iAR
Institute for Arthritis Research
Institut für Rheumaforschung
Institut pour la recherche en rhumatologie

# ANNUAL REPORT 2015/2016

## Institute for Arthritis Research (iAR)

Turning Research into clinical application for Arthritis care

# FOREWORD BY THE CHAIRMAN

## PROFESSOR DR. CEM GABAY

Our organisation, the Institute for Arthritis Research (iAR) is now eight years old. It was created to support research in rheumatic and musculoskeletal disorders and more generally the mechanisms associated with inflammatory responses. The four institutions (the Universities of Geneva, Lausanne and Zurich, and the Laboratory in Ticino) have benefitted from the generosity of donors which enabled us to support many projects in basic research (more details later in this report). Furthermore, the organisation supported the training of young researchers, the establishment of a new group led by a young professor in Geneva, as well as scientific exchange at an annual symposium, which is open to both young researchers and established scientists. Finally, our association has also supported congresses and conferences.

In this past year, we have decided to move towards an axis of translational research which involves the development of anti-inflammatory therapies using the knowledge and expertise acquired through the basic research. For this activity, we are collaborating with a startup company called AIDD which is based in the Lake Geneva basin, and with other organisations in both Switzerland and Europe. This strategy is founded on our determination to create links between our laboratory research and clinical applications which will directly benefit patients.

In the context of our activities to acquire more visibility and attract the resources necessary for our activities we are very happy to welcome Judith Safford to our organisation, who will be supporting our communication and fundraising activities. Her extensive experience acquired during many years working for non-profit organisations will certainly benefit iAR.

Certain members of our association, although they are still working actively as scientists, will reach retirement age in the next years. Therefore, when thinking about the future development of the iAR, it is vital to plan the inclusion of new members in the coming years, in order to guarantee that the objectives of the organisation are upheld over time.

Finally, our work would not be possible without the funding from foundations and other charitable funds. We thank all those who make our work possible.

Professor Cem Gabay
Chairman

Geneva, March 2017

# WHAT IS iAR? VISION, OBJECTIVES AND ACHIEVEMENTS

The Institute of Arthritis Research (iAR) was established in Lausanne in 2009 as a non-profit, tax-exempted association under Swiss law. The organisation was initiated and first led by the late Prof. Jürg Tschopp with a starting donation of 10 million CHF paid over five years. Its founding members are four Swiss laboratories in the field of arthritis research and immunology. The current Chairman is Prof. Cem Gabay from the University of Geneva, Division of Rheumatology. Vice-Chairman is Prof. Steffen Gay from the University of Zurich, who has recently been appointed by the European Council into the Scientific Panel of Health (SPH).

The Institute of Arthritis Research creates the unique opportunity in Switzerland to conduct interdisciplinary research combining the work of basic research groups as well as laboratories linked to clinical Departments. It thus enables cross-feeding between Swiss University research centres, which benefits both the research and the training of students and junior scientists.

The main objective of the iAR is to enable the transfer of basic research in the laboratory to translational opportunities and clinical applications, such as preventive measures, tools for diagnosis and therapeutic measures, with the aim to directly benefit patients suffering from rheumatic diseases.

The achievements of iAR include:

- The development of a research network in Switzerland with collaborative research projects and publications in leading journals (Nature, Blood, Immunity, Arthritis & Rheumatology).
- The development of international collaborations.
- The establishment of a common facility for the deposition of reagents at the Department of Biochemistry, University of Lausanne.
- The Establishment of a new professorship in Arthritis Research at University of Geneva.
- Strengthened education in arthritis research through support to the Annual Joint Congress of the International Cytokine Society and the International Society for Interferon and Cytokine research.
- An Annual Conference held in Lausanne, where researchers from the member groups present their work and exchange ideas.
- Strategic expansion to drug discovery by screening existing compound libraries for small molecules able to inhibit or activate key pathways previously identified in the pathological process of arthritis.

Presentation at the Annual Conference

# THE iAR RESEARCH CENTRES

**University of Geneva**

The two Rheumatology laboratories are affiliated to the Division of Rheumatology, Department of Internal Medicine Specialities and the Department of Pathology-Immunology at the University of Geneva School of Medicine.

In the group led by Professor Cem Gabay research is primarily focused on the pathogenesis of inflammatory responses in arthritis and other inflammatory diseases, with a special interest in the field of cytokines. Cytokines are small proteins that mediate communication between cells. Their critical role in immune and inflammatory responses is now well demonstrated by the successful development of therapies targeting cytokines in the management of rheumatoid arthritis and other rheumatic diseases. Among the different cytokines, our research is particularly focused on cytokines of the interleukin-1 family. In close interaction with the clinical Departments we have access to biological samples from patients. In addition, our laboratory uses different experimental models of inflammatory diseases. We are also leading and participating in clinical trials with anti-cytokine therapies in patients with rheumatic diseases.

In the group led by Professor Monique Gannagé, which was established by the iAR, the focus is on the effects of autophagy in arthritis diseases. Autophagy is a fundamental process for degrading and recycling cellular components. Recent advances in understanding the pathway have showed that autophagy is involved in many pathological processes, such as infection, cancer and neuro-degeneration. In particular, mutations in autophagy essential genes can cause diseases. Interestingly, disturbances in the autophagic machinery have been associated with immunological disorders. Our research focuses on the contribution of the pathway in regulating immune and inflammatory responses. Using both clinical samples and experimental models of arthritis, we are analysing the implication of autophagy in the pathogenesis of rheumatoid arthritis and ankylosing spondylitis.

**University of Lausanne**

The Department of Biochemistry (DB) is part of the Faculty of Biology and Medicine of the University of Lausanne (UNIL) and teaches medicine, biology and immunology. It belongs to the Center of Immunity and Infection Lausanne (CIIL) which regroups scientists of UNIL and University hospital working in immunology and infectious diseases.

The research aims to contribute to the understanding of immune processes and elimination of immunological disorders by studying inflammation, cell differentiation and cell signalling, with a strong focus on the discovery and functional characterization of molecular pathways. This research has provided valuable insights into the stress-related activation of inflammatory processes in both Rheumatoid Arthritis (RA) and Osteoarthritis (OA). The research continues into deciphering how the molecular mechanisms of mechanical and oxidative stress affect inflammation. A second line of research, with the WHO Immunology Research and Training center (housed by the DB since 1963), studies parasitic diseases and the immune response they elicit.

**University of Zürich**

The Center of Experimental Rheumatology is at the Department of Rheumatology, University Hospital Zürich. The Center studies the molecular and cellular aspects of rheumatic diseases in a clinical setting. The European League Against Rheumatism (EULAR) has awarded it the status of a “Center of Excellence in Rheumatology” since

2005. This 5-year award, which has been granted 3 times successfully, is based on the record of scientific publication. The significant support by the iAR was pivotal for the published papers, as it was for six European funded projects

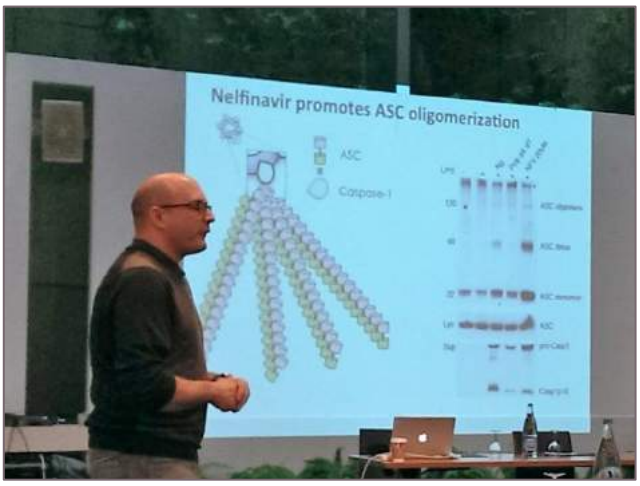
Research at the Institute of Rheumatology, Zürich

The research is focused on the epigenetics of rheumatic diseases. Epigenetic imprinting by environmental factors is at the core of experimental molecular research. Epigenetics is the study of heritable changes in genome functions that do not alter the nucleotide sequence within the DNA, in simpler terms, epigenetics stably regulates gene expression. Different biochemical processes act in a fine-tuned concert to regulate gene expression in both health and disease. The research related to rheumatic diseases has resulted in numerous new insights and novel diagnostic and therapeutic strategies are on the horizon which will be implemented in future research.

**Institute for Research in Biomedicine, Bellinzona**

The Institute for Research in Biomedicine (IRB) was founded in 2000 with the goal of advancing the study of human immunology, with particular emphasis on the mechanisms of host defence. The IRB works within a wide international network of collaborations and provides teaching and training programs for graduate students from Swiss and foreign Universities. Managing Director is Prof. Dr. Antonio Lanzavecchia, who is also ETH Zurich Professor for Human Immunology.

The crosstalk between immune cells and the bone is at the center of the emerging interdisciplinary field of Osteoimmunology. Researchers at the IRB, a recognized center of excellence for human immunology, aim to obtain insights into the molecular, cellular and systemic interactions between cells and molecules of the adaptive immune system and the skeletal system. Using new high throughput cellular screening platforms, they explore the immune response in rheumatic diseases, such as rheumatoid arthritis and ankylosis spondylitis, and how the response changes following therapy with biological agents.




Fabio Martinon presenting at the iAR Conference

# ORGANISATIONAL STRUCTURE

## Board of Directors

**Prof. Cem Gabay: Chairman**

Cem Gabay obtained his medical degree at the University of Geneva where he specialised in Medicine and Rheumatology. He also did clinical training at the 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 Specialities at the University of Geneva in 2013. He was President of the Swiss Society of Rheumatology from 2008 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 250 articles. His research focuses on various aspects of cytokine biology and on clinical and translational aspects of Rheumatoid arthritis.

**Prof. Nicolas Fasel, General Secretary**

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 protozoan parasites. From September 2006 to December 2016, he was director of the Department of Biochemistry. Since July 2015, Nicolas Fasel is Vice-Dean for Research and Innovation of the Faculty of Biology and Medicine of UNIL.

**Prof. Steffen Gay, Vice Chairman**

Professor Steffen Gay 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 and serves since 2016 as a consultant to the Department of Rheumatology in Zurich.

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 72. He is an 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 and in 2015 MASTER of the American College of Rheumatology.

# ORGANISATIONAL STRUCTURE

## Scientific Advisory Board

**Prof. Sir Marc Feldman FRS**

Marc Feldmann is Professor of Cellular Immunology Kennedy Institute of Rheumatology at Oxford University, UK.

His work is focused on how autoimmune diseases are triggered, and particularly the role of cytokines and how they drive processes such as inflammation, immunity and cell growth. Together with Ravinder N. Maini their research led to the identification of TNF (tumour necrosis factor) as a therapeutic target for rheumatoid arthritis. From 1984 they examined the pathogenesis of rheumatoid arthritis, specifically the role played by the various signalling molecules, the cytokines, in regulating the disease processes. This work led them to realise that the disease could be treated by blocking the action of TNF with anti-TNF antibodies, called cA-2.

Extensive clinical trials showed that blocking the activity of TNF not only had a very beneficial effect on joint inflammation in a large majority of patients, but could also delay joint destruction. Millions of sufferers from various rheumatic disorders worldwide now receive treatment with TNF inhibitors, the drugs developed as a result of this path-breaking research.

**Professor Lars Klareskog**

Lars Klareskog is Professor for Rheumatology and Director of the Research Center for Molecular Medicine at the Karolinska Institutet at Karolinska university hospital in Stockholm, Sweden.

The Center's research is focused on translational research in inflammatory rheumatic diseases, mainly arthritis, SLE, Sjögrens syndrome and myositis with some activities in sclerodermia and vasculitis. It also carries out basic research related to inflammatory diseases within immunology, genetics and epidemiology. An example breakthrough is that his team discovered and could explain why people with a genetic disposition (HLA risk gene) and testing ACPA-positive have a significantly higher risk of developing Rheumatoid Arthritis, if they also smoke.

His work is characterised by great breath and diversity. His is an accomplished mathematician, biochemist, immunologist, geneticist and epidemiologist. A belief in the importance of fostering collaboration and exchange also characterises his work. He has been a guest professor at the Harvard Medical School, the Imperial College London (Kennedy Institute of Rheumatology), the Hospital of Special Surgery der Cornell University, as well as in Seattle, Leeds und Denver (University of Colorado). From 1995 until 2012 he was a member of the Nobel Committee.

## Communication & Fundraising

**Dr. Judith Safford**

Judith Safford received her training in Economics and Business studies at the University of Freiburg im Breisgau, Germany. In addition, she has a Diploma in Non-profit Management from the Fribourg University, Switzerland. She has worked for over 20 years in diverse non-profit organisations. Affected by Ankylosing Spondylitis since her early twenties, she is highly motivated to support efforts to increase research in Arthritis diseases and find new treatments to relieve the widespread suffering that Arthritis still causes.

# FINANCIAL INFORMATION

1st October 2015 – 30th September 2016

| | 2015/16 | 2014/5 |
|---|---|---|
| Cash at banks | 1’421’061 | 1'357’016 |
| Reserved for projects | 365’000 | 1'000’000 |
| Donations | 470’000 | 375’000 |
| Administration & Fundraising | 40’955 | 35’879 |

Details are available on request. Please contact info@iar-suisse.ch

# DONATIONS

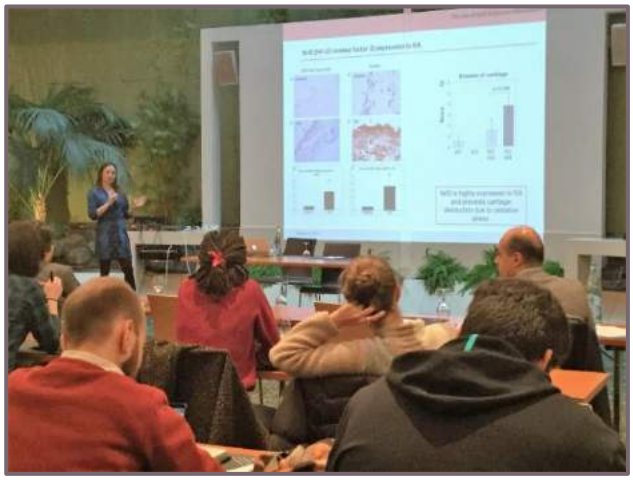
The Institute for Arthritis Research is a tax-exempted charity organisation in accordance with Art. 33 §1 Bst. i of Federal Law on direct federal tax / DBG; SR 642.11.

The research projects in 2015/16 were mainly supported by the Uniscientia-Foundation, Georg und Bertha Schwyzer-Winiker-Foundation, Ernst Göhner-Foundation and the Mäxi-Foundation.

Without these generous donations, the essential research work carried out by the member researcher institutes of the iAR would not be possible. We thank all these organisations and all others who have contributed to the work of iAR.

Our accounts details for donations:

Banque Raiffeisen
Voie du Chariot 7
1003 Lausanne-Haute-Broye-Jorat
Account name: Institute for Arthritis Research
IBAN: CH16 8045 1000 0066 9359 4



Jennifer Palomo presenting at the Annual iAR Symposium:
The role of new IL-1 cytokines in skin inflammation

# SCIENTIFIC REPORT

# 2015/2016

## Turning Research in clinical application for Arthritis care


# NON-TECHNICAL SCIENTIFIC SUMMARY

**University of Geneva: Group 1**

Our center is involved both in basic research and in clinical research working with patients.

The basic research is directed towards a better understanding of certain mediators of inflammation called cytokines, and more specifically the cytokines in the family of the interleukin (IL)-1. We use different models of disease which allow us to better define the role played by the cytokines and subsequently to develop medications which will specifically target the agents of inflammation and thus treat inflammatory disorders. The most spectacular example was the use of one of these approaches to treat a young girl who was affected by a genetic inflammatory disease that was potentially fatal. Another example was a European clinical study led by our institute to treat a serious inflammatory disease affecting adults.

Our objective is to continue to link our fundamental research with applications which will benefit patients.

The team of group 1 in Geneva

**University of Geneva: Group 2**

Autophagy is an important intracellular degradation system which helps cells to regulate their content. During this process, small vesicles called autophagosomes break down intracellular components such as proteins or pathogens (viruses or bacteria). This process of autophagy is active in various medical disorders, particularly during cell stress or inflammation.

We are interested in the role played by autophagy in the deregulation of the innate and adaptive immune response in autoimmune and inflammatory disorders, in particular rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Our initial observation is that in patients suffering from RA autophagy is activated in the inflamed joints. Preliminary results have identified autophagy as a mechanism regulating the immune response and we hope that our research will clearly establish whether autophagy is involved in the deregulation of the immune response in RA.

In AS we are examining the role of autophagy in the degradation of HLA-B27 molecules, which are involved in the mechanism which leads to the disease. Our initial observation is that autophagy is involved in the degradation and internalisation of the HLA molecules, but not of HLA-B27. We are studying the molecular mechanisms of this phenotype and hope that this approach will help us to better understand the causes of AS.

**University of Lausanne**

The main research interest of the group focuses on the definition of molecular pathways involved in immune response in human inflammatory pathologies and infectious diseases. In our studies, we use model systems to understand the innate immune response related to inflammation, focusing on viral infections, the production of a small protein (cytokine) used in cell signalling

called interferon-beta (IFN-beta), and the oxidative stress induced by these infections. Our major contributions in the last years are to demonstrate the impact of these infections on relapses after drug treatment or subsequent infections and the relevance of IFN-beta on these pathologies, and the identification of reactive oxygen detoxification pathways which are relevant in Rheumatoid Arthritis.

**University of Zürich**

The focus of the Center of Experimental Rheumatology is to characterise the local cells of connective tissue in joints (synovial fibroblasts) and their influence on the destructive inflammation in rheumatoid arthritis (RA). With the Clinic for Rheumatology now under the leadership of Prof. Oliver Distler, the Center of Systemic Inflammatory Diseases has been merged with the Center of Experimental Rheumatology. Thus, fundamental research in the areas of scleroderma and complex regional pain syndrome are now also covered by the Center of Experimental Rheumatology. In our studies, we characterise the epigenetic mechanisms and factors which play a role in the development of disease and might possibly be used therapeutically. Another focus is around non-coding RNA molecules. Here we study both the already well described microRNA molecules, and the still relatively unknown PIWI-interacting RNA and long non-coding RNA molecules. This new area of research might help us to shed light on the mechanisms which lie behind the epigenetic changes in rheumatic disorders. Finally, we are tackling the functional analysis of connecting tissue cells, e.g. synovial fibroblasts and skin fibroblasts and their role in the development of disease.

Clinical research at the laboratories at Zürich University

# UNIVERSITY OF GENEVA

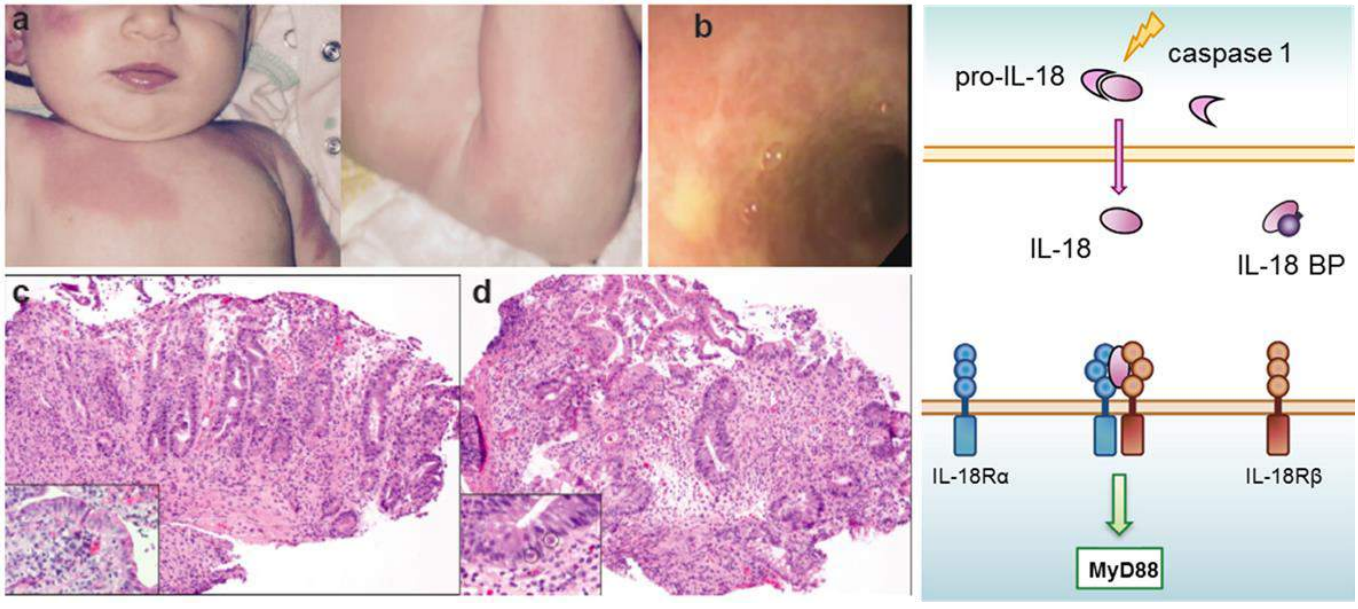
**Research Focus 1**

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

Members: Gaby Palmer – PhD, Praxedis Martin, PhD – Jennifer Palomo, PhD – Maria Stella Lombardi, PhD –– Damien Dietrich, MD-PhD student – Charlotte Girard, MD-PhD student – Dominique Talabot-Ayer, technician – Emiliana Rodriguez, technician – Corine Gilliéron, technician – Sabina Troccaz, technician

The aim of our current work is focused on better understanding the role of the interleukin (IL)-1 family of cytokines that comprises IL-1, IL-18, IL-33, Il-36, IL-37, and IL-38. We are 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. More recently we have been working on the role of IL-36 and IL-38 in immune response related to skin (see references 3, 6, 7, 10)

We are also working on IL-18 in inflammatory rheumatic diseases using both human samples from patients with inflammatory diseases (see references 2 and 5) and in experimental models in the mouse. The results led to an ongoing clinical trial using an IL-18 antagonist in adult onset-Still's disease, an inflammatory rheumatic condition. Furthermore, the use of an IL-18 antagonist in a 3-month old child with a severe hereditary inflammatory disorder led to a full remission with a follow-up of more than a year (see references 2). This success has led to a clinical trial in children with this orphan disease.




A baby with a severe and sometimes lethal inflammatory disease who was recently successfully treated with an inhibitor of IL-18 in collaboration with our research group.
Published by S. Canna et al. JACI 2016

We have also examined the role of signalling pathways involved in the modulation of inflammatory responses in macrophages and other myeloid cells (see reference 8). Our group is involved in various collaborations with laboratories in France, Spain, and USA

**Publications**

1. Santiago L., Menaa C., arias M., Martin P., Jaime-Sanchez P., Metkar S., Comas L., Erill N., Gonzalez-Rumayor V., Esser E., Galvez E.M., Raja S., Simon M.M., Sprague S.M., Gabay C., Martinez-Lostao L., Pardo J., Froelich C.J.: Granzame A contributes to inflammatory arthritis through stimulation of osteoclastogenesis. Arthritis Rheumatol 2017; 69: 320-334
2. Canna S., Girard C., Malle L., de Jesus A., Romberg N., Kelsen J., Surrey L.F., Russo P., sleight A., Schiffrin E., Gabay C., Goldbach-Mansky R., Behrens E.M.: Life-threatening NLRC4-associated hyperinflammation successfully treated with Interleukin-18 inhibition. J Clin Immunol Allergy 2016
3. Palomo J., Mastelic-Gavillet B., Woldt E., Troccaz S., Rodriguez E., Palmer G., Siegrist C.-A., Gabay C.: IL-36-induced toxicity in neonatal mice involves TNF-α production by myeloid cells. J Immunol 2016; 197: 2239-49
4. Agoro R., Piotet-Morin J., Palomo J., Michaudel C., Vigne S., Maillet I., Chenuet P., Guillou N., Bérichel J.L., Kisielow M., Flodby U.P., Bert M.L., Quesniaux V., Muller M., Padova F.D., Ryffel B., Gabay C., Couturier-Maillard A.: IL-1R1-MyD88 axis elicits papain-induced lung inflammation. Eur J Immunol 2016; 46: 2531-2541
5. Girard C., Rech J., Brown M., Allali D., Roux-Lombard P., Spertini F., Schiffrin E., Schett G., Manger B., Bas S., Del Val G., Gabay C.: Elevated serum levels of free interleukin-18 in adult onset Still's disease. Rheumatology 2016; 55: 2237-2247
6. Dietrich D., Martin P., Flacher V., Sun Y., Jarossay D., Brembilla N., Arnett H.A., Palmer G., Towne J., Gabay C.: Interkeukin-36 potently stimulates human M2 macrophages, Langerhans cells and keratinocytes to produce pro-inflammatory cytokines. Cytokine 2016; 84: 88-98
7. Boutet M.A., Bart G., Penthoat M., Amiaud J., Brulin B., Charrier C., Morel F., Lecron J.C., Rolli-Derkinderen M., Bourreille A., Vigne S., Gabay C., Palmer G., Le Goff B., Blanchard F.: Distinct expression of IL-36α, β, ϒ, their antagonist IL-36Ra and IL-38 in psoriasis, rheumatoid arthritis, and Crohn's disease. Clin Exp Immunol 2016; 184: 159-73
8. Lombardi M.S., Gilliéron C., Dietrich D., Gabay C.: SIK inhibition in human myeloid cells modulates TLR and IL-1R signaling and induces an anti-inflammatory phenotype. J Leukoc Biol 2016; 99: 711-21
9. Martin P., Palmer G., Rodriguez E., Woldt E., Mean I., James R.W., Smith D.E., Kwak B.R., Gabay C.: Atherosclerosis severity is not affected by a deficiency in IL-33/ST2 signaling. Immun Inflamm Dis. 2015; 3: 239-246
10. Segueni N., Vigne S., Palmer G., Bourigault M.-L., Olleros M.L., Vesin D., Garcia I., Ryffel B., Quesniaux V.F.J., Gabay C.: Limited contribution of IL-36 versus IL-1 and TNF pathways in host response to mycobacterial infection. PlosOne 2015; 10: e0126058
11. Talabot-Ayer D., Martin P., Vesin C., Seemayer C., Vigne S., Gabay C., Palmer G.: Severe neutrophil-dominated inflammation and enhanced myelopoiesis in IL-33-overexpressing CMV/IL-33 Mice. J Immunol 2015; 194: 750-60

**Research Focus 2**

Group Leader: Monique Gannagé, MD, PhD Monique.ghannage@unige.ch

Members: Jennifer Niven, Postdoctoral associate- Natacha Madelon, Postdoctoral associate - Gracia Gangath master student- Assunta Caruso, technician

Macroautophagy is a major catabolic pathway in the cells, which constantly delivers cytoplasmic constituents and organelles to the lysosomal compartment for degradation. The pathway is an important contributor of cellular homeostasis, and therefore is active and up-regulated in various conditions of cellular stress and inflammation. In this context macrautophagy has been implicated in shaping the innate and adaptive immune responses by acting at multiple and diverse levels such as cytokine secretion, and antigen presentation. Therefore, it is not surprising that macroautophagy has recently been linked to the initiation and onset of autoimmune diseases. The best and more documented role of autophagy in the pathogenesis of autoimmune and inflammatory human disorders is its contribution to Crohn's disease (CD). Indeed in CD patients, the ATG16L1 risk allele, one of the strongest genetic risk factor of the disease is associated with functional defects in bacterial clearance and antigen presentation. In systemic lupus erythematous (SLE), two genome wide association studies have identified 2 SNP variants of the ATG5 gene associated with the disease. Interestingly in rheumatoid arthritis (RA) the SNP rs548234, located 133kb from the ATG5 region was shown to be associated to the risk of developing RA.

The focus of our laboratory is the contribution of autophagy to the pathogenesis of rheumatoid arthritis and ankylosing spondylitis.

In order to address the contribution of macroautophagy to the adaptive immune response during arthritis, we used two mice models of arthritis, the collagen induced arthritis model (CIA), and the antigen induced arthritis (AIA) model in mice deficient for autophagy in their dendritic cells or in their macrophages. In the AIA model, we found that mice lacking autophagy in their dendritic cells (DC/ATG5-/-) showed enhanced cartilage destruction and bone erosion compare to their littermate controls. In the CIA model, clinical scores were more severe in (DC/ATG5-/-) mice. Interestingly, the Th17 response in DC/ATG5-/- mice was significantly increased in both models of arthritis. We have shown that the mechanism behind this phenotype is related to the instability of regulatory T cells (Tregs) in context of inflammation, in DC/ATG5-/- mice. Indeed using Tregs transfer upon antigen induced arthritis, we were able to demonstrate their switch to Th17 in the context of inflammation. This work identifies autophagy as a negative regulator of the immune response in an arthritis mouse model.

During the course of RA, our preliminary results indicate that autophagy is up regulated in synovial biopsies of patients using at least two different methods immunohistochemistry and quantitative PCR. Further characterization of cellular subsets up-regulating autophagy are now being performed. In parallel, we have analysed the role of autophagy in the degradation of 3 auto-antigens relevant to RA: fibrinogen, alpha-enolase and the intermediate filament vimentin. We find that autophagy regulates the degradation of the vimentin in different cell types including dendritic cells, and synovial fibroblasts. We are now investigating the contribution of the pathway to antigen presentation and citrullination of two specific DR4 restricted vimentin epitopes.

Finally we have defined a new role for macroautophagy in controlling both the internalization and degradation of MHC class I molecules, in mouse antigen presenting cells. The precise molecular

mechanism involves the adaptor-associated kinase 1 (AAK1), which binds LC3 and MHC class 1 molecules and targets them to autophagosomes. We are now translating this finding in human samples. Our preliminary data using CRISPR/Cas 9 generated cell lines that are deficient for autophagy essential genes, have shown an involvement of autophagy in human HLA class 1 surface expression and degradation. Interestingly HLA-B27 seems not to be affected by gain and loss of functions experiments. Our aim is to address the molecular mechanism behind this phenotype and to understand why B27 escape autophagic degradation.

**Publications:**

1. Keller CW, Loi M, Ewert S, Quast I, Theiler R, Gannagé M, Münz C, De Libero G, Freigang S, Lünemann JD The autophagy machinery restrains iNKT cell activation through CD1D internalization. Autophagy. 2017 Mar 15:1-12
2. Monica Loi, Monique Gannagé and Christian Münz: ATGs help MHC class II, but inhibit MHC class I, antigen presentation Autophagy, 2016 Sep : (12(9) : 1681-2
3. Loi M, Lippmann A, Steinbach K, Barreira da Silva R, Nowag H, Albrecht R, Garcia-Sastre A , Merkler D, Münz C* and Gannagé M.: Macroautophagy proteins control MHC class I levels on dendritic cells and shape antiviral CD8+ T cell responses. Cell Report. 2016 May 3;15(5):1076-87.
4. Fonteneau J, Brilot F, Munz C, Gannagé M,: The tumor antigen NY-ESO-1 mediates direct recognition of melanoma cells by CD4+ Tcells after intercellular antigen transfer. J Immunol. 2016 Jan 1;196(1):64-71.
5. Guidelines for the Use and Interpretation of Assays for Monitoring Autophagy Klionsky D, Abdelmohsen K, Abe A, Gannagé M, Zong, Antonio Zorzano, and Zughaier S . Autophagy. 2016 Jan 2;12(1):1-222.
6. Duares F, Niven J, Hugues S and Gannagé M.: Macroautophagy in endogenous processing of self- and pathogen-derived antigens forMHC class II presentation. Front Immunol. 2015 Sep 22;6:459.
7. Niven J, Hoare J, McGowan D, Devarajan G, Itohara S, Gannagé M, Teismann P, Crane I.: S100B Up-Regulates Macrophage Production of IL1β and CCL22 and Influences Severity of Retinal Inflammation. PLoS One. 2015 Jul 23; 10(7):e0132688.

# UNIVERSITY OF LAUSANNE

Group leader: Prof. Nicolas Fasel PhD, Nicolas.Fasel@unil.ch

Members: Dr. Remzi Onur Eren,Dr. Nathalie Isorce, Dr. Filipa Pinheiro Teixeira, Dr. Matteo Rossi, Dmitry Kopelyanskiy, Baijayanti Jha

In the last years, a growing amount of evidence supports the involvement of viral infections in the pathology of rheumatoid arthritis (RA). Toll-like receptors (TLRs) expressed by macrophages or RA synovial fibroblasts could play a major role in initiating a potent, type 1 interferon driven, pro-inflammatory response. Indeed, several viruses, including alphaviruses, HCV, HIV and parvovirus B19 have been found in the synovial tissue and have been implicated in the development of RA. Thus, TLRs could play a fundamental role in the initiation and self-perpetuation of RA, inducing the production of pro-inflammatory cytokines, which lead to the recruitment of inflammatory cells and consequent tissue damage, resulting in cell death and release of more TLR ligands, creating a vicious cycle.

In Lausanne, we first focused on the importance of TLR3, which can be activated by dsRNA viruses. Using a model system based on *Leishmania* parasites, which harbor a viral cytoplasmic dsRNA, we searched for signaling pathways implicated in the survival of macrophages and determined a TLR3 dependent axis, which induced miR-155 and phosphorylation of AKT1. In parallel, we reported the essential role of IFN-β in driving the production of IL-6 and TNF-α. We furthermore examined the relevance of IL-17 in the inflammatory response and in the spreading of inflammation to secondary sites in immuno-compromised situations. We additionally demonstrated that inflammation can be reactivated by subsequent infection and determined the importance of TLR3, IFN-β and its activation in the poor responsiveness to specific drugs.

In clinically related investigations, we demonstrated that co-infection could be predictive of clinical complications such as first-line treatment failure, increased and reactivated inflammation, and symptomatic relapses, which are relevant in RA. Our data may guide treatment strategies, to better predict, avoid, and manage the complications of such hyper-inflammatory processes . This in turn could have an impact on potential synergistic therapeutic effects for inflammatory diseases with, or without, a viral component.

**Publications:**

1. Implication of different domains of the Leishmania major metacaspase in cell death and autophagy. M. Casanova, I.J. Gonzalez, C. Sprissler, H. Zalila, M. Dacher, L. Basmaciyan, G.F : Späth, N. Azas and N. Fasel. Cell Death Diseases. Oct 22;6:e1933 (2015)
2. *Leishmania*-RNA virus presence in *L. guyanensis* parasites increases the risk of first-line treatment failure and symptomatic relapse. E. Bourreau, M. Ginouves, G. Prévot, M.-A. Hartley, J-P. Gangneux, F. Robert-Gangneux, J. Dufour, D. Sainte Marie, A. Bertolotti, F. Pratlong, R. Martin, F. Schütz, P. Couppié, N. Fasel and C. Ronet. J. Infectious Diseases DOI: 10.1093/infdis/jiv355 (2016)
3. Severe Cutaneous Leishmaniasis in a Human Immunodeficiency Virus Patient Coinfected with Leishmania braziliensis and Its Endosymbiotic Virus L. Parmentier, A. Cusini, N. Müller, H. Zangger, M.-

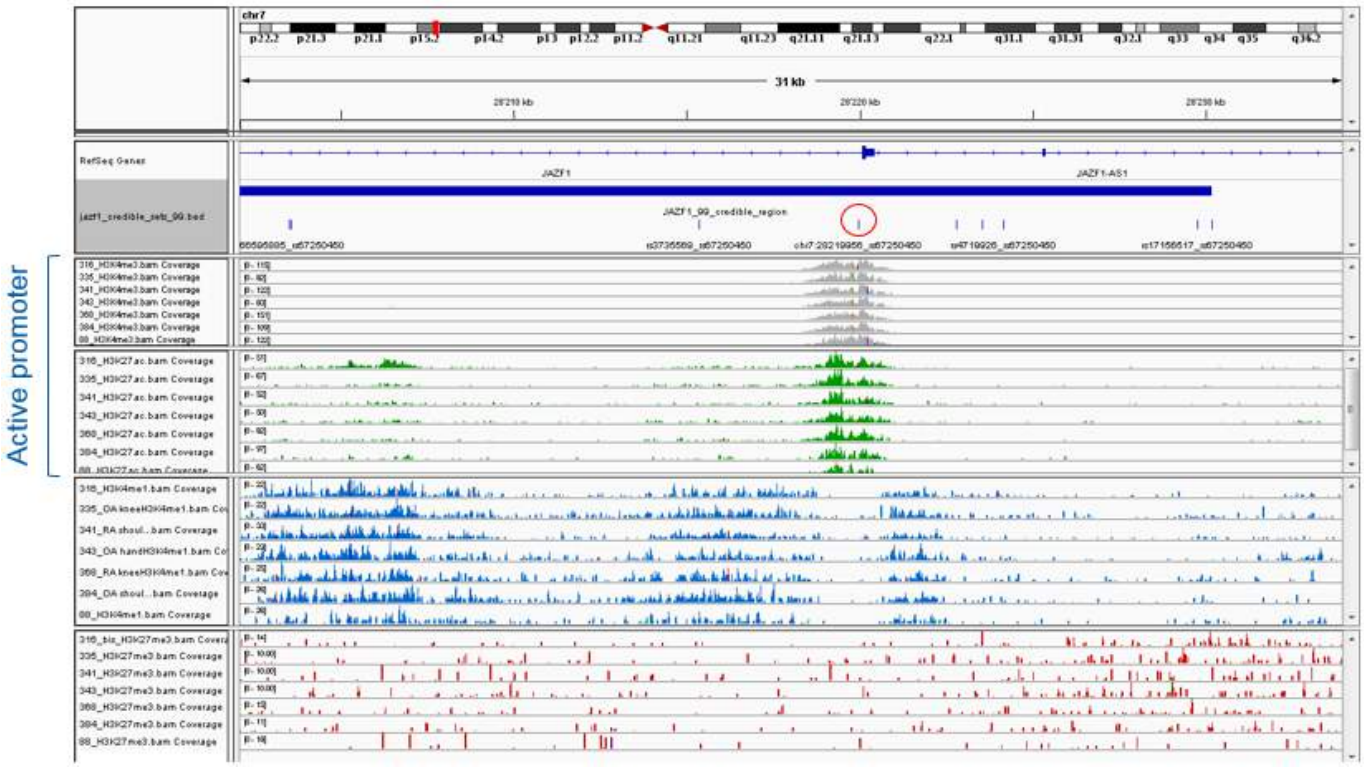
A. Hartley, C. Desponds, P. Castiglioni, P. Dubach, C. Ronet, S. M. Beverley and N. Fasel. Am J Trop Med Hyg doi: 10.4269/ajtmh.15-0803 (2016)

4. Caspase-mediated cleavage of raptor participates in the inactivation of mTORC1 during cell death. R. Martin, C. Desponds, R. O. Eren, M. Quadroni, M. Thome and N. Fasel. Cell Death and Discovery 2, 16024; doi:10.1038/cddiscovery.2016.24 (2016)
5. Raptor hunted by caspases. R. Martin, M. Thome, F. Martinon and N. Fasel. Cell Death and Diseases doi:10.1038/cddis.2016.153 (2016)
6. A functional BH3 domain in an aquaporin from Leishmania infantum. C. M. Genes, H. de Lucio, V. M. Gonzalez, P. Sanchez-Murcia, E. Rico, F. Gago, N. Fasel and A. Jimenez-Ruiz. Cell Death and Discovery 2, 16043 doi:10.1038/cddiscovery.2016.43 (2016)
7. Unveiling the Role of The Integrated Endoplasmic Reticulum Stress Response in *Leishmania* infection. K.L. Dias-Teixeira, R.M. Pereira, J.S. Silva, N. Fasel N, B.H. Aktas and U.G. Lopes. Front. Immunol. doi: 10.3389/fimmu.2016.00283 (2016)
8. *Leishmania* RNA virus dependent metastatic leishmaniasis is mediated by IL-17A in the absence of IFN-α. M.-A. Hartley, E. Bourreau, M. Rossi, P. Castiglioni, R. O. Eren, F. Prevel, P. Couppié, S. M. Hickerson, P. Launois, S. M. Beverley, C. Ronet and N. Fasel. PLoS Pathog 12(9): e1005852. doi:10.1371/journal.ppat.1005852 (2016)
9. Antiviral response promotes *Leishmania* parasite persistence by increasing macrophage survival. R. O. Eren, M. Reverte, M. Rossi, M.-A. Hartley, P. Castiglioni, F. Prevel, R. Martin, C. Desponds, L.-F. Lye, S. K. Drexler, W. Reith, S.M. Beverley, C. Ronet and N. Fasel. Cell Host and Microbes (20(3) pp. 318-328)(2016)
10. Tilting the balance between RNA interference and replication eradicates Leishmania RNA virus 1 and mitigates the inflammatory response. E. A. Brettmann, J.S. Shaik, H. Zangger, L.F. Lye, F.M. Kuhlmann, N.S. Akopyants, D.M. Oschwald, K.L. Owens, S.M. Hickerson, C. Ronet, N. Fasel and S.M. Beverley, *Proceedings of the National Academy of Sciences of the United States of America* 113(43) pp. 11998-12005 (2016)

## UNIVERSITY OF ZÜRICH

**Epigenetic analysis of synovial fibroblasts**

Synovial fibroblasts play a key role in the destructive and inflammatory processes in RA. The advancements in techniques to interrogate epigenetic modifications and chromatin interactions allowed us to widen our analysis of epigenetic modifications in synovial fibroblasts. We generated a large dataset from synovial fibroblasts isolated from different joints of patients with rheumatoid arthritis, osteoarthritis and patients with joint pain. We performed DNA genotyping, RNA sequencing of long and short RNA and built genome-wide maps of six different histone marks based on chromatin immunoprecipitation DNA sequencing and DNA methylation data. Our histone Chip-Seq includes H3K27ac, H3K4me3, H3K4me1, H3K27me3, H3K36me3 and H3K9me3. This data set will be complemented with ATAC-seq analyses to capture open chromatin sites and chromosome conformation capture analyses (capture HiC), which will generate maps of physical interactions between regulatory DNA elements, e.g. enhancers and promoters. Integration of all this different data sets is done in collaboration with the UK Center of Genetics and Genomics at the University of Manchester and will provide deep insight into genome-wide chromatin landscapes of synovial fibroblasts from different joints. This comprehensive data set will also enable us to identify causal RA risk variants that are effective in synovial fibroblasts and map them to specific joint regions and to explore the functional impact of identified joint specific risk variants on synovial fibroblast biology.




Identification of active promoter regions by mapping of histone marks (H3K4me3 in grey, H3K27ac in green, H3K4me1 in blue, H3K27me3 in red). Overlap with RA associated risk single nucleotide polymorphisms (SNPs) showed a specific SNP (red circle) in the promoter region, which points towards direct functional effects of this SNP in synovial fibroblasts.

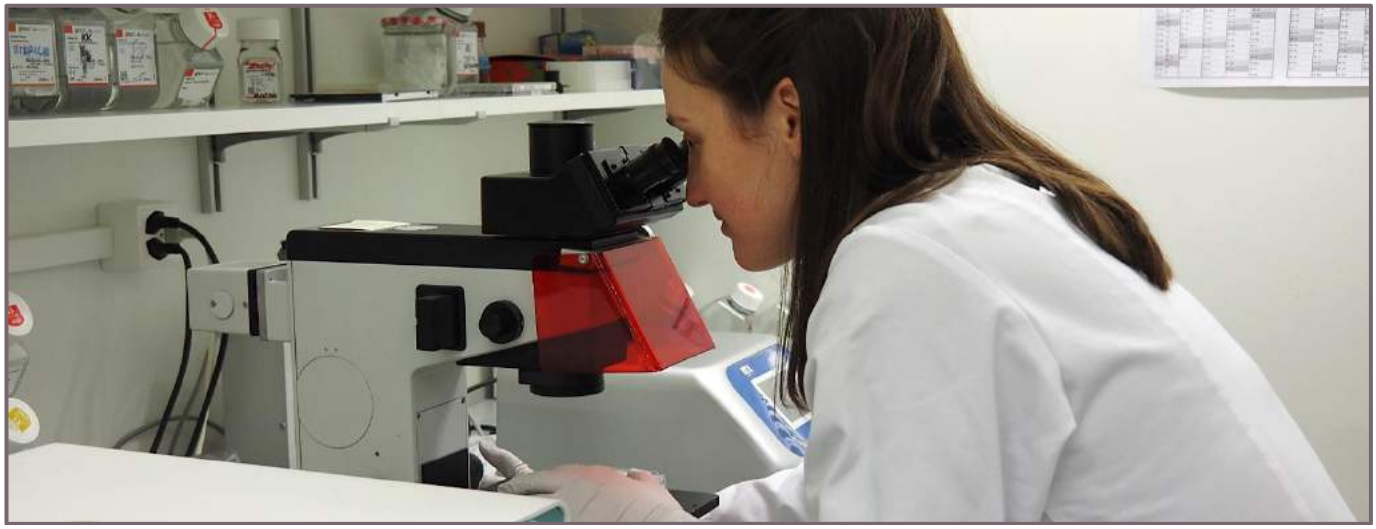
**Publication:**

Epigenetically-driven anatomical diversity of synovial fibroblasts guides joint-specific fibroblast functions. Frank-Bertoncelj M, Trenkmann M, Klein K, Karouzakis E, Rehrauer H, Bratus A, Kolling C, Armaka M, Filer A, Michel BA, Gay RE, Buckley CD, Kollias G, Gay S, Ospelt C. Nat Commun. 2017 Mar 23;8:14852. doi: 10.1038/ncomms14852.

We have also continued our work on mechanisms of DNA de- and re-methylation in synovial fibroblasts. DNA is globally hypomethylated in synovial fibroblasts of patients with RA, which contributes to their invasive behavior. Previously, we showed that these cells could be remethylated by supplementation with methyl donors such as betaine. Now we could show that alterations in the expression of microRNAs, in particular the upregulation of miR-29, which targets DNMT3A, might limit the efficiency of betaine if it is used as DNA remethylating agent.

**Publication:**

MicroRNAs interfere with DNA methylation in rheumatoid arthritis synovial fibroblasts. Gaur N, Karouzakis E, Glück S, Bagdonas E, Jüngel A, Michel BA, Gay RE, Gay S, Frank-Bertoncelj M, Neidhart M. RMD Open. 2016 Oct 14;2(2):e000299. eCollection 2016.



**Epigenetic analysis of macrophages**

Activation of macrophages and overexpression of TNFα is associated with RA pathogenesis. However, the mechanism of TNFα overexpression is still unknown. 5-methylocytosine (5-mC) is an epigenetic modification that is associated with silenced genes. Recent studies showed that it is converted to 5-hydroxylmethylocytosine (5-hmC) and reactivates gene expression through the action of the family of Ten-Eleven-Translocation (TET1-3) enzymes. In our study, we show that levels of 5-hmC were increased globally and specifically in the TNFα promoter during monocyte to macrophage differentiation. Furthermore, the levels of 5-hmC were increased during LPS stimulation of macrophages. Inhibition of TET1 decreased the levels of 5-hmC and TNFα expression respectively. In conclusion, we showed that TET1 contributes to the activation of macrophages through the regulation of 5-hydroxymethylation in the promoter of TNFα. Thus, the TET1 enzyme is promising therapeutic target to inhibit the persistent inflammation caused by macrophages in RA.

**Publication:**

Characterization of a DNA demethylation pathway during inflammation in macrophages. Sun F, Gay RE, Michel BA, Ye S, Gay S, Neidhart M, Karouzakis E. Ann Rheum Dis 74(S2):169, 2015

## Further Publications relevant to iAR work

Whitaker JW, Boyle DL, Bartok B, Ball ST, Gay S, Wang W, Firestein GS. Integrative omics analysis of rheumatoid arthritis identifies non-obvious therapeutic targets. PLoS One. 22;10(4):e0124254. 2015

Aradi B, Kato M, Filkova M, Karouzakis E, Klein K, Scharl M, Kolling C, Michel BA, Gay RE, Buzas EI, Gay S, Jüngel A. Protein tyrosine phosphatase nonreceptor type 2 (PTPN2), an important regulator of IL-6 production in rheumatoid arthritis synovial fibroblasts. Arthritis Rheumatol. 2015

Messemaker TC, Frank-Bertoncelj M, Marques RB, Adriaans A, Bakker AM, Daha N, Gay S, Huizinga TW, Toes RE, Mikkers HM, Kurreeman F. A novel long non-coding RNA in the rheumatoid arthritis risk locus TRAF1-C5 influences C5 mRNA levels. Genes Immun 2015

Klein K, Gay S. Epigenetics in rheumatoid arthritis. Curr Opin Rheumatol. Jan;27(1):76-82 2015

Gay S. Micro-RNA in der Pathogenese rheumatischer Erkrankungen. Drug Res (Stuttg). 65 (Suppl 1):18, 2015.

Engler A, Tange C, Frank-Bertoncelj M, Gay RE, Gay S, Ospelt C. Regulation and function of SIRT1 in rheumatoid arthritis synovial fibroblasts. J Mol Med (Berl), 2016

Meulenbelt IM, Bhutani N, den Hollander W, Gay S, Oppermann U, Reynard LN, Skelton AJ, Young DA, Beier F, Loughlin J. The first international workshop on the epigenetics of osteoarthritis. Connect Tissue Res 30:1-12, 2016

Kato M, Ospelt C, Kolling C, Shimizu T, Kono M, Yasuda S, Michel B, Gay R, Gay S, Klein K, Atsumi T. AAA-ATPase p97 suppresses apoptotic and autophagy-associated cell death in rheumatoid arthritis synovial fibroblasts. Oncotarget. 7(39):64221-64232. doi: 10.18632/oncotarget.11890. 2016

Garn H, Bahn S, Baune BT, Binder EB, Bisgaard H, Chatila TA, Chavakis T, Culmsee C, Dannlowski U, Gay S, Gern J, Haahtela T, Kircher T, Müller-Ladner U, Neurath MF, Preissner KT, Reinhardt C, Rook G, Russell S, Schmeck B, Stappenbeck T, Steinhoff U, van Os J, Weiss S, Zemlin M, Renz H. Current concepts in chronic inflammatory diseases: interactions between microbes, cellular metabolism and inflammation. J Allergy Clin Immunol 138:47-56, 2016

Klein K, Gay RE, Gay S. Synoviale Fibroblasten - Hauptakteure in der rheumatoiden Arthritis. Z Rheumatol, Volume 75, Issue 6, pp 560–564, 2016

Gaur N, Karouzakis E, Glück S, Bagdonas E, Jüngel A, Michel BA, Gay RE, Gay S, Frank-Bertoncelj M, Neidhart M. MicroRNAs interfere with DNA methylation in rheumatoid arthritis synovial fibroblasts. RMD Open. 14; 2(2): e000299, 2016

Pleštilová L, Neidhart M, Russo G, Frank-Bertoncelj M, Ospelt C, Ciurea A, Kolling Ch, Gay R, Michel B, Vencovský J, Gay S, Jüngel A. Expression and Regulation of PIWIL-Proteins and PIWI-Interacting RNAs in Rheumatoid Arthritis. PLoS One. 11(11): e0166920. doi: 10.1371, 2016

Klein K, Kabala PA, Grabiec AM, Gay RE, Kolling C, Lin LL, Gay S, Tak PP, Prinjha RK, Ospelt C, Reedquist KA. The bromodomain protein inhibitor I-BET151 suppresses expression of inflammatory genes and matrix degrading enzymes in rheumatoid arthritis synovial fibroblasts. Ann Rheum Dis. 75:422-9, 2016

Angiolilli C, Grabiec AM, Ferguson BS, Ospelt C, Malvar Fernandez B, van Es IE, van Baarsen LG, Gay S, McKinsey TA, Tak PP, Baeten DL, Reedquist KA. Inflammatory cytokines epigenetically regulate rheumatoid arthritis fibroblast-like synoviocyte activation by suppressing HDAC5 expression. Ann Rheum Dis 75(2):430-8, 2016

Iwamoto N, Vettori S, Maurer B, Brock M, Pachera E, Jüngel A, Calcagni M, Gay RE, Whitfield ML, Distler JH, Gay S, Distler O. Downregulation of miR-193b in systemic sclerosis regulates the proliferative vasculopathy by urokinase-type plasminogen activator expression. Ann Rheum Dis 75(1):303-10, 2016

## IMPRESSUM

Text: Cem Gabay, Monique Gannagé, Nicolas Fasel, Martin Kuendig, Caroline Ospelt, Judith Safford

Translations: Martin Kuendig, Nicolas Fasel, Judith Safford

Photos: Thomas Wommelsdorf (Title page), Judith Safford, (pp. 2,3,7,11,19)

## CONTACTS

SCIENTIFIC COORDINATION
Prof. Cem Gabay
Hopitaux Universitaire de Genève
Head, Division of Rheumatology
Avenue Beau-Séjour 26
1211 Geneva
+41 22 372 35 00
cem.gabay@hcuge.ch
www.iar-suisse.ch

COMMUNICATIONS & FUNDRAISING
Dr. Judith Safford
c/o Lienhard AG
Bleicherweg 45
8027 Zurich

+41 78 635 27 28
judith.safford@iar-suisse.ch
www.iar-suisse.ch