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

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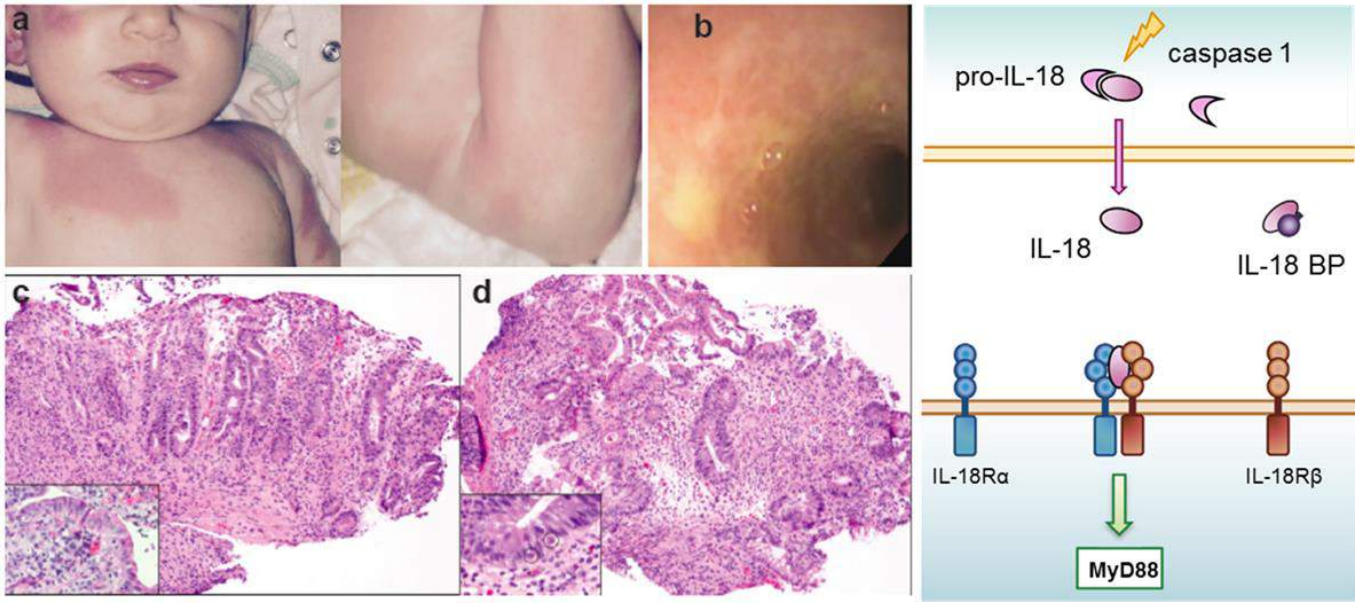
The aim of our current work is focused on better understanding the role of the interleukin (IL)-1 family of cytokines that comprises IL-1, IL-18, IL-33, Il-36, IL-37, and IL-38. We are using experimental models of arthritis and other experimental models of inflammatory diseases. In particular, we have 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

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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
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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
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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

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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:

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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.
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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.

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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.-

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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)
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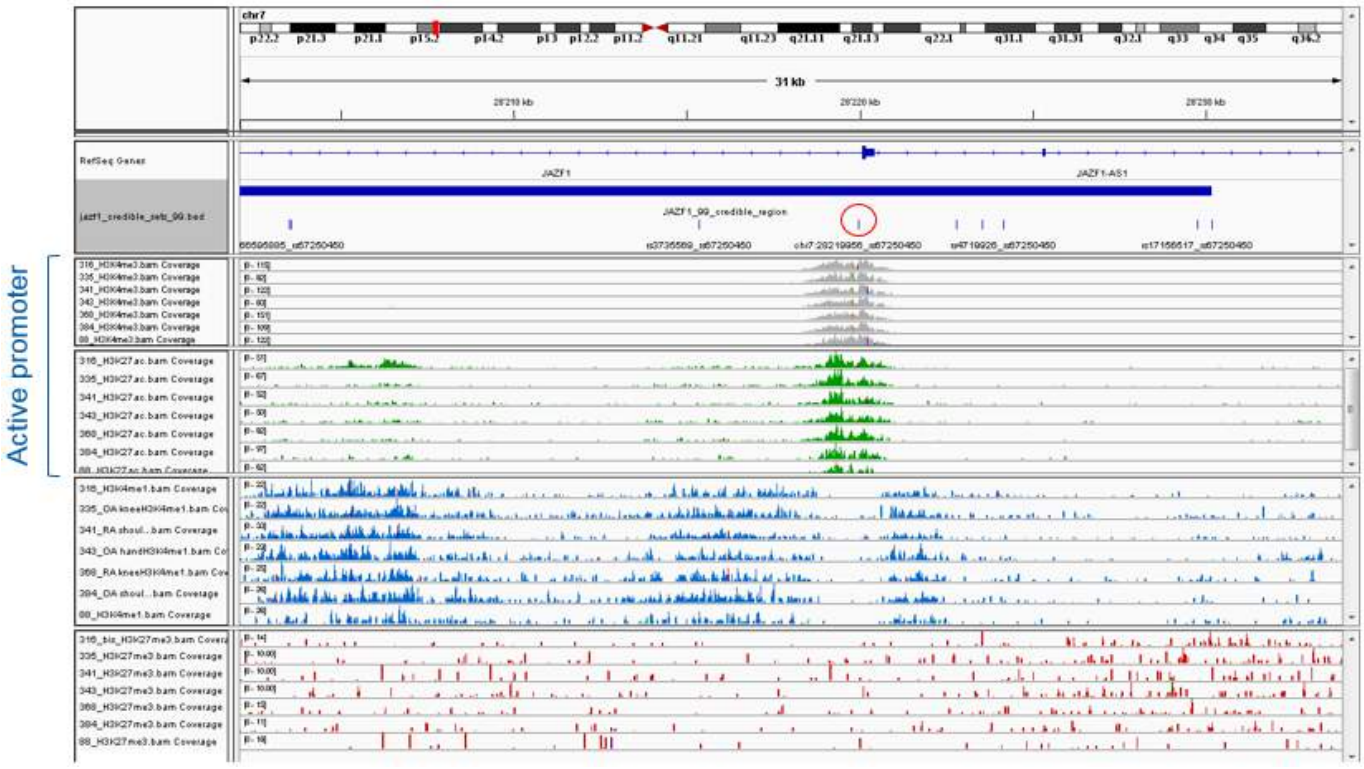
6. A functional BH3 domain in an aquaporin from Leishmania infantum. C. M. Genes, H. de Lucio, V. M. Gonzalez, P. Sanchez-Murcia, E. Rico, F. Gago, N. Fasel and A. Jimenez-Ruiz. Cell Death and Discovery 2, 16043 doi:10.1038/cddiscovery.2016.43 (2016)
7. Unveiling the Role of The Integrated Endoplasmic 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.

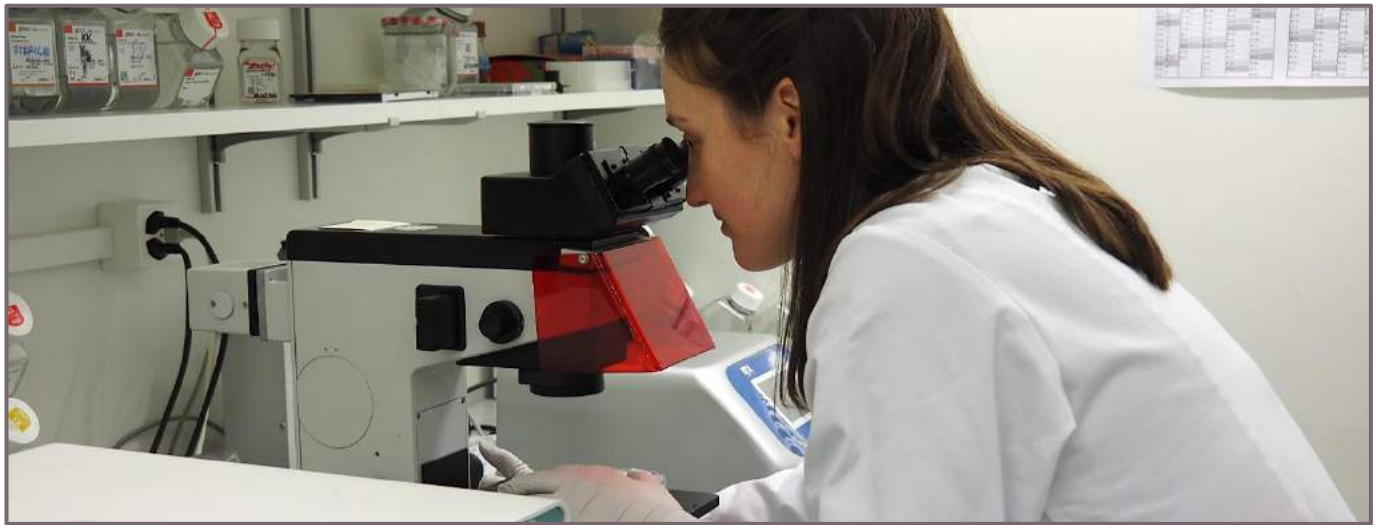
Publication:

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

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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

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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

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IMPRESSUM

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