the tumour microenvironment. This project aims at investigating the role of chemokines, in particular CXCL12, and HMGB1 for synergistic activities promoting breast cancer cell migration, invasion and metastasis.

Funding

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ADITEC: Advanced Immunization Technologies
FP7 –280873 / 2011-2015

European Union
TIMER: Targeting Novel Mechanisms of Resolution in Inflammation
FP7 –281608 / 2012-2015

European Union
Marie Curie IEF Fellowship to Valentina Cecchinato
FP7 - PEOPLE-IEF-2008 / 2009-2012

European Union
Marie Curie IEF Fellowship to Valentina Cecchinato
FP7 - PEOPLE-IEF-2008 / 2009-2012

Swiss National Science Foundation
Impact of multiple chemokine expression in human disease
3100A0- 118048-1 / 2008-2012

Swiss National Science Foundation
Impact of multiple chemokine expression in human disease
310003A- 143718 / 2013-2015

Swiss National Science Foundation – Swiss HIV Cohort Study
Impact of multiple chemokine expression in human disease
719 / 2013-2014

San Salvatore Foundation
The role of chemokine synergy-inducing molecules in controlling the tumour microenvironment , cell migration and metastasis
2011-2014

Novartis Stiftung für Medizinisch-Biologische Forschung
Dampening Inflammation in Autoimmunity by Targeting Chemokine synergy-inducing molecules 2012-2013

Jubilee Foundation Novartis
Fellowship to Lorenzo Raeli 2013

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Mario Mellado
Centro Nacional de Biotecnología, Madrid (ES)

Costantino Pitzalis
William Harvey Institute, London (UK)

PEOPLE & FINANCES

SECTION 2

ORGANIZATION

iAR is a tax-exempted association located at University of Lausanne. It consists presently of four independent research institutes and is headed by Prof. Cem Gabay at Division of Rheumatology University of Geneva. Each research groups has its own laboratory spaces, researchers, and administrative personnel provided by their institutions or additional grants. The research groups are independent but committed to collaborate on common projects to achieve iAR objectives.

Board Members

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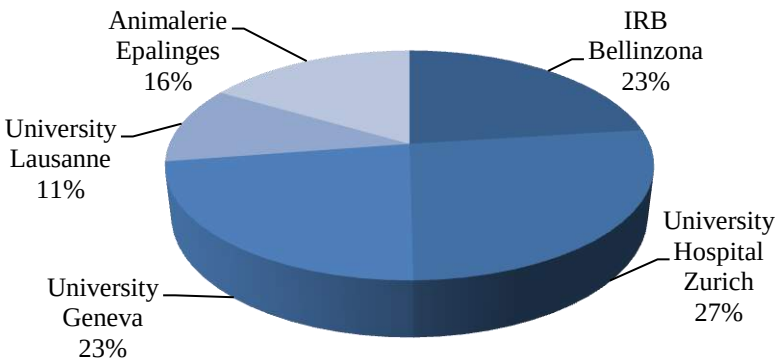
Professor of Rheumatology and
Director of the Center for Molecular Medicine
Karolinska Institute in Stockholm / Sweden

DONORS

The initial period 2010 – 2014 was financed by a generous donation from Mäxi Foundation.

FINANCIAL DATA 2011/12

The iAR has received a donation in 2011 of 2.1 MCHF and in 2012 of 1.6 MCHF that was used to support the 4 participating institutions and the transgenic mouse repository facility located in Lausanne. This funding will also support the future "junior group" that will be established in Geneva in 2013. The iAR accounts have been audited with a positive evaluation by an external organism in 2012.



Financial allocation of funds in 2012

Balance Sheet as of September 30th 2012 (In Swiss Francs)

ASSETS	30.09.2012	30.09.2011
1. Liquidity	1'019'021	268'370
2. Taxes	231	313
Total Assets	1'019'252	268'683

LIABILITIES	30.09.2012	30.09.2011
1. Costumers Deposit	981'647	221'647
2. Profit *vs.* Loss Carried Forward	47'035	19'450
3. Profit vs. Loss Financial Year	(9'430)	27'585
Total Liabilities	1'019'252	268'683

PUBLICATIONS

SECTION 3

Peer Reviewed Publication

A neutralizing antibody selected from plasma cells that binds to group 1 and group 2 influenza A hemagglutinins. Corti D, Voss J, Gamblin SJ, Codoni G, Macagno A, Jarrossay D, Vachieri SG, Pinna D, Minola A, Vanzetta F, Silacci C, Fernandez-Rodriguez BM, Agatic G, Bianchi S, Giacchetto-Sasselli I, Calder L, Sallusto F, Collins P, Haire LF, Temperton N, Langedijk JP, Skehel JJ, Lanzavecchia A. Science 2011; 333(6044):850-6

A functional BCR in human IgA and IgM plasma cells.
Pinto, D., E. Montani, M. Bolli, G. Garavaglia, F. Sallusto, A. Lanzavecchia and D. Jarrossay. Blood. 2013; 121:4110-4114.

A role for mitochondria in NLRP3 inflammasome activation. Zhou R, Yazdi AS, Menu P, Tschopp J. Nature 2011; 469: 221-225.

Adiponectin relation to skin changes and dyslipidemia in systemic sclerosis.
Tomčík M, Arima K, Hulejová H, Kuklová M, Filková M, Braun M, Beláček J, Novák M, Bečvář R, Vencovský J, Haluzík M, Gay S, Müller-Ladner U, Distler O, Senolt L. Cytokine 58:165-8, 2012

Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis?Frommer KW, Schäffler A, Büchler C, Steinmeyer J, Rickert M, Rehart S, Brentano F, Gay S, Müller-Ladner U, Neumann E. Ann Rheum Dis 2012; 71:1724-32

Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis?
Frommer KW, Schäffler A, Büchler C, Steinmeyer J, Rickert M, Rehart S, Brentano F, Gay S, Müller-Ladner U, Neumann E. Ann Rheum Dis 71:1724-32, 2012

Altered expression of miR-203 in rheumatoid arthritis synovial fibroblasts and its role in fibroblast activation.Stanczyk J, Ospelt C, Karouzakis E, Filer A, Raza K, Kolling C, Gay R, Buckley CD, Tak PP, Gay S, Kyburz D. Arthritis Rheum 2011; 63:373-81

An Anti-HIV-1 V3 Loop Antibody Fully Protects Cross-Clade and Elicits T-Cell Immunity in Macaques Mucosally Challenged with an R5 Clade C SHIV.
Watkins, J. D., N. B. Siddappa, S. K. Lakhashe, M. Humbert, A. Sholukh, G. Hemashettar, Y. L. Wong, J. K. Yoon, W. Wang, F. J. Novembre, F. Villinger, C. Ibegbu, K. Patel, D. Corti, G. Agatic, F. Vanzetta, S. Bianchi, J. L. Heeney, F.Sallusto, A. Lanzavecchia and R. M.Ruprecht. PLoS One. 2011; 6:e18207.

AntagomiR directed against miR-20a restores functional BMPR2 signalling and prevents vascular remodelling in hypoxia-induced pulmonary hypertension.
Brock M, Samillan VJ, Trenkmann M, Schwarzwald C, Ulrich S, Gay RE, Gassmann M, Ostergaard L, Gay S, Speich R, Huber LC. Eur Heart J. 2012 [Epub ahead of print]

Antibody phage display assisted identification of junction plakoglobin as a potential biomarker for atherosclerosis.
Cooksley-Decasper S, Reiser H, Thommen DS, Biedermann B, Neidhart M, Gawinecka J, Cathomas G, Franzeck FC, Wyss C, Klingenberg R, Nanni P, Roschitzki B, Matter C, Wolint P, Emmert MY, Husmann M, Amann-Vesti B, Maier W, Gay S, Lüscher TF, von Eckardstein A, Hof D. PLoS One 7(10):e47985, 2012

Articular inflammation is controlled by myeloid cell-derived interleukin-1 receptor antagonist during the acute phase of arthritis in mice.
Lamacchia C, Rodriguez E, Palmer G, Vigne S, Martin P, Talabot-Ayer D, Seemayer CA, Gabay C. Ann Rheum Dis 2012; 71: 281-7

Association of circulating miR-223 and miR-16 with disease activity in patients with early rheumatoid arthritis.
Filková M, Aradi B, Senolt L, Ospelt C, Vettori S, Mann H, Filer A, Raza K, Buckley CD, Snow M, Vencovsky J, Pavelka K, Michel BA, Gay RE, Gay S, Jüngel A. Ann Rheum Dis, 2013 [Epub ahead of print]

ATP induced brain-derived neurotrophic factor expression and release from osteoarthritis synovial fibroblasts is mediated by purinergic receptor P2X4.
Klein K, Aeschlimann A, Jordan S, Gay RE, Gay S, Sprott H. PLoS one 7:e36693, 2012

Autoimmunity and inflammation are independent of class II transactivator type PIV-dependent class II major histocompatibility complex expression in peripheral tissues during collagen-induced arthritis.Waldburger JM, Palmer G, Seemayer C, Lamacchia C, Finckh A, Christofilopoulos P, Baeten D, Reith W, Gabay C. Arthritis Rheum 2011; 63: 3354-63

Autotaxin expression from synovial fibroblasts is essential for the pathogenesis of modeled arthritis.
Nikitopoulou I, Oikonomou N, Karouzakis E, Sevastou I, Nikolaidou-Katsaridou N, Zhao Z, Mersinias V, Armaka M, Xu Y, Masu M, Mills GB, Gay S, Kollias G, Aidinis V. J Exp Med 209:925-33, 2012

Backseat drivers —The hidden influence of microbial viruses on disease. M.A. Hartley, H. Zangger, C. Ronet and N. Fasel. Current Opinion in Microbiology. 2012; doi.org/10.1016/j.mib.2012.05.011

BAFF levels in patients with ankylosing spondylitis and response to anti-tumor necrosis factor treatment.
Niederer F, Scherer A, Kyburz D, Gay RE, Gay S, Michel BA, Ciurea A. Joint Bone Spine Epub ahead of print, 2012

Broadly neutralizing antiviral antibodies.
Corti, D. and A. Lanzavecchia.
Annu Rev Immunol. 2013; 31:705-742.

Cartilage destruction in granulomatosis with polyangiitis (Wegener's granulomatosis) is mediated by human fibroblasts after transplantation into immunodeficient mice.
Kesel N, Köhler D, Herich L, Laudien M, Holl-Ulrich K, Jüngel A, Neidhart M, Gay S, Gay RE, Csernok E, Lamprecht P, Gross WL, Schumacher U, Ullrich S. Am J Pathol 180:2144-55, 2012

Chemokines in immunopathology: From dark sides to clinical translation.
Mantovani, A., M. Locati and M. Uguccioni.
Immunol Lett. 2012; 145:1.

Citrullination enhances the pro-inflammatory response to fibrin in rheumatoid arthritis synovial fibroblasts.
Sanchez-Pernaute O, Filkova M, Gabucio A, Klein M, Maciejewska-Rodrigues H, Ospelt C, Brentano F, Michel BA, Gay RE, Herrero-Beaumont G, Gay S, Neidhart M, Juengel A. Ann Rheum Dis 72:1400-1406, 2013

Cross-neutralization of four paramyxoviruses by a human monoclonal antibody.
Corti, D., S. Bianchi, F. Vanzetta, A. Minola, L. Perez, G. Agatic, B. Guarino, C. Silacci, J. Marcandalli, B. J. Marsland, A. Piralla, E. Percivalle, F. Sallusto, F. Baldanti and A. Lanzavecchia.
Nature. 2013; 501:439-443.

CXCR5 Expressing Human Central Memory CD4 T Cells and Their Relevance for Humoral Immune Responses.
Chevalier, N., D. Jarrossay, E. Ho, D. T. Avery, C. S. Ma, D. Yu, F. Sallusto, S. G. Tangye and C. R. Mackay.
J Immunol. 2011; 186:5556-5568.

DCs: a dual bridge to protective immunity.
Sallusto, F.
Nat Immunol. 2013; 14:890-891.

Detection of *Leishmania* RNA virus in *Leishmania* parasites. H. Zangger, C. Ronet, C. Desponds, F. M. Kuhlmann, J.Robinson, M.-A. Hartley, F. Prével, P. Castiglioni, F. Pratlong, P. Bastien, N. Müller, L. Parmentier, N. Gore Saravia, S. M. Beverley and N. Fasel. PLoS Negl Trop Dis. 2013; doi: 10.1371/journal.pntd.0002006

Dissecting the human immunologic memory for pathogens.
Zielinski, C. E., D. Corti, F. Mele, D. Pinto, A. Lanzavecchia and F. Sallusto.
Immunol Rev. 2011; 240:40-51.

Downregulation of microRNA-34a* in rheumatoid arthritis synovial fibroblasts promotes apoptosis resistance.
Niederer F, Trenkmann M, Ospelt C, Karouzakis E, Neidhart M, Stanczyk J, Kolling C, Gay RE, Detmar M, Gay S, Jüngel A, Kyburz D. Arthritis Rheum 64:1771-79, 2012

Downregulation of microRNA-34a* in rheumatoid arthritis synovial fibroblasts promotes apoptosis resistance.Niederer F, Trenkmann M, Ospelt C, Karouzakis E, Neidhart M, Stanczyk J, Kolling C, Gay RE, Detmar M, Gay S, Jüngel A, Kyburz D. Arthritis Rheum 2012; 64:1771-79

Dual role of autophagy in stress-induced cell death in rheumatoid arthritis synovial fibroblasts.
Kato M, Ospelt C, Gay RE, Gay S, Klein K. Arthritis Rheum. 2013 [Epub ahead of print]

Emergence of New Pandemic GII.4 Sydney Norovirus Strain Correlates with Escape from Herd Immunity.
Debbink, K., L. C. Lindesmith, E. F. Donaldson, V. Costantini, M. Beltramello, D. Corti, J. Swanstrom, A. Lanzavecchia, J. Vinje and R. S. Baric.
J Infect Dis. 2013;

ER stress activates the NLRP3 inflammasome via an UPR-independent pathway. Menu P, Mayor A, Zhou R, Tardivel A, Ichijo I, Mori K, Tschopp J. Cell Death Dis 2012; 3:e261

EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis.
Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, Gabay C, Catrina AI, Cope AP, Cornelis F, Dahlqvist SR, Emery P, Eyre S, Finckh A, Gay S, Hazes JM, van der Helm-van Mil A, Huizinga TW, Klareskog L, Kvien TK, Lewis C, Machold KP, Rönnelid J, Schaardenburg DV, Schett G, Smolen JS, Thomas S, Worthington J, Tak PP. Ann Rheum Dis 71:638-41, 2012

Fetal Human Cytomegalovirus Transmission Correlates with Delayed Maternal Antibodies to gH/gL/pUL128-130-131 Complex during Primary Infection.
Lilleri, D., A. Kabanova, M. G. Revello, E. Percivalle, A. Sarasini, E. Genini, F. Sallusto, A. Lanzavecchia, D. Corti and G. Gerna.
PLoS One. 2013; 8:e59863.

Functionally distinct subsets of human FOXP3+ Treg cells that phenotypically mirror effector Th cells.
Duhen, T., R. Duhen, A. Lanzavecchia, F. Sallusto and D. J. Campbell.
Blood. 2012; 119:4430-4440.

Fra-2 transgenic mice as a novel model of pulmonary hypertension associated with systemic sclerosis.
Maurer B, Reich N, Juengel A, Kriegsmann J, Gay RE, Schett G, Michel BA, Gay S, Distler JH, Distler O. Ann Rheum Dis 71:1382-87, 2012

High throughput cellular screens to interrogate the human T and B cell repertoires.
Corti, D., F. Sallusto and A. Lanzavecchia.
Curr Opin Immunol. 2011; 23:430-435.

HMGB1 and leukocyte migration during trauma and sterile inflammation.
Venereau, E., M. Schiraldi, M. Uguccioni and M. E. Bianchi.
Mol Immunol. 2013, 55:76– 82.

HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4.
Schiraldi, M., A. Raucci, L. M. Munoz, E. Livoti, B. Celona, E. Venereau, T. Apuzzo, F. De Marchis, M. Pedotti, A. Bachi, M. Thelen, L. Varani, M. Mellado, A. Proudfoot, M. E. Bianchi and M. Uguccioni.
J Exp Med. 2012; 209:551-563.

Human antibodies against dengue enhance dengue viral infectivity without suppressing type I interferon secretion in primary human monocytes.
Kou, Z., J. Y. Lim, M. Beltramello, M. Quinn, H. Chen, S. N. Liu, L. Martnez-Sobrido, M. S. Diamond, J. J. Schlesinger, A. de Silva, F. Sallusto and X. Jin.
Virology. 2011; 410:240-247.

Human Th17 subsets.
Sallusto, F., C. E. Zielinski and A. Lanzavecchia. Eur J Immunol. 2012; 42:2215-2220.

Identification of a genetic variant for joint damage progression in autoantibody-positive rheumatoid arthritis.
Knevel R, Klein K, Somers K, Ospelt C, Houwing-Duistermaat JJ, van Nies JA, de Rooy DP, de Bock L, Kurreeman FA, Schonkeren J, Stoeken-Rijsbergen G, Helmer Q, van der Linden MP, Kern M, Manjarrez-Orduno N, Rodriguez-Rodriquez L, Stinissen P, Huizinga TW, Toes RE, Gay S, Gregersen PK, Somers V, van der Helm-van Mil AH. Ann Rheum Dis, 2013 [Epub ahead of print]

Identification of microRNA-221/222 and microRNA-323-3p association with rheumatoid arthritis via predictions using the human tumour necrosis factor transgenic mouse model.
Pandis I, Ospelt C, Karagianni N, Denis MC, Reczko M, Camps C, Hatzigeorgiou AG, Ragoussis J, Gay S, Kollias G. Ann Rheum Dis 71:1716-23, 2012

IL-36 Signaling Amplifies Th1 Responses by Enhancing Proliferation and Th1 Polarization of Naïve CD4+ T cells. Vigne S, Palmer G, Martin P, Lamacchia C, Strebel D, Rodriguez E, Olleros ML, Vesin D, Garcia I, Ronchi F, Sallusto F, Sims JE, Gabay C. Blood 2012; 120(17): 3478-3487

IL-36R ligands are potent regulators of dendritic and T cells. Vigne S, Palmer G, Lamacchia C, Martin P, Talabot-Ayer D, Rodriguez E, Ronchi F, Sallusto F, Dinh H, Sims JE, Gabay C. Blood 2011; 118: 5813-23

Improved flow cytometric assessment reveals distinct microvesicle (cell-derived microparticle) signatures in joint diseases.
György B, Szabó TG, Turiák L, Wright M, Herczeg P, Lédeczi Z, Kittel A, Polgár A, Tóth K, Dérfalvi B, Zelenák G, Böröcz I, Carr B, Nagy G, Vékey K, Gay S, Falus A, Buzás EI.
PLoS One 7:e49726, 2012

Immunogenetic Mechanisms Driving Norovirus GII.4 Antigenic Variation.
Lindesmith, L. C., M. Beltramello, E. F. Donaldson, D. Corti, J. Swanstrom, K. Debbink, A. Lanzavecchia and R. S. Baric.
PLoS Pathog. 2012; 8:e1002705.

Increased recycling of polyamines is associated with global DNA hypomethylation in rheumatoid arthritis synovial fibroblasts.
Karouzakis E, Gay RE, Gay S, Neidhart M. Arthritis Rheum 64:1809-1817, 2012
Gross O, Yazdi A, Thomas CJ, Masin M, Heinz LX, Guarda G, Quadroni Q, Drexler SK, Tschopp J.

In-depth analysis of the antibody response of individuals exposed to primary dengue virus infection.
de Alwis, R., M. Beltramello, W. B. Messer, S. Sukupolvi-Petty, W. M. Wahala, A. Kraus, N. P. Olivarez, Q. Pham, J. Brian, W. Y. Tsai, W. K. Wang, S. Halstead, S. Kliks, M. S. Diamond, R. Baric, A. Lanzavecchia, F. Sallusto and A. M. de Silva. PLoS Negl Trop Dis. 2011; 5:e1188.

Inflammasome activators induce interleukin-1α secretion via distinct pathways with differential requirement for the protease function of Caspase-1. Immunity 2012; 36:388-400

Leishmania RNA Virus controls the severity of mucocutaneous leishmaniasis. A. Ives, C. Ronet, F. Prevel, G. Ruzzante, S. Fuertes Marraco, F. Schutz, H. Zangger, M. Revaz-Breton, L.-F. Lye, S.M. Hickerson, S. M. Beverley, H. Acha-Orbea, P. Launois, N. Fasel* and S. Masina. *Corresponding author. Science. 2011; 331, 775-778, doi: 10.1126/science.1199326

***Leishmania* RNA virus: when the host pays the toll.** M. A. Hartley, C. Ronet, Zangger H, S. M. Beverley and N. Fasel N. Front. Cell. Inf. Microbio. 2012; 2:99. doi: 10.3389/fcimb.2012.00099

Levels of target activation predict antifibrotic responses to tyrosine kinase inhibitors.
Maurer B, Distler A, Dees C, Khan K, Denton CP, Abraham D, Gay RE, Michel BA, Gay S, Distler JH, Distler O. Ann Rheum Dis. 2013 [Epub ahead of print]

Long-term amelioration of established collagen-induced arthritis achieved with short term therapy combining anti-CD3 and anti-TNF treatments. Dépis F, Hatterer E, Lamacchia C, Waldburger JM, Gabay C, Reith W, Kosco-Vilbois M, Dean Y**.** Arthritis Rheum 2012; 64: 3189-98

Memory T Cells in Latent Mycobacterium tuberculosis Infection Are Directed against Three Antigenic Islands and Largely Contained in a CXCR3(+)CCR6(+) Th1 Subset.
Lindestam Arlehamn, C. S., A. Gerasimova, F. Mele, R. Henderson, J. Swann, J. A. Greenbaum, Y. Kim, J. Sidney, E. A. James, R. Taplitz, D. M. McKinney, W. W. Kwok, H. Grey, F. Sallusto, B. Peters and A. Sette. PLoS Pathog. 2013; 9:e1003130.

MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. Kurowska-Stolarska M, Alivernini S, Ballantine LE, Asquith DL, Millar NL, Gilchrist DS, Reilly J, Ierna M, Fraser AR, Stolarski B, McSharry C, Hueber AJ, Baxter D, Hunter J, Gay S, Liew FY, McInnes IB. Proc Natl Acad Sci USA 2011; 108(27):11193-8

miR-146a and NF-κB1 Regulate Mast Cell Survival and T Lymphocyte Differentiation.
Rusca N, Dehò L, Montagner S, Zielinski CE, Sica A, Sallusto F, Monticelli S. Mol Cell Biol 2012; 32(21):4432-44

Muco-cutaneous leishmaniasis in the new world: The ultimate subversion. C. Ronet, S.M. Beverley and N. Fasel. Virulence. 2011; 2(6), 547-52

Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release.
Venereau, E., M. Casalgrandi, M. Schiraldi, D. J. Antoine, A. Cattaneo, F. De Marchis, J. Liu, A. Antonelli, A. Preti, L. Raeli, S. S. Shams, H. Yang, L. Varani, U. Andersson, K. J. Tracey, A. Bachi, M. Uguccioni and M. E. Bianchi.
J Exp Med. 2012; 209:1519-1528.

Negative regulators take center stage.
Monticelli, S. and F. Sallusto.
Nat Immunol. 2012; 13:719-720.

Nicotinamide phosphoribosyltransferase/visfatin expression by inflammatory monocytes mediates Regulation arthritis pathogenesis.
Présumey J, Courties G, Louis-Plence P, Escriou V, Scherman D, Pers YM, Yssel H, Pène J, Kyburz D, Gay S, Jorgensen C, Apparailly F. Ann Rheum Dis. [Epub ahead of print], 2013

OMIP-018: Chemokine receptor expression on human T helper cells.
Brodie, T., E. Brenna and F. Sallusto.
Cytometry A. 2013; 83:530-532.

Pathogen-induced human TH17 cells produce IFN-γ or IL-10 and are regulated by IL-β.
Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M, Monticelli S, Lanzavecchia A, Sallusto F. Nature 2012; 484(7395):514-8

Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 cis-interface.Di Zenzo G, Di Lullo G, Corti D, Calabresi V, Sinistro A, Vanzetta F, Didona B, Cianchini G, Hertl M, Eming R, Amagai M, Ohyama B, Hashimoto T, Sloostra J, Sallusto F, Zambruno G, Lanzavecchia A. J Clin Invest 2012; 122(10):3781-90

Persistent antigen and germinal center B cells sustain T follicular helper cell responses and phenotype.
Baumjohann, D., S. Preite, A. Reboldi, F. Ronchi, K. M. Ansel, A. Lanzavecchia and F. Sallusto.
Immunity. 2013; 38:596-605.

Plasmodium falciparum **Metacaspase PfMCA-1 Triggers a z-VAD-fmk Inhibitable Protease to Promote Cell Death.** B. Meslin, A.H. Beavogui, N. Fasel* and S. Picot. *Corresponding author. PLoS ONE. 2011; 6(8): e23867.
doi:10.1371/journal.pone.0023867

Platelet-derived serotonin links vascular disease and tissue fibrosis. Dees C, Akhmetshina A, Zerr P, Reich N, Palumbo K, Horn A, Jüngel A, Beyer C, Krönke G, Zwerina J, Reiter R, Alenina N, Maroteaux L, Gay S, Schett G, Distler O, Distler JH. J Exp Med 2011; 208(5):961-72

Possible mechanisms involved in chemokine synergy fine tuning the inflammatory response.
Gouwy, M., M. Schiraldi, S. Struyf, J. Van Damme and M. Uguccioni.
Immunol Lett. 2012; 145:10-14.

Processing of metacaspase into a cytoplasmic catalytic domain mediating cell death in *Leishmania major.* H. Zalila, I. J. Gonzalez, M. Belen Delgado, C. Desponds, C. Schaff, and N. Fasel. Molecular Microbiology. 2011; doi:10.1111/j.1365-2958.2010.07443.x

Rational Engineering of a Human Anti-Dengue Antibody through Experimentally Validated Computational Docking.
Simonelli, L., M. Pedotti, M. Beltramello, E. Livoti, L. Calzolai, F. Sallusto, A. Lanzavecchia and L. Varani. PLoS One. 2013; 8:e55561.

Regulation of matrixmetalloproteinase-3 and matrix-metalloproteinase-13 by SUMO-2/3 through the transcription factor NF-κB.
Frank S, Peters MA, Wehmeyer C, Strietholt S, Koers-Wunrau C, Bertrand J, Heitzmann M, Hillmann A, Sherwood J, Seyfert C, Gay S, Pap T. Ann Rheum Dis, 2013 [Epub ahead of print]

Resistin in idiopathic inflammatory myopathies.
Filkova M, Hulejova H, Kuncova K, Plestilova L, Andres Cerezo L, Mann H, Klein M, Zamecnik J, Gay S, Vencovsky J, Senolt L. Arthritis Res Ther 11;14(3):R111, 2012

Role of lymphoid chemokines in the development of functional ectopic lymphoid structures in rheumatic autoimmune diseases.
Corsiero, E., M. Bombardieri, A. Manzo, S. Bugatti, M. Uguccioni and C. Pitzalis.
Immunol Lett. 2012; 145:62-67.

Role of TLR9 Signaling in Experimental *Leishmania braziliensis* Infection. T. Weinkopff, A. Mariotto, G. Simon, Y. Hauyon-La Torre, F. Auderset, S. Schuster, H. Zangger¸ N. Fasel, A. Barral and F. Tacchini-Cottier. Infection and Immunity. 2013; doi: 10.1128/IAI.01401-12

Strain-Transcending Fc-Dependent Killing of Plasmodium falciparum by Merozoite Surface Protein 2 Allele-Specific Human Antibodies.
Stubbs, J., S. Olugbile, B. Saidou, J. Simpore, G. Corradin and A. Lanzavecchia.
Infect Immun. 2011; 79:1143-1152.

Systems Analysis of MVA-C Induced Immune Response Reveals Its Significance as a Vaccine Candidate against HIV/AIDS of Clade C.
Gomez, C. E., B. Perdiguero, V. Jimenez, A. Filali-Mouhim, K. Ghneim, E. K. Haddad, E. D. Quakkerlaar, J. Delaloye, A. Harari, T. Roger, T. Dunhen, R. P. Sekaly, C. J. Melief, T. Calandra, F. Sallusto, A. Lanzavecchia, R. Wagner, G. Pantaleo and M. Esteban.
PLoS One. 2012; 7:e35485.

T-cell trafficking in the central nervous system.
Sallusto, F., D. Impellizzieri, C. Basso, A. Laroni, A. Uccelli, A. Lanzavecchia and B. Engelhardt.
Immunol Rev. 2012; 248:216-227

T cell responses to known allergen proteins are differently polarized and account for a variable fraction of total response to allergen extracts.
Oseroff, C., J. Sidney, R. Vita, V. Tripple, D. M. McKinney, S. Southwood, T. M. Brodie, F. Sallusto, H. Grey, R. Alam, D. Broide, J. A. Greenbaum, R. Kolla, B. Peters and A. Sette.
J Immunol. 2012; 189:1800-1811.

The death domain-containing protein Unc5CL is a novel MyD88-independent activator of the pro-inflammatory IRAK signaling cascade. Heinz LX, Rebsamen M, Rossi DC, Staehli F, Schroder K, Quadroni M, Gross O, Schneider P, Tschopp J. Cell Death Differ 2012; 19:722-731

The MSC marker CD248 (Endosialin) is a negative regulator of bone formation.
Naylor AJ, Azzam E, Smith S, Croft A, Poyser C, Duffield JS, Huso DL, Gay S, Ospelt C, Cooper MS, Isacke C, Goodyear S, Rogers MJ, Buckley CD. Arthritis Rheum, 2012 [Epub ahead of print]

The pattern-recognition receptor NOD1 promotes production of inflammatory mediators in rheumatoid arthritis synovial fibroblasts.
Yokota K, Miyazaki T, Hemmatazad H, Gay RE, Kolling C, Fearon U, Suzuki H, Mimura T, Gay S, Ospelt C. Arthritis Rheum 64:1329-37, 2012

The therapeutic potential of immune cross-talk in leishmaniasis. M.A. Hartley, K. Kohl, C. Ronet, and N. Fasel. Clinical Microbiology and Infection. 2013; doi: 10.1111/1469-0691.12095

Therapeutic Efficacy of Antibodies Lacking FcgammaR against Lethal Dengue Virus Infection Is Due to Neutralizing Potency and Blocking of Enhancing Antibodies.
Williams, K. L., S. Sukupolvi-Petty, M. Beltramello, S. Johnson, F. Sallusto, A. Lanzavecchia, M. S. Diamond and E. Harris.
PLoS Pathog. 2013; 9:e1003157.

The TNFα-induced miR-18a activates rheumatoid arthritis synovial fibroblasts through a feedback loop in NF-κB signaling.
Trenkmann M, Brock M, Gay RE, Michel BA, Gay S, Huber LC. Arthritis Rheum 65:916-27, 2013

T regulatory cells are markers of disease activity in multiple sclerosis patients.
Dalla Libera, D., D. Di Mitri, A. Bergami, D. Centonze, C. Gasperini, M. G. Grasso, S. Galgani, V. Martinelli, G. Comi, C. Avolio, G. Martino, G. Borsellino, F. Sallusto, L. Battistini and R. Furlan.
PLoS One. 2011; 6:e21386.

Type I interferon inhibits interleukin-1 production and inflammasome activation.Guarda G, Braun M, Staehli F, Tardivel A, Mattmann C, Förster I, Farlik M, Decker T, Du Pasquier RA, Romero P, Tschopp J. Immunity 2011; 34: 213-223

Type I Interferon Drives Dendritic Cell Apoptosis via Multiple BH3-Only Proteins following Activation by PolyIC In Vivo. S. A. Fuertes-Marraco, C. L. Scott, P. Bouillet, A. Ives, S. Masina, D. Vremec, E. S. Jansen, L. A. O'Reilly, P. Schneider, N. Fasel, K. Shortman, A. Strasser, H. Acha-Orbea. PLoS ONE. 2011; 6(6): e20189. doi:10.1371/journal.pone.0020189

Vascular endothelial growth factor aggravates fibrosis and vasculopathy in experimental models of systemic sclerosis.
Maurer B, Distler A, Suliman YA, Gay RE, Michel BA, Gay S, Distler JH, Distler O.
Ann Rheum Dis, 2013 [Epub ahead of print]

Visfatin/pre-B cell colony-enhancing factor (PBEF): a proinflammatory and cell motility-changing factor in rheumatoid arthritis.
Meier FM, Frommer KW, Peters MA, Brentano F, Lefèvre S, Schröder D, Kyburz D, Steinmeyer J, Rehart S, Gay S, Müller-Ladner U, Neumann E. J Biol Chem 287:28378-85, 2012

Abstracts

33rd European Workshop for Rheumatology Research (EWRR)
Borbala Aradi, Maria Filkova, Stephanie Kasper, Kerstin Klein, Michael Bader, Michael Scharl, Beat A Michel, Renate E Gay, Edit I Buzas, Steffen Gay, Astrid Jüngel. TNFα-induced Protein Tyrosine Phosphatase Nonreceptor Type 2 (PTPN2) as a negative regulator of inflammation in rheumatoid arthritis., EWRR; Ann Rheum Dis 2013;**72**:Suppl 1; Praque (CZ)/February 2013

Global Spine Congress
Hakozaki M, Klawitter M, Kobayashi H, Quero L, Ospelt O, Gay S, Liebscher T, Sekiguchi M, Boos N, Ferguson S, Wuertz K. Expression and regulation of toll-like receptors (TLRs) in human intervertebral disc cells. P016.
Hong Kong (CHN)/April 2013

EULAR Annual European Congress
Ospelt C, Engler A, Künzler P, Gay RE, Michel BA, Gay S. Smoking induces expression of MIC ligands of the activating immune receptor NKG2D. Ann Rheum Dis 72(S3):794, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Klein K, Gay RE, Michel BA, Lin LL, Gay S, Ospelt C. Toll-like receptor stimulation induces tolerizable and n
on-tolerizable effects in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 72(S3):795, 2013 Madrid (ES)/June 2013

EULAR Annual European Congress
Kato M, Ospelt C, Michel BA, Gay RE, Gay S, Klein K. Dual role of autophagy in stress-induced cell death in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 72(S3):807, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Bagdonas E, Karouzakis E, Gay R, Gay S, Neidhart M. The adverse effect of methotrexate on synovial fibroblasts in vitro. Ann Rheum Dis 72(S3):893, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Filkova M, Ospelt C, Vettori S, Šenolt L, Mann H, Vencovský J, Pavelka K, Michel BA, Gay RE, Gay S, Jüngel A. Levels of mir-16 in serum associate with response to therapy in patients with early rheumatoid arthritis. Ann Rheum Dis 72(S3):395, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Iwamoto N, Vettori S, Maurer B, Brock M, Jüngel A, Calcagni M, Gay RE, Distler JH, Gay S, Kawakami A, Distler O. mir-193b induces UPA in SSc and contributes to the proliferative vasculopathy via UPAR independent pathways. Ann Rheum Dis 72(S3):130, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Engler A, Gay RE, Michel BA, Gay S, Ospelt C. SIRT1 regulates cigarette smoke-induced IL8 expression and TNFA-mediated IL6 release in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 72(S3):139, 2013.
Madrid (ES)/June 2013

EULAR Annual European Congress
Frank Bertoncelj M, Michel BA, Gay RE, Pisetsky DS, Gay S, Jüngel A. Microparticle-associated Poly(I:C) is resistant to RNaseIII degradation and protects rheumatoid arthritis synovial fibroblasts from TRAIL-induced apoptosis. Ann Rheum Dis 72(S3):177, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Aradi B, Kato M, Filková M, Kasper S, Klein K, Bader M, Scharl M, Michel BA, Gay RE, Buzás EI, Gay S, Jüngel A. Protein tyrosine phosphatase nonreceptor type 2 (PTPN2) is an important regulator of inflammation and autophagy in rheumatoid arthritis. Ann Rheum Dis 72(S3):187, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Karouzakis E, Trenkmann M, Filer A, Raza K, Gay RE, Michel BA, Buckley C, Gay S, Neidhart M. Differential DNA methylation of TBX5 transcription factor in synovial fibroblasts from resolving arthritis and rheumatoid arthritis at different stages of evolution. Ann Rheum Dis 72(S3):189, 2013. Madrid (ES)/June 2013

EULAR Annual European Congress
Trenkmann M, Brock M, Frank Bertoncelj M, Gay RE, Michel BA, Huber LC, Gay S. Epigenetic repression of the long noncoding RNA hotair regulates NF-KB signaling and the expression of matrix metalloproteases in synovial fibroblasts. Ann Rheum Dis 72(S3):201, 2013. Madrid (ES)/June 2013

Symposium of the Zurich Center for Integrative Human Physiology (ZIHP)
Aradi B, Filková M, Kasper S, Klein K, Bader M, Scharl M, Michel BA, Gay RE, Buzas EI, Gay S, Jüngel A. Protein tyrosine phosphatase non-receptor type 2 (PTPN2) inhibits the production of IL-6 in rheumatoid arthritis synovial fibroblasts. Zürich (CH)/August 2013

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Gay S. Future direction of pathogenesis and treatment for rheumatic disorders. Arth Res Ther 14(S1) O1, 2012
Tokyo (J)/November 2012

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Müller-Ladner U, Lefèvre S, Zimmermann B, Tarner IH, Dinser R, Pap T, Gay S, Neumann E. Evidence for synovial fibroblasts spreading rheumatoid arthritis Arth Res Ther 14(S1) O15, 2012. Tokyo (J)/November 2012

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Engler A, Jüngel A, Kolling C, Michel BA, Gay RE, Gay S, Ospelt C. Cigarette smoke downregulates HDAC2 in rheumatoid arthritis synovial fibroblasts. Arth Res Ther 14(S1) P11, 2012
Filkova M, Ospelt C, Stanczyk J, Vettori S, Šenolt L, Frank M, Kolling C, Michel BA, Gay RE, Gay S, Jüngel A. MicroRNAs in rheumatoid arthritis: possible biomarkers and therapeutic targets. Arth Res Ther 14(S1) P14, 2012
Tokyo (J)/November 2012

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Frank M, Dahlhaus M, Filkova M, Kolling C, Michel BA, Kyburz D, Rozman B, Gay RE, Pisetsky D, Gay S, Jüngel A. Immune cell - derived microparticles contribute to the resistance of rheumatoid arthritis synovial fibroblasts to death receptor-mediated apoptosis. Arth Res Ther 14(S1) P15, 2012. Tokyo (J)/November 2012

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Ospelt C, Camici GG, Brentano F, Künzler P, Kolling C, Gay RE, Michel BA, Gay S. Smoking induces expression of ligands of the immune receptor NKG2D. Arth Res Ther 14(S1) P58, 2012. Tokyo (J)/November 2012

8th Global Arthritis Research Network (GARN) Meeting and 1st Bio-Rheumatology International Congress (BRIC)
Pandis I, Ospelt C, Karagianni N, Denis M, Reczko M, Camps C, Hatzigeorgiou A, Ragoussis J, Gay S and Kollias G. Association of microRNA-221/222 and-323-3p with rheumatoid Arthritis via predictions using the human TNF transgenic mouse model. Arth Res Ther 14(S1) P59, 2012. Tokyo (J)/November 2012

EULAR Annual European Congress
Trenkmann M, Brock M, Gay RE, Speich R, Michel BA, Gay S, Huber LC. The TNF-alpha-induced mir-18a activates rheumatoid arthritis synovial fibroblasts through a positive feedback loop in NF-kappa b signalling. Ann Rheum Dis 71(S3):58, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Vettori S, Brock M, Iwamoto N, Maurer B, Jüngel A, Gay RE, Calcagni M, Valentini G, Distler J, Gay S , Distler O. Micro-RNA-145 down-regulation in systemic sclerosis is limited to skin fibroblasts and influenced by epigenetic modifications and negative feedback loop by TGF-ß. Ann Rheum Dis 71(S3):58, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Maurer B, Akhmetshina A, Gay RE, Schett G, Michel BA, Gay S, Distler JH, Distler O. VEGF induces vasculopathy and fibrosis in vivo closely resembling human systemic sclerosis. Ann Rheum Dis 71(S3):116, 2012
Berlin (DE)/Juni 2012

EULAR Annual European Congress
Grabiec AM, Ospelt C, van Baarsen LGM, van Es IE, Gay S, Tak PP, Reedquist KA. Analysis of protein acetylation and histone deacetylase expression in the synovial tissue reveals complex relationships between epigenetic regulatory mechanisms and inflammation in rheumatoid arthritis. Ann Rheum Dis 71(S3):156, 2012.
Berlin (DE)/Juni 2012

EULAR Annual European Congress
Frank Bertoncelj M, Rozman B, Michel BA, Gay RE, Pisetsky DS, Distler O, Gay S, Jüngel A. Surface proteins on microparticles can induce resistance of synovial fibroblasts to apoptosis mediated by death receptors. Ann Rheum Dis 71(S3):325, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Karouzakis E, Trenkmann M, Niederer F, Gay RE, Michel BA, Kyburz D, Gay S, Neidhart M. DNA methylation analysis identified TBX5 as an important transcription factor in rheumatoid arthritis. Ann Rheum Dis 71(S3):489, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Klein K, Michel BA, Gay RE, Gay S, Ospelt C. Functional analysis of the primary cilium in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 71(S3):491, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Klein K, Stanczyk Feldges J, Michel BA, Gay RE, Gay S, Ospelt C. The expression of HDAC6 is reduced in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 71(S3):491, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Frank S, Striethолt S, Wehmeyer C, Peters MA, Kollias G, Gay S, Pap T. SUMO-2/3 regulates apoptosis and MMP expression in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis 71(S3):495, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Filkova M, Ospelt C, Šenolt L, Vettori S, Mann H, Michel BA, Vencovský J, Pavelka K, Gay RE, Gay S, Jüngel A. Circulating MIR-223 is downregulated in sera of patients with early RA after treatment with methotrexate. Ann Rheum Dis 71(S3):506, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Lapinska A, Bielecki M, Distler O, Domyslawska I, Chyczewski L, Sierakowski S, Gay S, Kowal K, Kowal-Bielecka O. Increased production of leukotrienes by peripheral blood mononuclear cells is associated with more severe disease and worse prognosis in patients with systemic sclerosis. Ann Rheum Dis 71(S3):479, 2012
Berlin (DE)/Juni 2012

EULAR Annual European Congress
Niederer F, Scherer A, Tamborrini G, Michel BA, Gay RE, Gay S, Kyburz D, Ciurea A. BAFF levels in patients with ankylosing spondylitis and response to anti-tumor necrosis factor treatment. Ann Rheum Dis 71(S3):648, 2012
Berlin (DE)/Juni 2012

EULAR Annual European Congress
Vettori S, Maurer B, Iwamoto N, Filkova M, Cuomo G, Gay RE, Valentini G, Gay S, Distler O. Circulating microRNAs in systemic sclerosis patients reflect microRNA profile of cultured scleroderma fibroblasts and correlate with distinct disease features. Ann Rheum Dis 71(S3):686, 2012. Berlin (DE)/Juni 2012

EULAR Annual European Congress
Presumey J, Courties G, Charbonnier LM, Escriou V, Scherman D, Pers YM, Louis-Plence P, Yssel H, Pène J, Kyburz D, Gay S, Jorgensen C, Apparailly F. Innovative anti-inflammatory strategy in arthritis by using PBEF SIRNA-mediated silencing in LY6Chigh monocytes. Ann Rheum Dis 71(S3):130, 2012. Berlin (DE)/Juni 2012

American College of Rheumatology (ACR) Annual Meeting
Karouzakis E, Trenkmann M, Gay RE, Michel BA, Gay S and Neidhart M. Epigenome analysis of rheumatoid arthritis synovial fibroblasts revealed TBX-5 as a novel transcription factor in chemokine regulation. Arthritis Rheum 64:S183, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Engler A, Gay RE, Michel BA, Gay S and Ospelt C. SIRT6 regulates cigarette smoke induced MMP1 expression in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 64:S189, 2012

American College of Rheumatology (ACR) Annual Meeting
Bagdonas E, Karouzakis E, Jungel A, Ospelt C, Gay RE, Gay S, Michel BA and Neidhart M. Methyl supplementation of rheumatoid arthritis synovial fibroblasts regulates the expression of transcription factors and matrix metalloproteinases. Arthritis Rheum 64:S190, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Trenkmann M, Brock M, Gay RE, Michel BA, Huber LC and Gay S. The epigenetically repressed long noncoding RNA hotair influences the expression of matrix metalloproteases in synovial fibroblasts. Arthritis Rheum 64:S388, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Frank Bertoncelj M, Rozman B, Michel BA, Gay RE, Pisetsky DS, Distler O, Gay S and Jüngel A. Activation of NF-Kb via Poly(I:C)-induced monocyte-derived microparticles decreases TRAIL-induced apoptosis of rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 64:S392, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Maurer B, Akhmetshina A, Gay RE, Michel BA, Gay S, Distler JHW and Distler O. Differences in the activation levels and expression patterns of the molecular targets of tyrosine kinase inhibitors may account for the heterogeneous treatment responses. Arthritis Rheum 64:S649, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Klein K, Michel BA, Vogetseder A, Gay RE, Gay S and Ospelt C. Functional analysis of the primary cilium in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 64:S760, 2012. Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Filkova M, Ospelt C, Vettori S, Senolt L, Mann HF, Michel BA, Vencovsky J, Pavelka K, Gay RE, Gay S and Jüngel A. Circulating mir-223 is associated with disease activity and may predict the response to therapy in treatment naïve patients with early rheumatoid arthritis. Arthritis Rheum 64:S898, 2012 Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Kowal-Bielecka OM, Lapinska A, Bielecki M, Distler O, Domyslawska I, Chyczewski L, Sierakowski S, Gay S and Kowal K. Increased synthesis of leukotrienes by peripheral blood mononuclear cells is associated with more severe disease and worse prognosis in patients with systemic sclerosis. Arthritis Rheum 64:S968, 2012 Chicago (USA)/November 2012

American College of Rheumatology (ACR) Annual Meeting
Knevel R, Klein K, Somers K, Ospelt C, Houwing-Duistermaat JJ, van Nies J, de Rooy DPC, de Bock L, Schonkeren J, Stoeken-Rijsbergen G, Kiridly J, Rodriguez-Rodriguez L, Helmer Q, Sinissen P, Huizinga TWJ, Toes REM, Gay S, Gregersen PK, Somers V and van der Helm-van Mil AHM.Genome-wide association study on the severity of joint destruction in autoantibody positive rheumatoid arthritis identifies a role for sperm associated antigen 16. Arthritis Rheum 64:S1132, 2012. Chicago (USA)/November 2012

Lectures & Seminars

Gordon Research Conference on "Tropical Infectious Disease: From Bench to Field" Invited speaker, Galveston, TX (March 2011)

Kinetoplastid Molecular and Biology Cell Meeting,Woods Hole (April 2011)

University of Tuebingen, Invited speaker, Tuebingen (May 2011)

Biozentrum, Basel (May 2011)

Infection and Immunity, Graduate School, Keynote speaker, Geneva (May 2011)

Trypanosomatids 2011 meeting, Invited speaker, Paris (May 2011)

COST action meeting, CM0801, Modena (October 2011)

Indo-Swiss Symposium; Invited speaker, Dehli (November 2011)

22nd Challenge in Virology and SAFE-ID, Invited speaker, Saanen (January 2012)

COST action meeting, BM0802, Milano (January 2012)

XIVèmes Journées Francophones de Virologie, Invited Speaker, Paris (March 2012)

Department of Rhumatology, Invited speaker, University of Zurich (April, 2012)

Gabba Lecture, Invited speaker, Porto, Portugal (May 2012)

European Academy of Microbiology on "Co-infections 2012", Invited speaker, Halle, Germany (June 2012)

Gordon Research Conference on "Host-Pathogen interaction", Invited speaker, Newport, USA (June 2012)

COST action meeting, CM0801, Edinburgh (October 2012)

ITM 54th Annual Colloquium, Pathogens'survival strategy, Invited speaker, Antwerpen (December 2012)

World Leishmania V meeting, Invited speaker, Brazil (April, 2013)

American Society of Parasitology (Annual Meeting) and Quebec Molecular Parasitology, Keynote speaker, Quebec, Canada (26th-29th June 2013)

European Society of Virology, Invited speaker, Lyon (September 2013)

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