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Foundation for Research in Rheumatology

Promoting health through effective research in individuals with rheumatic and musculoskeletal diseases

May 2023

FOREUM

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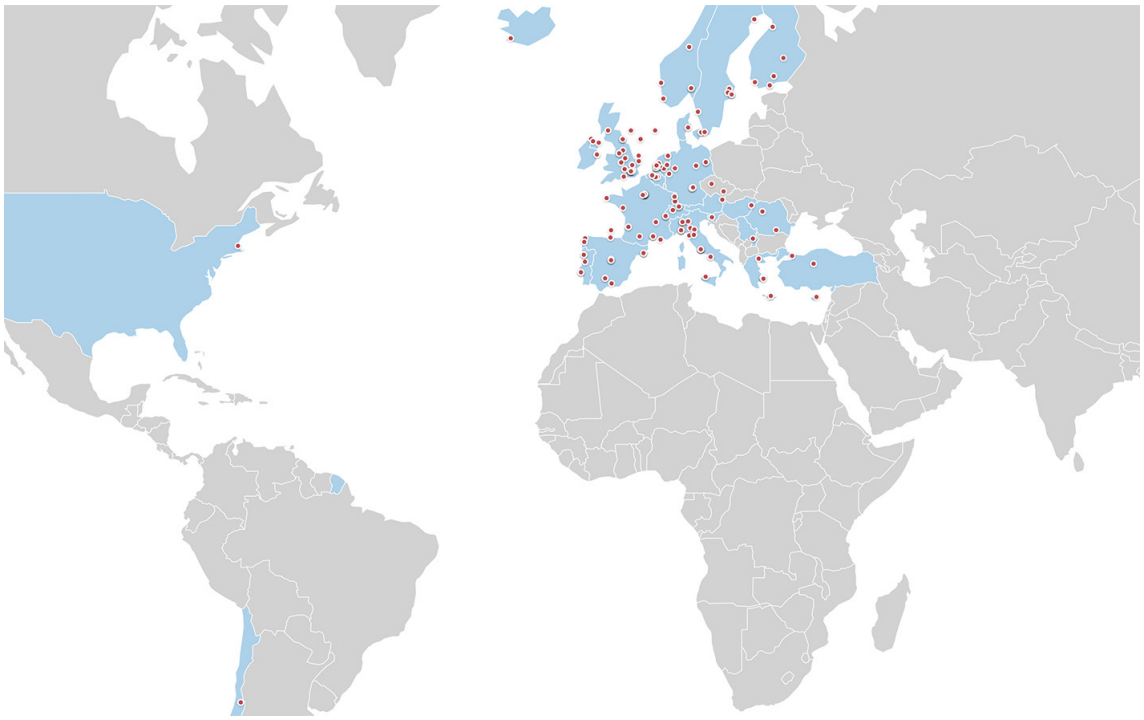
FOREUM Foundation

FOREUM is dedicated to promote research in rheumatic and musculoskeletal diseases (RMDs) as an independent research funding body based in Switzerland.
To achieve its goal, FOREUM seeks to raise funds from interested commercial and non-commercial donors that share FOREUM's vision and goals: recognising that research and innovation in this field are crucial for improving both the prevention and the management of RMDs and, hence, the living, working and socio-economic conditions of the more than 120 million people in Europa variously afflicted by RMDs.
To initiate research of the highest quality oriented towards a broad range of RMDs FOREUM periodically announces calls to which applications are considered. Basic and applied research of highest quality will be supported to reduce the burden of disease for people with RMDs. Only peer-reviewed research proposals that fulfil this ambition shall be considered for funding.
Between 2014 and beginning of 2023 FOREUM funded 77 projects, totaling to over EUR 20 million in grants. FOREUM funded projects involve more than 100 research institutions across Europe, several networks as well as patient organisations.



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FOREUM Donors

FOREUM Foundation for Research in Rheumatology seeks to raise funds from interested commercial and non-commercial donors that share FOREUM's vision and goals. Without this support we would not be here nor could we fulfil our mission for the benefit of researchers and patients. It is with gratitude that we acknowledge the following donors for their generous support and financial donations for 2022:

Platinum

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FOREUM is supported by EULAR, the European Alliance of Associations for Rheumatology. Whereas FOREUM will define its strategic goals and operations independently, the intention is that it will coordinate its research activities with EULAR in order to avoid unnecessary overlap or otherwise inefficient deployment of precious research resources.

FOREUM Structure

FOREUM Foundation for Research in Rheumatology is directed and supervised by an international Board of Trustees comprising renowned researchers and scientific experts in rheumatology. An international Executive Committee defines the strategic agenda for FOREUM, coordinates operational aspects and evaluates and decides on funding of peer-reviewed research proposals. The committee also includes a patient representative. An international Scientific Committee of experts from relevant fields of rheumatology acts as an advisory body for all scientific and methodological aspects. The committee includes patient and health professionals' representatives. The organisational structure thus ensures that FOREUM fulfils a need in rheumatology research and acts according to the highest standards and ethics of scientific research.

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- MA Andrea Beljan,
  FOREUM Project Coordinator

2013

Call for research proposals in the area of Osteoarthritis (OA)

Osteoarthritis (OA) affects a substantial proportion of the European population. The OA burden in terms of individuals and health economies will likely be rising in coming years due to ageing and increased prevalence of obesity.

The call was launched in **2013**, and out of 46 letters of intent 4 projects were selected for funding:

- Pro-resolving mediators in osteoarthritis: homeostatic signals in the joint organ
- Intrinsic regeneration of osteoarthritic cartilage by unloading involves peri-articular stem cell activity: a joint effort
- The Partnership for EARLy knee OsteoArthritis definition through imaging and tissue biomarkers (PEARL-OA)
- Micro RNAs as Biomarkers in Osteoarthritis

Pro-resolving mediators in OA: Homeostatic signals in the joint organ?

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 300.000
Project duration: 2014–2016

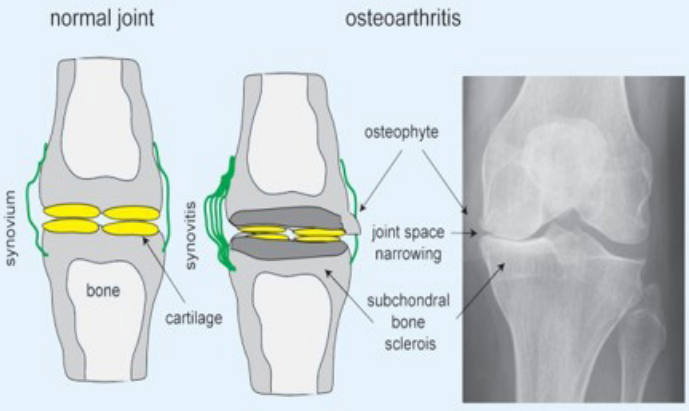
Project Url

www.foreum.org/projects/?id=120

Concept

Inflammation is a key component of OA in a large number of patients and a clear therapeutic target. This project explores the impact of molecules produced in the joint that have anti-inflammatory properties.

Such molecules are used by the body to limit the impact of inflammation. Understanding their production and effects in patients with joint disease could help in better controlling the deleterious effects of inflammation on the tissues of the joint, in particular the cartilage and the bone.



Final Results

Inflammation is the hallmark feature of many rheumatic and musculoskeletal diseases. The importance of inflammation is a factor that contributes to the severity and symptoms of osteoarthritis which was traditionally considered as degenerative joint disease.

Final report

Patient Voice

For this laboratory project, based on novel technologies, patients have not been directly involved in the design of the experiments.
However, the development of novel strategies will clearly benefit the patients.
See final report for outcomes for the patients.

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Project Team/Centres

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Intrinsic regeneration of osteoarthritic cartilage by unloading involves peri-articular stem cell activity: a joint effort

Project Lead

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Funding and Timeline

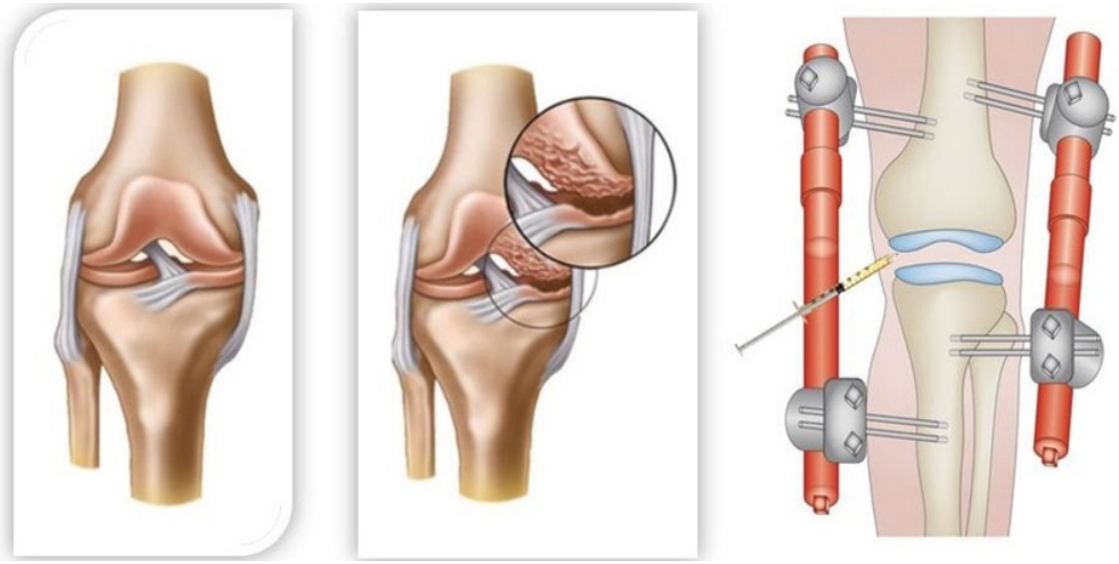
FOREUM research grant: EUR 300.000
Project duration: 2016–2019

Project Url

www.foreum.org/projects/?id=121

Concept

Spontaneous cartilage repair has recently been recognized as proof of concept in man. This team will delineate the unknown mechanisms by which mesenchymal stem cells (MSCs) in the context of the intraarticular milieu are involved in this repair activity.



Final Results

Upon distraction it suggested that MSC number initially decline in the synovial fluid (SF) (figure 1A-B). MSCs present in the SF showed changes in their gene expression profile upon KJD, most clearly observed during the treatment (3 weeks; figure 1C).
GDF5 and Grem1 presented with a statistically significant increased expression ($p<0.05$) during treatment while FAB4 expression was decreased. ACAN, PTH1R, and DDR expression had the tendency to increase over time. ADAMTS4, SOX9 and PTHLH expression showed a trend to decrease over time.

Preliminary proteomics analysis on the SF samples of the first 5 patients indicate a clear difference can be seen in the samples before vs during and after distraction (see figure 2). Exact interpretation needs further analyses of the remaining patients. In parallel to this study we have analyzed (in collaboration with Oxford) the synovial fluid of joint distraction patients (additional group in addition to this project) for mechano-sensitive de/regenerative markers. Of the 10 markers studied 4 were significant elevated (IL-6, TGF-B, MCP-1, FGF-2), 2 significant downregulated (Activin-A, LTBP-2) and 4 were not changed (IL-8, MMP-3, TIMP-1, TSG-6). These results can give further guidance to the analyses performed in Paris.
This explorative study provides for the first-time data on changes in SF MSC number and their gene and protein expression profiles upon knee joint distraction. As such, first clues are provided for the involvement of MSCs in the regenerative process induced by joint distraction for end-stage knee OA. Final results are expected this summer. Further studies are necessary to unravel the processes involved

Lay Summary

Worldwide, the general opinion is that OA joint cartilage cannot repair itself, as it has a limited number of cells in an abundant amount of extracellular matrix that is not vascularized. Working against this dogma, it was demonstrated that application of unloading by knee joint distraction (6 wks) leads to prolonged (>5 up to 9 yrs) intrinsic cartilage repair in combination with meaningful clinical efficacy. As this intrinsic cartilage repair activity is unique, this provides for the first time the opportunity to unravel and identify the mechanisms that are essential for this cartilage repair. The present project identified cells and metabolites that are present or induced by joint distraction to better understand and further refine joint distraction treatment.
It was studied whether intrinsic mesenchymal stem cell (MSC) activity plays a role in the observed cartilage repair activity. Synovial fluid (SF) in OA contains MSCs, of which the number is elevated in the early stages of OA. The discovery of this resident population of highly proliferative MSCs in SF whereby such cells have reproducibly good chondrogenic activity supports the concept that such MSCs, having a direct access to the damaged cartilage areas, and so may be key players in the reparative process as a result of joint distraction. A collaboration (UK/NL) has already shown that SF resident MSCs adhere to sites of cartilage injury in the canine OA model.
Pilot data (UK) using human OA joints showed an increased MSC proliferative response in subchondral bone areas directly adjacent to the denuded cartilage. Moreover, the in vitro pilot (UK) work demonstrated that the SF biochemical composition influences MSC cartilage adherence. Several mediators (cytokines, growth factors, lubricants, etc) as well as inflammatory cell subsets are changed by joint distraction as well. Within the consortium extensive expertise on delineating these ‘soluble’ and ‘inflammatory’ components of joint distraction in the OA joint (Fr) exist. A first impression is that these components are influenced by the distraction. Further analyses need to be performed to determine details. Using an animal model, we demonstrated for the first time that during the joint distraction the process is initiated but the actual repair process is most likely started after the treatment period once the joint is normally loaded again.
Although significant progress was made not all data is yet available. Additional research is necessary to enhance our understanding of the changes observed and to relate to clinical changes observed after knee joint distraction. Several follow-up studies are already initiated.

Publications

- Sanjurjo-Rodriguez C, Altaie A, Mastbergen S, Baboolal T, Welting T, Lafeber F, Pandit H, McGonagle D, Jones E. Gene Expression Signatures of Synovial Fluid Multipotent Stromal Cells in Advanced Knee Osteoarthritis and Following Knee Joint Distraction. Front Bioeng Biotechnol. 2020 Oct 14;8:579751. doi: 10.3389/fbioe.2020.579751. PMID: 33178674; PMCID: PMC7591809
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  Simon Mastbergen, Invited speaker at EORS 2019, Maastricht October 2019; Invited speaker at 6th Joint Preservation Congress at Warsaw, Poland September 2019
- The catabolic-to-anabolic shift in the osteoarthritic cartilage after knee joint distraction in dogs occurs after the distraction period. M.Teunissen, J. Popov-Celeketic, K.Coeleveld, B.P.Meij, F.P.J.G.Lafeber, M.A.Tryfonidou, S.C.Mastbergen
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  Poster presentation at ORS February 2019 / Osteoarthritis Cartilage. 2020 Mar;28(3):324-333

EULAR Abstracts

2019

- FRI0518:
  Longitudinal evaluation of synovial fluid and synovial fluid MSC transcript changes in subjects undergoing joint distraction
  http://scientific.sparx-ip.net/archiveeular

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The partnership for early knee OA definition through imaging and tissue biomarkers (PEARL-OA)

Project Lead

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Funding and Timeline

FOREUM pump prime grant: EUR 75.000
Project duration: 2015–2017

Project Url

www.foreum.org/projects/?id=122

Concept

Osteoarthritis (OA) is the fastest growing cause of disability worldwide. The development of OA structural and symptom-modifying therapy is hampered by the complex phenotypes of this disease and difficulties in accurate quantification of OA pathologies.
We used 2 existing, longitudinal cohorts, selected for «early» OA risk factors, and applied novel MRI analysis using active appearance models (Imorphics UK Ltd). We studied bone features associated with progression to clinical knee OA.

Final Results

Using the Swedish KANON cohort, an RCT which includes 121 individuals who experienced an acute anterior cruciate ligament (ACL) injury, we found that bone shape changes occur rapidly after ACL injury and are already evident at 3 months. These changes post-ACL tear are similar to those reported in established knee OA.
In the Osteoarthritis Initiative Cohort, it was found that bone shape predicted progression to total joint replacement, and that bone shape was associated with prevalent frequent knee symptoms but not incident symptoms.
On the basis of the 3D imaging biomarkers evolved through this grant, the applicants were part of a successful IMI application, APPROACH-OA, which will utilise these biomarkers to further explore the relationship of bone to OA development and progression.

Lay Summary

Osteoarthritis (OA) is the fastest growing cause of disability worldwide. The development of new OA treatments is hampered by the complexity of the disease which over time involves multiple joint tissues including bone and cartilage. We especially don't understand the early stages of the disease, a time when treatments may be effective. In this collaborative project we used two existing, longitudinal clinical and imaging cohorts, selected for "early" OA risk factors, and applied novel imaging (MRI) measures associated with progression of pre-symptomatic states to clinical knee OA.
Using the large American NIH Osteoarthritis Initiative cohort, which includes people at risk of

developing OA, we were able to show that the three-dimensional (3D) shape of the knee bones is positively associated with later progression to total knee replacement. In addition, we found that 3D bone shape is associated with current frequent OA knee symptoms but not with incident symptoms, which may represent early OA. Using the Swedish KANON cohort, which includes 121 people who have experienced an acute anterior cruciate ligament (ACL) injury, we found that bone shape changes occur rapidly after ACL injury and are already evident at 3 months. The changes to knee bone shape post-ACL tear are similar to those reported in established knee OA. We also found that the shapes of all the bones within the knee (the femur, tibia and patella) are different in people who have just suffered an ACL injury compared to young healthy individuals without an injury. This suggests that people at risk of subsequent injury could be identified and advised to pursue sports with less chance of high impact injury.

The results of this work will inform further studies to explore the relationship of bone to OA development and progression, funded through a large collaborative European grant. Ultimately, the aim of this work is to revolutionise our understanding of the mechanisms of OA progression, define pre-OA asymptomatic and symptomatic states, identify post-traumatic OA risk factors and enable targeted OA interventions.

Publications

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Micro RNAs as biomarkers in OA

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Funding and Timeline
FOREUM pump prime grant: EUR 75.000
Project duration: 2014–2016

Project Url
www.foreum.org/projects/?id=123

Objectives

OA is still classified based on changes in joint tissues that are visible on conventional radiographs. This scoring system, however, does not accommodate emerging information about disease mechanisms.

Our proposal aimed to identify and validate miRNAs as future blood biomarkers for monitoring OA pathophysiological processes in cartilage via a 2 step approach:

– Identify miRNA signatures reporting on underlying disease processes and predicting severe OA of the hip and/or knee joint
– Validation and confirmation in additional cohorts across Europe and towards OA in additional joints such as hand OA.

Final Results

Notably, the results of the pilot study appeared a stepping stone in accessing larger grant money which concurrently established extension of our research question; a high quality miRNA sequencing data set was established in overlapping human samples of cartilage and plasma. Preliminary data analyses showed promising correlation of miRNAs detected in plasma and cartilage, suggesting that circulating miRNA could indeed report on cartilage specific processes. As such the results of the project are bound to deliver biomarkers that reflect diversity in OA pathophysiology with difficult diagnosis.

Lay Summary

Up until now strikingly little progress has been made in the development of disease modifying osteoarthritis (OA) drugs. Lack of insight into the diversity of underlying OA pathophysiology and absence of tools to stratify patients based on required mode of action have likely contributed to the diminished progress. For that matter, the pump and prime project “Micro RNAs as Biomarkers in Osteoarthritis” encouraged exploration of a potential new biomarkers source being micro RNAs (miRNA). miRNAs are small RNA molecules regulating (disease) processes in tissues.

Unique is the fact that miRNAs can be secreted as messenger from tissues into the circulation

where they were found to reflect ongoing (pathophysiological) conditions. Based on a compelling initial study of Beyer et al. 2014, we hypothesize that miRNAs are valuable molecular biomarkers for predicting underlying OA disease pathophysiology and respective progression. In the pump and prime project we were able to establish isolation of miRNAs from relative small amount of plasma (100 µL) that was of excellent quality and quantity for next generation RNA-sequencing and RT-qPCR. As such significant differences in circulating miRNAs between OA cases and controls were identified.

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Project Team/Centres

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- Prof. dr. med. C Ospelt, University Hospital Zurich, SWITZERLAND

2014

Call for research proposals in the area of Systemic Lupus Erythematosis (SLE)

SLE affects people across the European population. The SLE burden in terms of individuals and health economies remains significant in the absence of sufficient highly effective therapeutics, predictive biomarkers and optimized treatment strategies.

The call was launched in **2014**, and out of 30 letters of intent 4 projects were selected for funding:

- Next Generation Sequencing (NGS) in Peripheral Blood and Hematopoietic Stem Cells (HSC) in SLE: Mechanisms of Disease, Novel Therapeutic Targets and Biomarkers for Disease Activity and Response to Therapy
- REFRACT - Refractory lupus nephritis: a tissue-based pathophysiological approach performed within the frame of RING, a clinical trial designed to test the efficacy of rituximab
- NET-ting the autoreactive B cell memory by therapeutically targeting the humoral autoimmunity in patients with systemic lupus erythematosus
- Deciphering the role of ROS and neutrophils in the SLE pathogenesis

Next generation sequencing (NGS) in peripheral blood and hematopoietic stem cells (HSC) in SLE: mechanisms of disease, novel therapeutic targets and biomarkers for disease activity and response to therapy

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 300.000
Project duration: 2016–2019

Project Url
www.foreum.org/projects/?id=124

Concept

Several types of cells are involved in SLE, all of which originate from HSCs. We have used RNA-Seq and genome-wide association studies to uncover genes and their products (RNA or proteins) that can be used as markers to predict patients more likely to develop severe lupus and respond to therapy. We also sought to interrogate the HSC in the bone marrow so to identify targets for new therapies.

Objectives

Several types of cells are involved in SLE, all of which originate from HSC. We have used RNA Sequencing to uncover genes and their products (RNA or proteins) that can be used as markers to predict patients who may be more susceptible to certain serious manifestations of lupus as well as to interrogate the cells in the bone marrow (stem cells) to identify targets for new therapies.

Final Results

Human Peripheral Blood RNA-seq

RNA-seq resulted in a comprehensive characterization of the transcriptome in SLE finding a higher number of DEGs and eQTLs. We also used machine learning techniques in order to detect the smallest set of genes predicting SLE disease activity from the same dataset and found:

- Distinct transcriptome disturbances at inactive and active stages ("susceptibility and activity signature")
- The oxidative phosphorylation (mitochondrial hyperpolarization) pathway is implicated for the first time in the disease activity and severity
- Active nephritis has distinct transcriptome changes that reflect granulocyte activation, humoral immunity and the proteasome (all potentially drug-able targets)
- Organ involvement was predicted with high accuracy (accuracy=0.89, sensitivity=0.89, specificity=0.88 in the validation data) using 25 genes based on the elastic net generalised linear model. Among the 25 best predictors were MPO, ITGA3 and CD38.

– SLEDAI-2K could not be predicted with high accuracy (accuracy 0.75, sensitivity=0.79, specificity=0.67) using 50 genes based on the neural network model. Performance was still the same even when 1648 genes (after first feature selection step) were used as predictors of SLEDAI-2K.

Human HSC RNA-seq

– Transcriptome analysis of hematopoietic progenitors in the bone marrow of lupus vs healthy patients displayed enhanced proliferation/activation and myeloid skewing
– Comparable transcriptional profiles for both human and murine hematopoietic progenitors

Murine HSC RNA-seq

Bone marrow (BM) transcriptome analysis in lupus mice before and during the disease onset demonstrates:

– Hypercellular BM and HSCs
– Lupus bone marrow produces more myeloid progenitors
– Differentiation arrest in the myeloid level of hematopoietic tree by suppression of conventional regulators of granulopoiesis with alternative granulopoiesis pathway
– Transcriptome reprogramming reminiscent of "trained immunity"
– Aberrant myelopoiesis might contribute to persistent inflammation and flares

Lay Summary

SLE is the prototypic autoimmune disease and efforts are underway to better understand its cause and find new therapeutic approaches. To this end, we conducted a study where samples of SLE patients were analyzed to provide further insights into molecular (genomic) markers that predict the disease course, the response to different therapies and the damage caused by the disease to different tissues. For the first task, we used cutting edge biological and informatic approaches. Our identified novel genes and pathways that contribute to disease flares, severity and specific manifestations such as nephritis, which might be further explored as potential therapies. Following these analyses, we mapped a list of 15 genes that can predict major organ involvement (kidney, brain, etc.) in a given SLE patient, based upon the pattern of gene expression of these genes. Our analysis also confirmed the critical role of the immune system (e.g. over-expression of the antiviral interferon-alpha) in the causation of the SLE. These results could potentially assist the early diagnosis of SLE. Of interest, combining genetic variation (i.e. inter-individual changes in the DNA) with gene expression, we showed that besides immune cells in the blood, other organs such as the liver and the brain are involved in causing the disease.
In other studies run in parallel, we discovered that mouse and human bone marrow (the organ that makes the cells of the blood) in SLE produce more cells that cause inflammation. Moreover, a specific type of blood cells (neutrophils) is produced in a totally different fashion in SLE compared to healthy individuals. The comparison of hematopoietic progenitors between mice and humans provides a more clear picture of the biology of the lupus hematopoietic stem cell and a better understanding how bone marrow is involved in lupus.

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Project Team/Centres

- D Boumpas, University of Athens, GREECE (lead)
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REFRACT – Refractory lupus nephritis: a tissue-based pathophysiological approach

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 298.860
Project duration: 2016–2019

Project Url

www.foreum.org/projects/?id=125

Concept

Lupus nephritis (LN) remains a severe complication of SLE, impacting long-term survival and quality of life.
In REFRACT, we use kidney biopsies from LN patients in order to study molecular and cellular mechanisms underlying LN refractory disease.
One of the hypotheses to explain resistance to therapy is that the kidney itself is not only a target for autoantibodies but also acts as a true lymphoid organ that hosts immunologically relevant processes resulting in further local adaptive immune cell activation and differentiation.

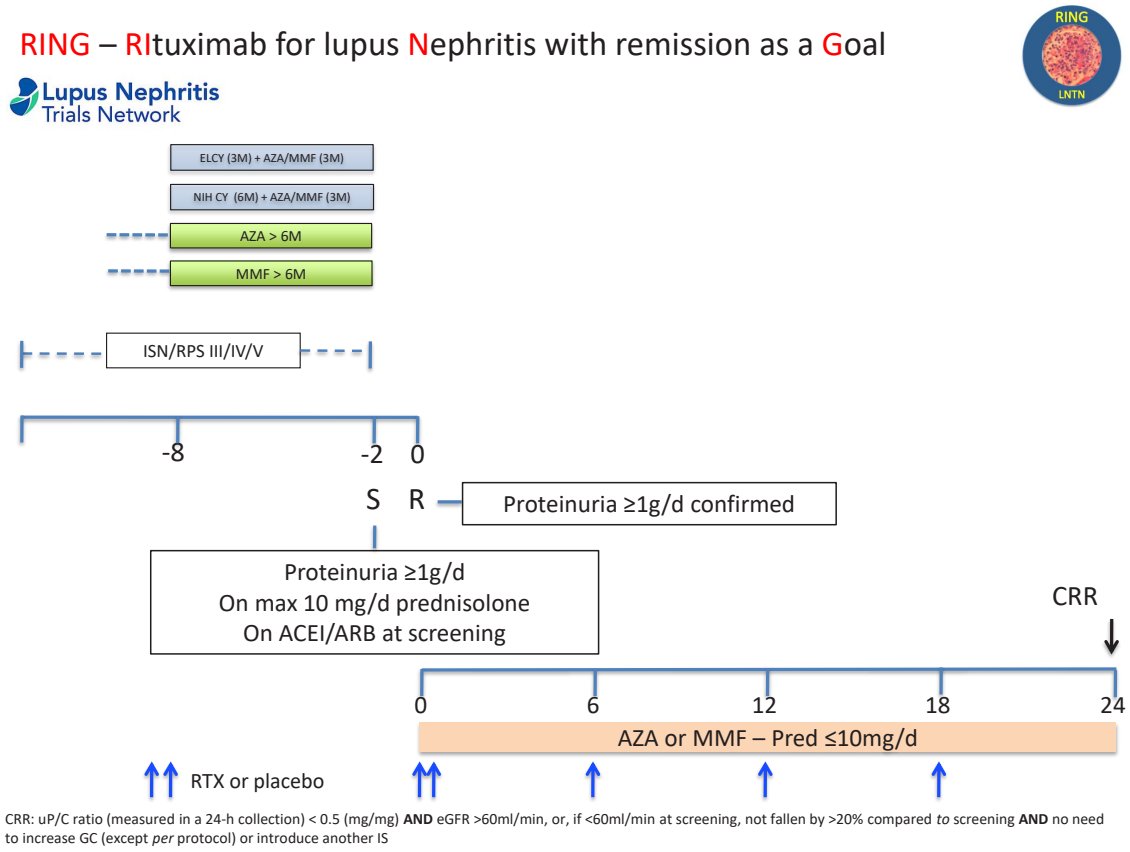
Objectives

The main objective of REFRACT is to unravel cellular and molecular mechanisms underlying renal injury in lupus nephritis (LN), in particular in cases not responding to standard of care immunosuppressive therapy, taking advantage of renal biopsy samples obtained within the frame of our investigator-initiated clinical trials.

Final Results

Our initial results, obtained in two independent sets of LN kidney biopsies, confirmed our hypothesis that intrarenal activation of adaptive immune effectors is associated with tubular damage and decreased renal function in LN (1).
Single cell gene expression profiling of (CD3-CD14-CD16-CD27+ CD38high) plasma cells (PC) was performed using kidney biopsies and blood from patients with a flare of class III/IV LN treated or not with mycophenolate mofetil (MMF). We obtained single kidney plasma cells that we compared with long-lived plasma cells from the bone marrow of heathy donors. In untreated patients, most PC were plasmablasts expressing multiple genes involved in cell division. By contrast, PC from the kidney of MMF-treated patients were over-expressing multiple plasmacell specific genes while not harboring a proliferative profile.
Similarly, single cell RNASeq and clonal expansion of CD8 T cells from kidney, urine and blood from patients with a severe flare of class III/IV LN showed the presence of clonally expanded CD8 T cells

with an activated phenotype. One of these clones displayed cytotoxic properties against cultured renal tubular cells that were abrogated after targeted deletion of the T Cell Receptor.



CRR: uP/C ratio (measured in a 24-h collection) < 0.5 (mg/mg) **AND** eGFR >60ml/min, or, if <60ml/min at screening, not fallen by >20% compared *to* screening **AND** no need to increase GC (except *per* protocol) or introduce another IS

Lay Summary

Lupus nephritis is a severe complication of systemic lupus erythematosus. It is caused by the deposition of anti-chromatin antibodies in the glomerular basement membrane, where they activate complement and recruit inflammatory cells, resulting in glomerulonephritis. Despite the use of corticosteroids and other immunosuppressive agents, 15% of lupus nephritis patients still develop end-stage renal disease after 10 years of evolution, a major issue in a population of mainly young women. The hypothesis underlying this research project is that the first systemic hit in lupus nephritis (deposition of autoantibodies) induces the recruitment in the kidney of a second wave of immune cells that play a predominant role in renal disease progression, independently of what happens at the systemic level. These cells cause persistent renal inflammation and lead to the accumulation of damage in a subset of patients, yet are not adequately tackled by present therapeutic strategies.

We performed in-depth molecular profiling studies on renal biopsies from patients with lupus nephritis, but also on kidneys from mice with lupus, at different stages of disease evolution. Our results confirmed our hypothesis:

accumulation of immune effectors in the kidney is toxic for renal resident cells. These cells are recruited and activated locally, and play an independent role in disease progression. Molecules they secrete (such as MMP7) can be measured in the serum, which provides clinicians with a new tool to evaluate disease severity. Our results open new avenues of research in the field of lupus nephritis, aiming at specifically interfering with intra-renal mechanisms of disease progression.

Patient Voice

SLE Europe was involved in the elaboration of this project and discussion of the results. Based on our data, SLE Europe and several European groups decided to apply together for follow-up grants, in order to keep characterize intra-renal immune effectors involved in disease progression in LN.

Publications

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Abstract

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Project Team/Centres

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- R van Vollenhoven, Karolinska Institutet, SWEDEN
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NET-ting the autoreactive B cell memory by therapeutically targeting the humoral autoimmunity in patients with SLE

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 300.000
Project duration: 2016–2019

Project Url

www.foreum.org/projects/?id=126

Concept

Patients with SLE typically have circulating autoantibodies against nuclear autoanti- gens, such as DNA, as a result of a humoral autoimmune response. The intension of this research project was to comprehensively study the humoral autoimmune response in SLE patients. To do so, an in-depth understanding of the origins of SLE-specific autoantibodies was established in a unique cohort of SLE patients who were treated with new biological therapies specifically targeted at the formation of autoantibodies.

Objectives

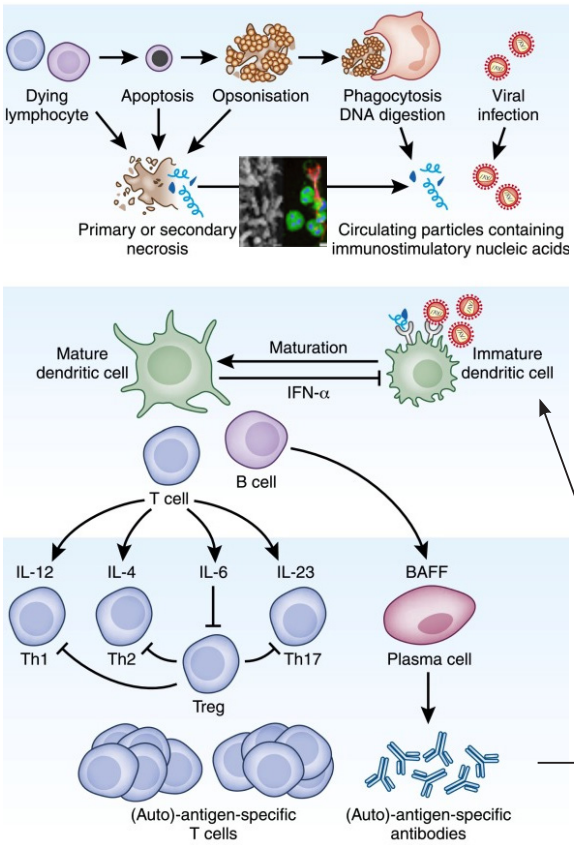
This consortium aimed at investigating the humoral autoimmune response in three different SLE patient cohorts treated with specific B cell-targeted therapies, i.e. Rituximab, Bortezomib and their combination.

The humoral autoimmune response was studied on different aspects in SLE patients before and after therapy, as follows:

- The induction of neutrophil extracellular traps to quantify the autoantigenic load of nuclear material;
- Degradation of neutrophil extracellular traps by SLE sera to quantify the autoantigenic load of nuclear material;
- Autoantibodies recognizing dsDNA, nucleosomes, histones, alphaenolase and C1q to quantify the humoral autoimmune products;
- Autoantigen-specific B cells recognizing dsDNA, nucleosomes, histones, alphaenolase and C1q to quantify the humoral autoimmune memory.

Final Results

The project validated novel assays for autoantigen monitoring in SLE patients in relation to treatment and clinical response. As such the researchers were able to combine autoantigen monitoring with autoantibody monitoring in SLE patients that were treated with RTX, RTX+BLM and BTZ, novel B-cell targeted strategies that differentially target B cell and plasma cell subsets. In a reverse



- Exposure of apoptotic/necrotic material
- Viral infections
- Neutrophil extracellular traps (NETs)

- Intolerant lymphocytes for nuclear antigens

- Development of auto antibodies against nuclear antigens

translational study, it was demonstrated that autoantibody levels decreased upon each treatment strategy, but the extent of targeted autoantibodies was most significant for RTX+BLM in a quantitative manner (reduced autoantibody repertoire) as well as a qualitative manner (reduced low, medium and highavidity anti-dsDNA autoantibodies). These effects were less pronounced for RTX only and not observed in BTZ-treated patients. Especially the reversal of anti-C1q to seronegative was associated with reduced IC-mediated inflammation and clinical disease activity, which happened most frequent after RTX+BLM, less after RTX and not after BTZ treatment. Lastly, hints of persisting
autoreactive memory in SLE patients were found despite a clinical response to B-cell targeted therapy. These observations collectively demonstrated the relevance of in-depth monitoring of the immunological effects of B-cell targeted strategies that have potential implications for the clinic.

Lay Summary

Patients with SLE typically have circulating autoantibodies against DNA as a result of a humoral (auto-)immune response. This research project has performed a comprehensive, reverse translational study to better understand the pathophysiology of the humoral autoimmune response in SLE patients. As such this project has monitored SLE-relevant autoantibodies as well as
autoantigens in 42 refractory SLE patients with renal involvement who were treated with experimental treatment regimens (i.e. rituximab, bortezomib or combination rituximab + belimumab). We found that although each treatment strategy reduced autoantibody levels there
were significant differences between these treatments and between patients. In general, achieving a reduction of autoantibody load, and ultimately achieving negativity of autoantibodies, and auto-

antigenic load was associated with beneficial clinical outcome and could be a key treatment target in SLE patients.
Altogether this project has established new ways to monitor autoantigens, autoantibodies and autoantibody-producing cells in SLE patients within the context of B-cell-targeted treatment strategies. As such, we have found hints of minimally residual autoimmunity after treatment despite clinical response to that treatment. Future studies should be aimed at applying these novel immunomonitoring tools to better detect en investigate MRA in SLE patients.

Patient Voice

The experimental nature of our research proposal limits the potential contribution of patient research partners. However, patient representatives were involved in the separate clinical trials at each collaborating centre which investigate therapeutic strategies that specifically target humoral autoimmunity. In addition, the project results are communicated to lupus patient organisations through lay summaries in patient magazines and presentations at meetings.

Publications

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Project Team/Centres

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Deciphering the role of neutrophil reactive oxygen species (ROS) in the SLE pathogenesis

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 150.000
Project duration: 2016–2019

Project Url

www.foreum.org/projects/?id=127

Concept

Neutrophils of SLE patients have reduced ability to form reactive oxygen species (ROS), which is associated with increased disease severity and organ damage. The researchers therefore wanted to investigate if this was due to genetic variants in the NCF1 gene.
ROS are important regulators of the immune system, and NCF1 gene variants were studied in relation to immunopathogenic mechanisms in SLE such as neutrophil extracellular traps (NETs), interferon (IFN) and presence of autoantibodies.

Objectives

A reduced ability of neutrophils to produce reactive oxygen species (ROS) has been associated with increased severity and organ damage in SLE. This fact prompted the researchers to ask if SLE patients are genetically predisposed to have low ROS production and how this would influence pathogenesis. The role of NCF1 gene variants in SLE was investigated and then related to disease phenotypes. Additionally, the researchers characterized the role of ROS and neutrophils in regulation of key immunopathogenic events in SLE, focusing on NETosis, type I interferon production and activation of adaptive immunity.

Final Results

In a first publication, a novel single nucleotide polymorphism (SNP) in the NCF1 gene was identified, resulting in a reduced function of the ROS-producing NADPH oxidase in neutrophils. The low-ROS-genotype was strongly associated with SLE, and within the SLE group patients with-low-ROS-genotype were diagnosed with SLE at a younger age. A total of 972 SLE patients, collected at four Swedish research centers, and 1016 healthy controls were genotyped in this study.
In a second manuscript (submitted for publication), an in-depth analysis of the effect of NCF1 genotype on several aspects of SLE was performed including neutrophil extracellular traps (NETs), serum interferon levels, autoantibody profiles and the presence of secondary antiphospholipid syndrome (APS).

The conclusion was that SLE patients with low-ROS-genotype have neutrophils with decreased ability to release NETs, higher serum IFN levels and presence of antiphospholipid antibodies. The low-ROS-genotype was also strongly associated with secondary APS.

Lay Summary

In patients with the autoimmune disease systemic lupus erythematosus (SLE), the immune system is over active, leading ta chronic inflammation and damage ta organs and tissues. This research project investigated a gene variant in a gene that is important for the production af oxygen radicals. Oxygen radicals have dual roles in the immune system and both enhance and dampen inflammation. The results showed that this gene variant leads to a lower production af oxygen radicals and that it is more common in SLE patients compared to healthy controls.

Patient Voice

Close collaboration with patients who took part in the projects.

Publications

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Project Team/Centres

– A Bengtsson, Lund University, SWEDEN (lead)
– A Blom, Lund University, SWEDEN
– N Heegard, Statens Serum Institut, DENMARK
– M Herrmann, Friedrich-Alexander University Erlangen, GERMANY
– R Holmdahl, Karolinska Institutet, SWEDEN
– F Ivars, Lund University, SWEDEN
– S Jacobsen, Copenhagen University, DENMARK

2015

Call for research proposals in the area of Spondylarthritis (SpA)

SpA comprise one of the most common of the inflammatory arthritidies in Europe, and consist of a spectrum of inflammatory diseases that affect primarily the peripheral joints and spine but can also involve other tissues like skin, gut and eyes. As such, SpA can mediate a substantial impact on those affected. Pathogenesis of SpA is imperfectly understood.

The call was launched in **2015**, and out of 16 letters of intent 3 projects were selected for funding:

- Role of Mucosal Antigens for the Pathogenesis of Spondyloarthritis
- Can Inertial Movement Sensors (IMUs) provide a valid and reliable way of measuring Spinal Mobility in Axial Spondyloarthritis (axSpa): a Clinimetric Evaluation
- Mechanistic studies of IL-17 versus TNF blockade in spondyloarthritis (SpA)

Role of mucosal antigens for the pathogenesis of Spondyloarthritis (SpA)

Project Lead

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Funding and Timeline

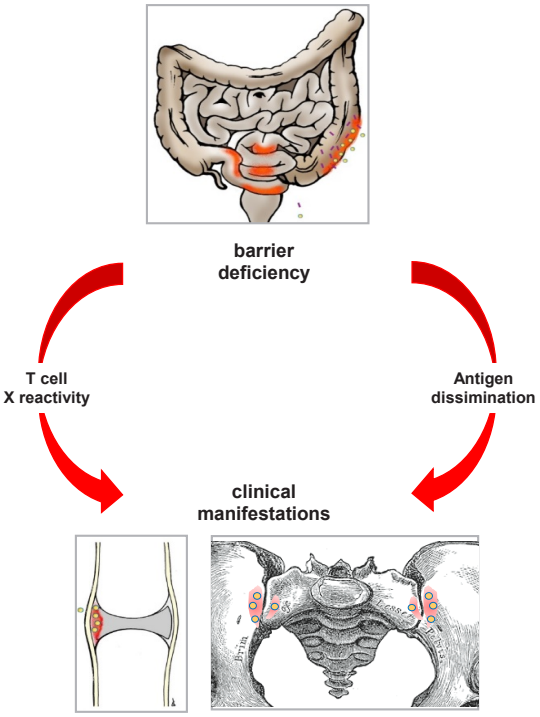
FOREUM research grant: EUR 300.000
Project duration: 2017–2020

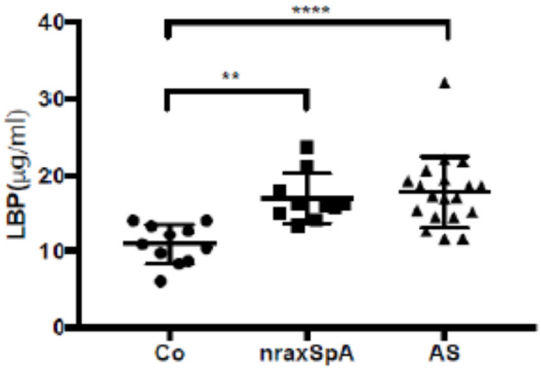
Project Url

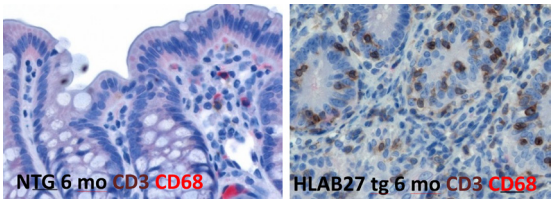
www.foreum.org/projects/?id=128

Concept

This project aims to improve the understanding of what causes and stimulates inflammation in SpA patients. Specifically, the project tests the hypothesis that the barrier function of the gut is impaired in SpA patients, which could promote the entry of bacterial components from the gut into the body. Such bacterial components can activate directly or indirectly pathogenic immune responses.







Final Results

Soluble biomarkers indicative of bacterial translocation in SpA

- lipopolyaccharide binding protein (LBP) is upregulated in axial SpA patients compa- red to controls.
- there is no difference according to disease state (i.e. nr-axial SpA and AS) and disease activity (i.e. BASDAIhigh and BASDAI low).
- In patients from GIANT cohort (Belgium) LBP serum levels were significantly higher in patients with chronic gut inflammation compared to patients without gut inflammation.

Cellular Biomarkers

In transcriptome analysis of CD14+ monocy- tes
957 Affymetrix probe sets were differen- tially
expressed between axSpA patients and HC
(Berlin). Coexpression analysis with refe- rence
transcriptomes found an overlap of these IDs
with late myeolopoesis and responses trigged
by G-CFS mobilization and by LPS and TNF suggesting changes in myelopoiesis.

Mechanism of translocation in HLA-B27 tg rats

- HLAB27tg rats spontaneously develop coli- tis as indicted by infiltration of CD3+ T cells.
- mRNA expression data of colon epithelial cells suggest dysregulation of tight junction molecules in HLA-B27tg rats. These differences could not be verified on protein level suggesting that translocation may occur despite unimpaired expression of tight junction molecules

Patient Voice

In the project patient-reported disease activity scores, patient reported functional scores as well as the patient acceptable symptom state (PASS) score are included to determine relations of translocation biomarkers to these patient reported outcome parameters.

Publications

EULAR Abstracts

2019

- FRI0360:
  Analysis of blood monocyte transcriptomes and bone marrow samples of patients with Axial Spondyloarthritis reveals their changes related to activation and Myelopoesis

http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

- U Syrbe, Charité, GERMANY (lead)
- M Breban, Université Versailles Saint-Quentin, FRANCE
- P Jacques, University Hospital Gent, BELGIUM
- D Elewaut, Center for Inflammation Research, BELGIUM

Can inertial movement sensors (IMUs) provide a valid and reliable way of measuring Spinal Mobility in Axial Spondylo-arthritis (axSpa)? A clinimetric evaluation

Project Lead

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Funding and Timeline

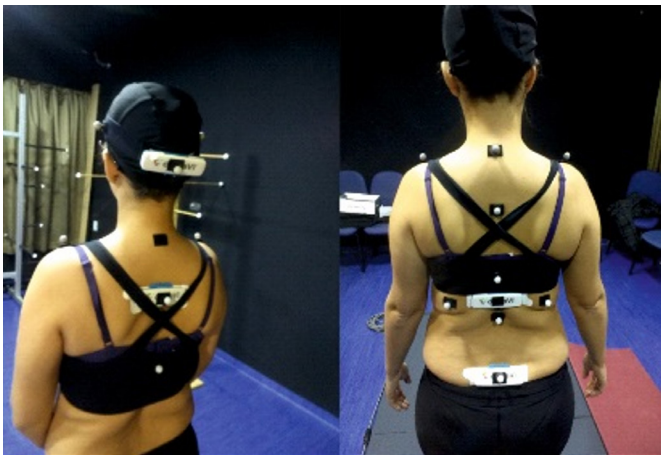
FOREUM resarch grant: EUR 270.000
Project duration: 2017–2021

Project Url

www.foreum.org/projects/?id=129

Concept

The main objective of this project is to test the accuracy and reliability of electronic sensors in measuring spinal movement and to develop a new outcome tool for spinal mobility. Current methods rely on tape measures/goniometers and are not reliable/responsive enough to evaluate new treatments for axSpa. We have now completed three validation studies – a reliability study, a criterion validity study comparing sensor accuracy to the UCOTrack© gait lab system, and an exploratory ambulatory study.
A multi-centre study is underway testing the responsiveness of our IMU spinal mobility index alongside MRI pre/post biologics. We have also developed a smartphone app to allow researchers to use these electronic spinal mobility tools.



Final Results

One of our early studies led by Philip Gardiner (Londonderry, UK) involved testing 40 patients with axSpA to find out if measurements of spinal mobility using the ViMove© sensor (DorsaVi) were reliable. The results confirmed that sensor measurements remain the same no matter which therapist was doing the test or if the test was repeated a week later. This is the first such study to demonstrate the reliability of spinal rotation tests, previously thought to be a weakness of older IMU technology. A composite score (IMU-ASMI) was developed, combining all of the planar movements in the cervical and lumbar spine to generate a new and reliable outcome score for spinal mobility.

The other core validation study led by Juan-Luis Garrido-Castro and Eduardo Collantes-Estevez (Cordoba, Spain) involved testing the sensor measurements against an accurate electronic motion detection system. Motion capture systems are widely regarded as the gold standard for measuring body movement accurately. This team had previously developed and validated the UCOTrack© motion capture system specifically to measure spinal mobility in axSpA. Their study established that ViMove© sensor tests have a high degree of accuracy, comparable to that of their motion capture system. A strong correlation was found between spinal mobility tests and structural damage scores based on x-rays. Their study also provided validation of a new sensor positioning protocol which includes the thoracic segment of the spine, particularly relevant for axSpA clinical studies.

The third study led by Fiona Wilson (Dublin, Ireland) recruited another group of 40 axSpA patients to test whether or not sensor tests of movement and function can be carried out accurately at home. In this study, patients carried out movement tests in clinic with and without supervision and then again at home using recorded video instructions. Patients then continued to wear them for up to 24 hours alongside completing some questionnaires and a symptom/activity diary. During this period they carried out several standardised functional tests. This study has demonstrated for the first time that unsupervised range of movement tests can be carried out accurately without supervision by following video instructions. These results open up new possibilities both for clinical research and for patient self-management.

The fourth pilot study in Cordoba tested the sensitivity to change of sensor tests against the UCOTrack system in 20 patients before and after starting biologic drugs. This study has shown that both the UCOTrack system and the IMU based spinal mobility score have significantly greater responsiveness to change compared to BASMI. This was part of a three-centre observational study using concurrent spinal mobility tests and MRI outcome scores led by Pedro Machado (London, UK) including Londonderry as a third study site. This MRI study is still underway, but we are confident that it will provide further information on the relationship between changes in MRI inflammation and changes in spinal mobility scores.

Lay Summary

Several meetings have been held in Londonderry with a patient interest group both at the design stage and when results have become available. Letters have been sent out to all participants in our reliability study to inform them of the results.

In Spain, a first meeting has been held for patients at initial stages. Some preliminary results have been presented to representatives of CEADE in their annual congress. During the national congress of family medicine for chronic patients (SEMERGEN 2018), patients and members of our research group presented an oral communication titled “keep moving: devices for evaluation and monitoring of mobility in rheumatic patients.”, which won the prize of the best oral communication of the congress.

Patient Voice

Patient research partners in Spain and the UK have attended workshops to discuss the project. Patients are also involved in the design process for the smartphone application. The feedback from patients involved in home measurement testing has been very positive.

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EULAR & ACR Abstracts

2018

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– SAT0659: Applying the OMERACT truth filter to a new electronic spinal mobility index for Axial Spondyloarthritis based on inertial measurement unit (IMU) sensors
– SAT0327: Segmental relationship between mobility, structural damage and disease activity in Axial Spondyloarthritis

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– Juan L. Garrido-Castro, Inmaculada Concepcion Aranda-Valera, Philip Gardiner, Pedro Machado, Joan Condell, Cristina Gonzalez-Navas, Eduardo Collantes Estevez. Responsiveness of spinal mobility measurements in axial spondyloarthritis using conventional and advanced metrology: a pilot study. Ann Rheum Dis, volume 80, supplement 1, year 2021, page 740
http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

– P Gardiner, Western Health and Social Care Trust, UNITED KINGDOM (lead)
– E Collantes Estevez, Fundacion para la Investigacion Biomedica de Córdoba, SPAIN
– J L Garrido Castro, University of Cordoba, SPAIN
– J Condell, University of Ulster, UNITED KINGDOM
– P Machado, University College London, UNITED KINGDOM
– F Wilson, Trinity College Dublin, IRELAND

Mechanistic studies of IL-17 versus TNF blockade in Spondyloarthritis (SpA)

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 300.000
Project duration: 2016–2019

Project Url

www.foreum.org/projects/?id=130

Concept

Both TNF and IL-17A are pivotal pathogenic cytokines in SpA. In this project, we hypothesize that blockade of IL-17A and TNF affects different pathophysiological pathways.

Objectives

We aim to identify specific biological effects by systematic translational comparison of IL-17A versus TNF blockade in SpA patients using combined molecular, cellular and imaging approaches with the overall goal to establish a path towards stratified medicine.

Goals/Milestones

- Kick-off meeting in March 2017
- First-patient-in in the 4 key studies (tissue immunopathology, cytokine profiles, PET-CT, micro-CT)
- Last-patient-out in the 4 key studies
- Analysis of the individual data sets
- Integration of the different data sets
- Completion of the publications and reports

Interim Results

Molecular and cellular pathways of inflammation

We examined gene expression profiles in biopsies retrieved from SpA patients before and after aIL_17A treatment (Fig. 1). Pathway analysis revealed that genes down-regulated upon the treatment genes were significantly enriched in biological processes related to immune and inflammatory responses and leukocyte activation and trafficking. Of interest, aIL-17 treatment did not affect expression of TNF. Surprisingly, the overlap in regulated genes between aIL-17A and aTNF treatments was rather small. Commonly and uniquely modulated by each treatment pathways are under investigation.

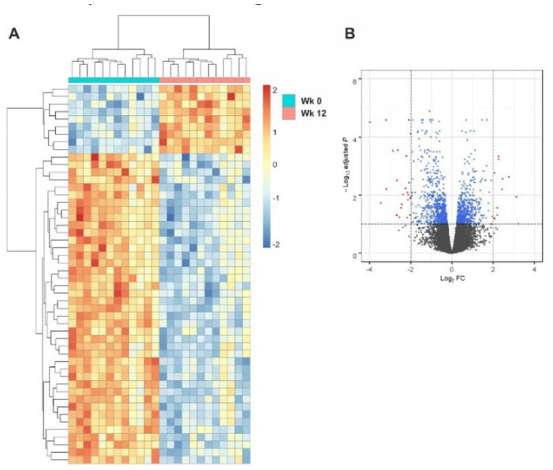
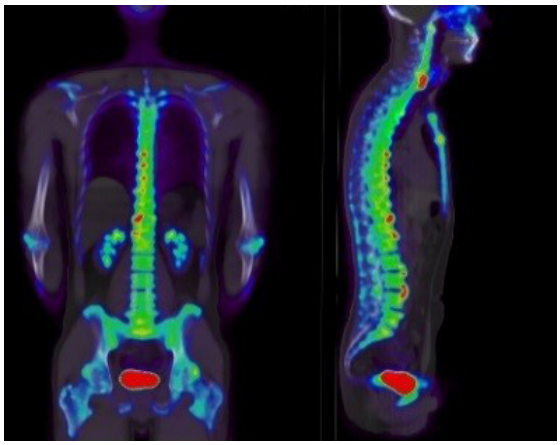
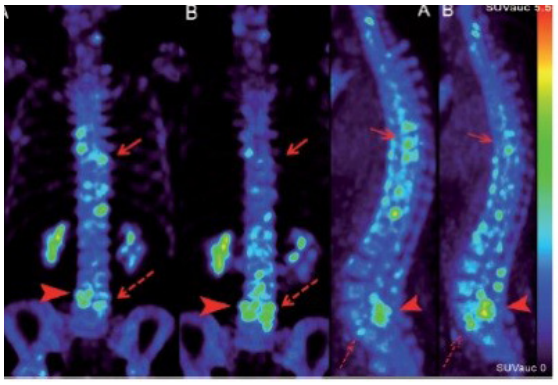


Figure 1. A. Hierarchical cluster analysis of differential expressed genes showing the log2 expression of the 100 most significantly regulated by the treatment with secukinumab genes. Normalized gene expression levels across samples are shown. B. A volcano plot. Red plots represented significant (p<0.01) and remarkable (fold change >4) differentially expressed genes.





Leukocytes cytokines responses

Analysis via whole-blood stimulation systems revealed that aTNF therapy induces profound changes in patients' innate immune response. Modular transcriptional repertoire analysis showed that aTNF therapy affects immune responses via direction of macrophage polarization and the inhibition of TNF- and IL-1-dependent feed-forward loops of NF-kB activation. aTNF treatment did not affect the IL-6/Th17 arm of the immune response, supporting the importance of IL-17 blockade as an alternative treatment for SpA. Furthermore we found that high expression of genes associated with leukocyte invasion/migration and inflammatory processes at baseline predisposes to favorable outcome of aTNF therapy, while high-level expression of cytotoxic molecules is associated with poor therapeutic responses to TNF-blockers.

Microarchitectural peripheral bone changes

IL-17A blockade led to significant improvement of signs and symptoms of PsA. MRI synovitis (P = 0.034) and signal in PDUS (P = 0.030) significantly decreased after 24 weeks of treatment. Bone erosions and enthesiophytes did not show any progression, and structural integrity and functional bone strength remained stable.

Axial inflammation and new bone formation

[18F]-fluoride PET-CT scans have been performed in 10 AS patients before and 12 weeks after aTNF treatment, and in 5 AS patients starting aIL-17A treatment (baseline). After aTNF treatment quantitative [18F]-fluoride uptake decreased significantly in the costovertebral and SI joints of clinical responders (p<0.03), in contrast to non-responders (Fig. 2). In the secukinumab cohort, at least one PET-positive lesion per patient was found in the cervical, thoracic and/or lumbar spine at locations such as anterior corners of vertebrae and in bridging syndesmophytes (Fig. 3).

Final Results

Inflammation and structural changes of the bone, including new bone formation, are key pathologic processes in SpA. TNF and IL-17 are key pathogenic cytokines in SpA and may act differently on these processes. Our studies showed that TNF inhibitors(i) had a more profound effect on systemic immune responses than IL-17i, which suggests that IL-17i may have a lesser impact on immune cells but more on non-immune cells or that IL-17i mainly affect cells in target tissues. Analysing synovial tissue, we observed that L-17i modulated multiple pathways related to new bone formation. Investigating systemic bone changes, we observed similar effects of both treatments on volumetric bone mineral density, stiffness and failure load estimates. In addition, PET-CT analysis demonstrated comparable efficacy of TNFi and IL-17Ai on inhibition of axial new bone formation. In summary, we showed that, in part, both inhibitors show an overlapping effect on systemic bone changes but differentially impact systemic immune responses.

Lay Summary

Clinical trials performed over the past decade have demonstrated that monoclonal antibodies targeting the proinflammatory cytokine interleukin (IL)-17A are effective in treating axial spondyloarthritis (axSpA). As a result, patients affected by axSpA now have the choice between Tumor necrosis factor alpha (TNF)-blockers and IL-17A inhibitors. The availability of two different drugs benefits patients, but it also raises important questions concerning their work mechanisms. The main goal of this research project was to understand how these two drugs act in patients. Our results demonstrate that, in part, TNFi and IL-17 show an overlapping effect on systemic bone changes and new bone formation, but differentially impact systemic immune responses. Particularly, anti-TNF therapy has major effects on systemic immune responses with potential implications for increased susceptibility to infectious microorganisms. In contrast, IL-17 inhibitors had a lesser impact on systemic immune responses than TNF-blockers, suggesting that they may act mainly on non-immune cells and/or directly in inflamed tissues. These data are supported by the modulation of disease-relevant immune and stromal pathways in the targeted tissues (synovium and skin) in response to IL-17Ai.

Patient Voice

A lay advisory board of patients will be instrumental in the interpretation of the data, in particular in addressing the question if and how the anticipated biologic profiles can be applied in a useful way to stratify individual patients or patient groups to aTNF versus aIL-17A treatment.

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Project Team/Centres

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- L Rogge, Institute Pasteur Paris, FRANCE
- C van der Laken, VU Medisch Centrum, THE NETHERLANDS
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2015

Call for research proposals in the area of Registers (RMD)

There is increasing interest in providing the maximal benefit for the Rheumatic and Musculoskeletal Diseases (RMD) community from the extraordinary resources contained in the large clinical registers that have been gathered over recent decades. Added value may include, for example, assessment of safety across different modes of action, real world comparison with outcomes from randomised trials, and integration of data from different registers or countries to address questions difficult to study in individual registers.

The call was launched in **2015**, and out of 19 letters of intent 4 projects were selected for funding:

- A pan-Nordic Rheumatology Register network
- IMPROVEMENT (improving the outcome in myositis spectrum diseases: core set variables harmonization and use from children to adulthood
- European Network of Pregnancy Registers in Rheumatology (EuNeP)
- Comorbidities in Juvenile Idiopathic Arthritis

Pan-Nordic RA register network

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 297.685
Project duration: 2017–2020

Project Url

www.foreum.org/projects/?id=116

Concept

Data from clinical practice is needed to understand the safety, effectiveness, and optimal use of available and emerging treatment options for inflammatory arthritis. We have demonstrated the value of our individual registers in assessing the safety and effectiveness of TNF-inhibitors in RA, AS/SpA and PsA. Many outstanding issues, particularly in AS/SpA and PsA, can, however, only be addressed through collaboration across registers. The Nordic countries have similar healthcare systems and other national registers that can be linked together. ARTIS (Sweden), DAN-BIO (Denmark), NOR-DMARD (Norway), ROB-FIN (Finland) and ICEBIO (Iceland) represent some of the largest registers of inflammatory arthritis and their therapies.

Final Results

- A standing collaborative network of clinical rheumatology researchers across the five Nordic countries was established, in the fields of RA, AS/SpA and PsA.
- In Sweden, Denmark, Norway, Finland and Iceland, linkages of the clinical register data to other national registers have been extended (SE, DK, FI and ICE) or performed for the first time (NO). This project is one of the first to employ export of patient-level data from these registers for central analysis, for all countries.
- In each of the specific projects performed, variables and definitions have been harmonised. One key learning so far is that this harmonisation is not only of technical nature, but also of contextual nature.
- Various analytical approaches have been employed, spanning from distributed (local) analyses using common data models and analysis protocols, via central analyses of (harmonised) pooled data, to federated analyses using local and harmonised data but a common central analysis-protocol.
- This project has successfully launched projects in different areas, see the list of abstracts/publications for projects.

Lay Summary

The scientific output from our project comes in the format of abstracts and original scientific reports. For the scientific community, the primary sharing of results is thus via scientific journals and international conferences.

For the research community, networking and building a Nordic network of the next generation of rheumatology researchers has been an integral part of our project. In this regard, our biannual project meetings have typically attracted some 20 participants, many of whom are junior scientists, and the "communication of results" has been in the format of communication of the possibility to work with, and also how to work with, collaborative studies centered on clinical issues addressed via clinical registers.

For the clinical profession and patients, we think that our results, particular those regarding the effectiveness and safety of drugs, should best be implemented as part of national treatment guidelines for the diseases concerned. Science is much about incremental knowledge gains. Each of the Nordic countries has its own algorithm for how these guidelines are updated. We regard this process as particularly important, as the guideline updates may systematically factor in all available new evidence. Beyond this, the project website has attracted attention (as measured by contacts taken with the project PI) from various of stakeholders, including patient organisations, the pharmaceutical industry, and e-health companies.

Publications

- Chatzidionysiou K, Aaltonen K, Nordström D, et al. SAT0669 How do we use biologics in patients with a history of malignancy? an assessment of treatment patterns using scandinavian registers. Annals of the Rheumatic Diseases 2017;76:1027. https://ard.bmj.com/content/76/Suppl_2/1027.2
- Glintborg B, Chatzidionysiou K, Askling J, et al. THU0361 Prescription patterns of biological disease modifying drugs and biosimilars in ankylosing spondylitis – a collaboration between biological registers in the five nordic countries. Annals of the Rheumatic Diseases 2017;76:341-342. https://ard.bmj.com/content/76/Suppl_2/341.2
- Hellgren K, Dreyer L, Arkema EV For the ARTIS Study Group, For the DANBIO Study Group, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Annals of the Rheumatic Diseases 2017;76:105-111. https://ard.bmj.com/content/76/1/105
- Hetland M, Østergaard M, Askling J, et al. FRI0450 Commonalities and differences in data collection across european spondyloarthritis registries. Annals of the Rheumatic Diseases 2017;76:656-657. https://ard.bmj.com/content/76/Suppl_2/656.3
- Jørgensen T, Dreyer L, Guðbjörnsson B, et al. FRI0518 Prescription patterns of tumour necrosis factor inhibitor and ustekinumab in psoriatic arthritis: a nordic population-based cohort study. Annals of the Rheumatic Diseases 2017;76:686. https://ard.bmj.com/content/76/Suppl_2/686.2
- B Glintborg, U Lindström, K Aaltonen, EK Kristianslund, B Gudbjornsson, K Chatzidionysiou, J Askling, D Nordström, ML Hetland, D Di Giuseppe, L Dreyer, LE Kristensen, TS Jørgensen, K Eklund, G Grondal, S Ernestam, J Joensuu, MRK Törmänen, H Skydsgaard, J Hagfors, TK Kvien, E Lie, K Fagerli, AJ Geirsson, H Jonsson, SA Provan, NS Krogh & LTH Jacobsson (2018) Biological treatment in ankylosing spondylitis in the Nordic countries during 2010–2016: a collaboration between five

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– Chatzidionysiou K, Hetland ML, Frisell T, et al. Opportunities and challenges for real-world studies on chronic inflammatory joint diseases through data enrichment and collaboration between national registers: the Nordic example. RMD Open 2018;4:e000655. doi: 10.1136/rmdopen-2018-000655.
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– Grøn KL, Arkema EV, Glintborg B The ARTIS Study Group, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. Annals of the Rheumatic Diseases 2019;78:320-327
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EULAR Abstracts

2017

- SAT0669: How do we use biologics in patients with a history of malignancy? An assessment of treatment patterns using Scandinavian registers.

2018

- OP0324: Risk of serious infections in rheumatoid arthritis patients treated with abatacept, rituximab and tocilizumab in denmark and sweden

2019

- OP0236: Similar one-year treatment retention of originator and biosimilar Etanercept. Results of a Nordic collaboration including 1015 patients with Spondyloarthritis
- FRI0082: Effectiveness of TNF inhibitors vs. non-TNF inhibitors (Abatacept, Tocilizumab and Rituximab)
- FRI0377: Identical two-year treatment retention of originator and biosimilar Infliximab. Results of a Nordic collaboration including 1319 patients with Spondyloarthritis
- SAT0365: Secular changes in patients with psoriatic arthritis starting first and subsequent course of biologic therapies – inflammatory hallmarks of lesser prominence: a Nordic population-based cohort study
- OP0005: Incidence of overall and site-specific cancers in TNF inhibitor treated patients with psoriatic arthritis: a population-base cohort study from 4 Nordic countries
- OP0261: Risk of neurological adverse events during tumour necrosis factor inhibitor treatment for arthritis: a population-base cohort study from DANBIO AND ARTIS

2020
- THU0394: Comparison of treatment retention of secukinumab and TNF-inhibitors in psoriatic arthritis. Observational data from a Nordic collaboration.
- FRI0275: One-year treatment retention of secukinumab versus tumor necrosis factor inhibitors in Spondyloarthritis. Results from Five Nordic biologic registries
- FRI0534: Patient-reported measures of disease activity in rheumatoid arthritis vary across the Nordic countries, results from a Nordic collaboration

2021
- OP0210: Pregnancy outcomes in relation to disease activity and anti-rheumatic treatment strategies in women with rheumatoid arthiritis – a matched cohort study from Sweden and Denmark K. Hellgren, A. E. Secher, B. Glintborg, A. Lilleoere Rom, B. Gudbjornsson, B. Michelsen, F. Granath, M. L. Hetland FOREUM acknowledgment
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ACR Abstracts

2017
- Glintborg B, Lindström U, Aaltonen K, Kristianslund EK, Gudbjornsson B, Chatzidionysiou K, Askling J, Nordström D, Lund Hetland M, Di Giuseppe D, Dreyer L, Jørgensen TS, Kristensen LE, Eklund K, Grondal G, Ernestam S, Joensuu J, Kvien TK, Lie E, Fagerli KM, Geirsson AJ, Jonsson H, Jacobsson LT. First Line Biological Treatment in Ankylosing Spondylitis, Prescription Rates, Baseline Demographics and Disease Activity. a Collaboration between Biological Registers in the Five Nordic Counties. Arthritis Rheumatol. 2017; 69 (suppl 10).
- Lederballe Grøn K, Arkema EV, Glintborg B, Askling J, Lund Hetland M. Baseline Characteristics and Rates of Hospitalized Infections in Patients with Rheumatoid Arthritis Treated with Non-TNF Inhibitors in Denmark and Sweden [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10).
  https://acrabstracts.org/

Project Team/Centres

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IMPROVEMENT – Improving the outcome in myositis spectrum diseases: core set variables harmonization and use from children to adulthood

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 300.000
Project duration: 2017–2020

Project Url

www.foreum.org/projects/?id=117

Concept

Myositis spectrum disorders (MSDs) inclu- de a wide range of conditions deeply affecting patients' prognosis and quality of life. Health problems related to MSDs include not only muscle (myositis), but also joints (arthritis/arthralgias), skin (typical cuta- neous lesions) and lungs (Interstitial lung disease).

The timing of onset of different MSDs'findings is generally variable and the risk of a not proper patients' classification is very high. The myositis expert community recognizes that other steps are necessary for the clarification of different MSD patterns (in both adulthood and childhood), instrumental and laboratory tests to apply and best treatment options.

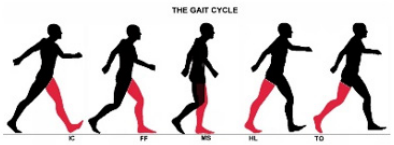
These steps are mandatory to improve patients' survival and quality of life, paying special attention to a very vulnerable period for pediatric patients carrying a chronic illness: the transition to an adult age.

Objectives

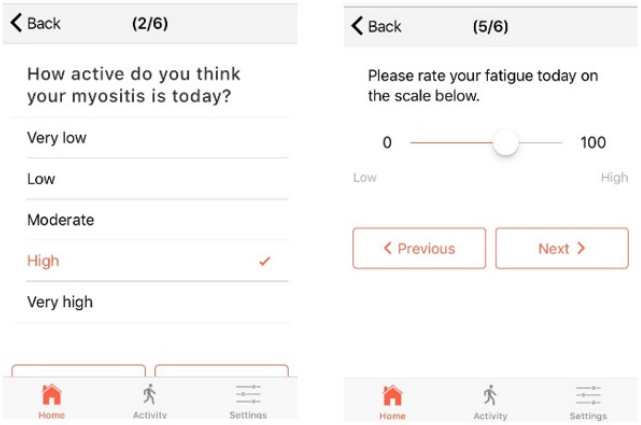
To harmonize the international MSDs registries EUMYONET and AENAS with national registries and hospital records; to create a longitudinal database to improve patients' follow-up, treatment and prognosis.

- Define and reach consensus among clinicians and patients on a minimum core set of myositis spectrum disease organ-specific measures to address unmet needs, further characterise disease subsets, evolution and treatment, building on existing work in AENEAS and Euromyositis
- To facilitate collection of longitudinal outcome data by harmonization of national registers
- To collect existing patient-recorded outcome data more frequently using smartphone applications for aiding patient engagement and clinical practice/research. To use this technology for streamlining the transition between adolescent and adult care in MSDs through harmonized data collection from adult and paediatric clinicians
- To facilitate standardized data capture from electronic hospital records by technical integration and initiate a common technological platform for the Euromyositis and AENEAS registers

MyoPAD gait sensor



MyoPAD smartphone-based app interface



Goals/Milestones

Y1: Teleconferences and ethical approvals, data collection harmonization and core set measure to share with other centers/groups, development of technologies, pilot testing of technologies in 12 sites, definition/agreement of core set, submission of LOINC definitions Y2: Clinical data collection from registers &analysis of shared data. Y3: Rolling out of technologies in other Research Partner sites, collection of longitudinal smartphone app data, collection of longitudinal clinic based PROM data, research partner meeting of group data shared analysis. Successful implementation of core data into an existing platform, Proof of concept that remote data system can be completed longitudinally

Interim Results

- A list of applicable measures has been obtained from the systematic literature review and from the analysis of existing datasets addressed to different myositis conditions. A survey will be send to selected centers/people, in order to understand which variables can be easily collected and for identify potentially lacking aspects.
- The process of harmonization will start after the definition of clinical variables that should be collected.
- A bespoke smartphone-based app has been designed that allows collection of myositis-specific patient reported outcome measurements at high frequency (up to daily).

Final Results

A myositis core-set variables were identified and an international database activated.
A method for continuous disease activity assessment has been developed.

Lay Summary

We defined a core variable set to to facilitate myositis research, a free to use database, and used an app to monitor disease remotely.

Patient Voice

Patients are involved in every phase of the project. Participants are invited through myositis centres and through already existing registries for myositis. Associazione Nazionale Malati Reumatici (ANMAR), Italy is involved as a patient organisation.

Publications

- Cavagna L, et al. Influence of Antisynthetase Antibodies Specificities on Antisynthetase Syndrome Clinical Spectrum Time Course. J Clin Med 2019;8:2013. https://www.mdpi.com/2077-0383/8/11/2013

EULAR Abstracts

2019

- FR0352: Differences in Antisynthetase Syndrome definition and related diagnostic performance. A systematic literature review informing the new ACR/EULAR classification criteria
- FR0335: Prognostic impact and clinical characteristics of interstitial pneumonia with autoimmune features in a multidisciplinary setting
- SAT0271: Relationship between Anti-mda5 antibodies and cancer: retrospective analysis of an international and multidisciplinary cohort
- SAT0286: Evaluation of swallowing in patients with Idiopathic Inflammatory Myopathies

http://scientific.sparx-ip.net/archiveeular/

ACR Abstract

2020

- Number 1061: Daily Myositis Symptom Changes Collected via a Smartphone-Based App Are Associated with Flare Occurrence – Providing Evidence of Potential Digital Biomarkers https://acrabstracts.org/abstract/daily-myositis-symptom-changes-collected-via-a-smartphone-based-app-are-associated-with-flare-occurrence-providing-evidence-of-potential-digital-biomarkers/

Project Team/Centres

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- L Wedderburn, University College London, UNITED KINGDOM
- M Gonzalez-Gay, Hospital Universitario Marqués de Valdecilla, SPAIN
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European network of pregnancy registers in rheumatology (EuNeP)

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 298.000
Project duration: 2017–2021

Project Url

www.foreum.org/projects/?id=118

Concept

The goal for all patients with inflammatory rheumatic disease (IRD) is to live a normal life without limitation in daily routine, including family planning and having children. Pregnancy counselling for these patients could be improved if better information on pregnancy outcomes and drug safety were available. However, robust data on pregnancies in women with IRD and on the safety of a substantial number of drugs taken before or during pregnancy are limited. Especially regarding rare outcomes or diseases, open questions can only be clarified by collaborative analysis of several databases. To foster joint approaches, pregnancy registers in France, Germany, Norway and Switzerland with prospective and multicentre data collection initiated the European Network of Pregnancy Registers in Rheumatology (EuNeP).

Rhekiss

RePreg
Reproduction and Pregnancy

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

NTNU
Faculty of Medicine
and Health Sciences
Department of neuromedicine
and Movement Science

NTNU
Department of neuromedicine
and Movement Science

Objectives

– To evaluate the nature and extent of existing data
– To define a common core data set as primary outcome
– To perform and publish a first joint data analysis on pregnancy outcomes as secondary outcome
– To enable newly setup pregnancy registers to use the methods and approaches already developed

Goals/Milestones

Year 1: Meetings of representatives from existing pregnancy registers in Europe; collection, evaluation and data analyses, definition of the first research question.
Year 2: Publication on structure and content of all registers, preparation of first data analysis, first steps for building up new pregnancy registers, preparation of a second publication, preparation of first joint data analysis.
Year 3: Publication of first joint data analysis, covering pregnancy outcomes under different exposures. Support of new registers, depending on the availability of funding for these registers in individual countries

Interim Results

Data items and methods of data collection in the participating registers were evaluated and summarized. Patient perspectives regarding pregnancy registers and their needs for information were identified with a survey. The core data set was developed by a EULAR task force and was published as a EULAR recommendation. Currently, the joint data analysis is being performed with the aim to analyse adverse pregnancy outcomes in women with axial spondyloarthritis.

Final Results

– A collaborative network of experts who already run pregnancy registers in Europe was established
– The nature and extent of the existing data as well as the method of data collection was evaluated and compared
– A common core data set with a minimum of data items to be collected by pregnancy registers in rheumatology was defined and published as EULAR recommendation
– A methodological approach for joint data analyses was developed including data harmonisation
– A first joint data analysis with pooled data of all registers on pregnancy outcomes in women with axial spondyloarthritis was performed

Lay Summary

The aim of this project was to bring together experts from across Europe who run pregnancy registers in rheumatology. Four European registers collaborate in the European Network of Pregnancy Registers in Rheumatology (EuNeP). Those registers are designed to collect information of patients with rheumatic diseases that wish to conceive, during and after pregnancy in order to gain more knowledge about how the rheumatic disease influences pregnancy and vice versa.
We have explored the structure of the collaborating registers, and how data is collected within registers. We have also collected information on the number and characteristics of patients with

different rheumatic diseases enrolled in the registers so far. The exploration of the existing data was very important and a prerequisite for the project's aim to analyse data from different registers together. Building upon this, a so called "core data set" for registers and observational studies that collect data of pregnant women with rheumatic diseases was defined. The "core data set" is like a template containing a list of variables that should be collected in the same way by all pregnancy registers for rheumatic diseases. This will help to harmonize data across registers and make them more comparable to facilitate joint data analyses.
One of the analyses in our network was a collaborative analysis using data from all four registers. Data from pregnant women with axial spondyloarthritis were analysed. It was investigated, how many babies were born at term and how the health of these neonates was. In addition, disease activity during the course of pregnancy was investigated. Using the data of all four EuNeP registers together increased the strength of the results.

Patient Voice

Patient participation is crucial to explore which questions regarding pregnancies are the most relevant for the patients. Two female patients (one with rheumatoid arthritis and one with systemic lupus erythematosus) are involved in identifying research questions of interest and in defining the core data set, with specific focus on the patient-reported outcomes.

Publications

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– Meissner Y., Fischer-Betz R., Andreoli L., Costedoat-Chalumeau N., De Cock D., Dolhain RJEM, Forger F., Goll D., Molto A., Nelson-Piercy C., Ozdemir R., Raio L., Rodriguez-Garcia S. C., Sciascia S., Wallenius M., Zbinden A., Zink A. and Strangfeld A. EULAR recommendations for a core data set for pregnancy registries in rheumatology. Ann Rheum Dis 2021;80(1):49-56.
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https://ard.bmj.com/content/79/Suppl_1/881

EULAR Abstracts

2018

– FRI0601: The nature and extent of data items collected across European pregnancy registers – first results of the European network of pregnancy registers in rheumatology (EUNEP)

2019
– OP0326: Development of a standardized minimal core data set for pregnancy registers in rheumatology – results of a EULAR task force
2020
– FRI0558: Pregnancy outcomes in patients with axial spondyloarthritis – a first joint analysis of a European collaboration of pregnancy registers
– AB0804: Pregnancy and psoriatic arthritis: A systematic literature review of disease activity and adverse pregnancy outcomes
2021
– AB0472: Pregnancy in women with psoriatic arthritis: A systematic literature review of disease activity and adverse pregnancy outcomes
http://scientific.sparx-ip.net/archiveeular/

ACR Abstracts

2018
– AB2426: Defining a Standardized Core Data Set for Pregnancy Registers in Rheumatic Diseases – an European Approach Abstract 2426. Arthritis Rheumatol. 2018; 70 (suppl 10). Accessed March 28, 2019.
https://acrabstracts.org/abstract/defining-a-standardized-core-data-set-for-pregnancy-registers-in-rheumatic-diseases-an-european-approach/
2020
– AB1498: Pregnancy outcomes in patients with axial spondyloarthritis – a first joint analysis of a European collaboration of pregnancy registers. Arthritis Rheumatol. 2020; 72 (suppl 10).
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Project Team/Centres

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Comorbidity in Juvenile Idiopathic Arthritis (JIA)

Project Lead

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Funding and Timeline

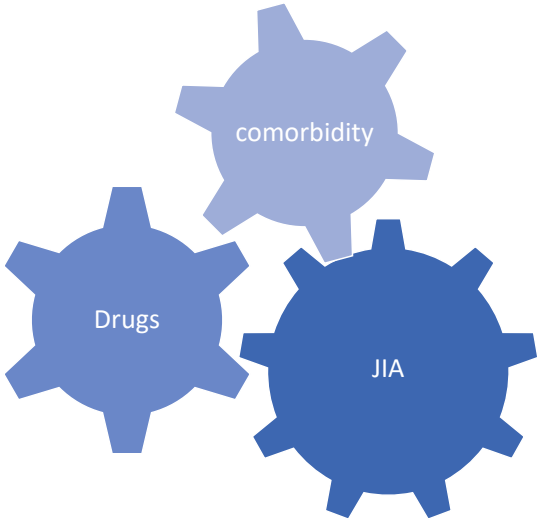
FOREUM research grant: EUR 300.000
Project duration: 2017–2020

Project Url

www.foreum.org/projects/?id=119

Concept

Comorbidity can be defined as the presence of two disorders or more occurring at the same time in a single patient. Children with chronic diseases such as JIA can develop complications of the disease itself, a new disease or drug related side effects that have a significant impact on the quality of life. In this project we want to study all significant events occurring before or after the onset of arthritis.



Objectives

The purpose of this project is to study the presence of comorbidity and symptoms developing under therapy of patients followed in the 3 largest JIA registries in Europe. We assume that comorbidity in a disease such as JIA significantly increases the burden of the disease and thus has major effects on quality of life.

Goals/Milestones

Months 1-3: check if ethical consent is indeed still valid. Contact patient organisations
Months 1-12 Baseline demographics. Start meeting with the 3 registries and patients to define methodologies of data collection, and priorities in analysis of the observed comorbidities. Write Knowledge Translation and Exchange plan. Define division of tasks and responsibilities
Months 13-18: collect rheumatological core outcome data and comorbidities
Month 18-24: analysis of observed variables, detect differences and limitations of present data.
Month 24: follow up meeting, with discussion of observed comorbidities and possible correlations. Prepare recommendations when needed. Contact adult registries.
Month 24-30: statistical analysis, monitoring of comorbidities (not at the sites).
Months 24: Plan future design of studies on the impact on quality of life. Meet with adult registries and agree on joint strategies
Month 36: Meeting with stakeholders

Interim Results

Three registries have identified the occurrence of selected comorbidities at registration and final follow-up. Furthermore, incidences on methotrexate and biologic therapy have been established. Currently, the registries are cooperating in the validation of a clinical prediction model for chronic uveitis.

Final Results

- Demographics of JIA patients. Metrics to measure success: compare with 2015 demographics, % recruited at onset of JIA, % recruited at start of therapy (MTX, or Biologic).
- Description of comorbidities, frequency of follow up, degree of missing data, analysis of correlation with multipara meters such as medication, disease duration, subtype.
- Prepare an evaluation plan for further analysis of the severity of these comorbidities and their impact on the quality of life
- Establish durable collaboration between the registries

Lay Summary

Firstly the group investigated the comorbidities in eight-thousand children and young people with JIA across three large registers. This analysis is the first and largest to investigate the occurrence of four important comorbidities and the role of anti-rheumatic drugs. Combined, these three registries represent one of the largest collection of cases of JIA worldwide and offer a unique setting for future JIA outcome studies. Rates of comorbidities were similar, although varicella vaccination in populations impacted comparability of varicella infections. With this article the group showed how JIA registers can collaborate.
The most common comorbid condition in JIA patients is an eye inflammation also called uveitis (JIA-U). While screening for JIA-U is of utmost importance, there is no international consensus on screening frequency and criteria, leaving clinicians with a large gap open for their own interpretation. Individual risk estimates for developing JIA-U were still unavailable to date. An individualized prediction model for JIA-U for clinical application WAS developed. With this it is possible to provide a guidance tool for clinicians and patients and parents to individually estimate the probability of uveitis occurring in newly diagnosed JIA patients. This article is free available online A clinical

prediction model for estimating the risk of developing uveitis in patients with juvenile idiopathic arthritis - PubMed (nih.gov) . Subsequently a model that predicts the risk for uveitis for an individual JIA patient after 2, 4 and 7 years of disease duration was developed. The robustness of this model was confirmed by using the data of our 3 separate cohorts in FOREUM. Risk estimates following our prediction model could be used to inform patients/parents and provide guidance in choice of uveitis screening frequency and arthritis drug therapy with the possible extra aim of preventing the onset of uveitis.
Furthermore it was looked into the role of immunosuppressive drugs in the development of inflammatory bowel disease (IBD) in children with JIA. Although it is rare, it occurs more often than in the general pediatric population and has a significant negative impact on quality of life. The group analysed the largest group of IBD development in JIA patients with 48 included cases. It was found that the 48 IBD cases in JIA are associated with enthesitis-related arthritis, a positive family history of autoimmune disease(s) and etanercept therapy (regardless if combined with methotrexate). Given the results of this study, it might be recommended to use adalimumab instead of etanercept as the biologic of first choice in ERA patients with a positive family history of autoimmune disease(s).
A durable collaboration between the registries was established and it is expect more studies to be performed together.

Patient Voice

ENCA (European Network for Children with Arthritis) representatives are part of our steering committee. ENCA has parents trained in research, epidemiology and health care amongst its members. Patient involvement through ENCA can help us analysing the relevance of these complications for the disease burden. They will be actively involved in ranking the importance of the observed comorbidities/ complications and thus in discussing priorities for further research.

Publications

– Van Straalen JW, Kearsley-Fleet L, Klotsche J, De Roock S, Minden K, Heiligenhaus A, Hyrich KL, De Boer JH, Lamot L, Olivieri AN, Gallizzi R, Smolewska E, Faugier E, Pastore S, Hashkes PJ, Herrera CN, Emminger W, Consolini R, Wulffraat NM, Ruperto N, Swart JF. Development and external validation of a prognostic prediction model for chronic uveitis in juvenile idiopathic arthritis. Arthritis & Rheumatology (IF=15.483 in 2021). 23 August 2022
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– Van Straalen JW, de RoockS, Giancane G, Alexeeva E, Koskova E, Mesa-del-Castillo P, Zulian F, Civino A, Montin D, Wulffraat NM, Ruperto N, Swart JF. Prevalence of familial autoimmunity in juvenile idiopathic arthritis: results from the international Pharmachild registry. Pediatr Rheumatol. (IF=3.413 in 2021) Nov 2022 20:103.
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- Kearsley-Fleet L, Klotsche J, van Straalen JW, Costello W, D'Angelo G, Giancane G, Horneff G, Klein A, Láday M, Lunt M, de Roock S, Ruperto N, Schoemaker C, Vijatov-Djuric G, Vojinovic J, Vougiouka O, Wulffraat NM, Hyrich KL, Minden K, Swart JF. Burden of comorbid conditions in children and young people with juvenile idiopathic arthritis: a collaborative analysis of 3 JIA registries Rheumatology (Oxford). (IF=7.046) 2021 Oct 6;keab641. doi: 10.1093/rheumatology/keab641.
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- van Straalen JW, Giancane G, Amazrhar Y, Tzaribachev N, Lazar C, Uziel Y, Telcharova-Mihaylovska A, Len CA, Miniaci A, Boteanu AL, Filocamo G, Mastri MV, Arkachaisri T, Magnolia MG, Hoppenreijs E, de Roock S, Wulffraat NM, Ruperto N, Swart JF.
- A clinical prediction model for estimating the risk of developing uveitis in patients with juvenile idiopathic arthritis.
- Rheumatology (Oxford). (IF=7.046) 2021 Jun 18;60(6):2896-2905. doi: 10.1093/rheumatology/keaa733.
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EULAR Abstracts

2019

- OP0058: Development of inflammatory bowel disease during treatment with Etanercept in patients with Juvenile Idiopathic Arthritis; Roline Krol, Joost F. Swart, Gabriella Giancane, Sytze De Roock, Troels Herlin, Pavla Dolezalova, Helga Sanner, Gordana Susic, Flávio R. Sztajnbok, D Maritsi, Tamas Constantin, V Vargova, Sujata Sawhney, Marite Rygg, Sheila Knupp D.E. Oliveira, Marco Cattalini, Ellen Norda, Claudia Magalhaes, Alberto Martini, Nico Wulffraat, Nicolino Ruperto

http://scientific.sparx-ip.net/archiveeular/

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- C Schoemaker, Dutch JIA parent organisation, THE NETHERLANDS

2016

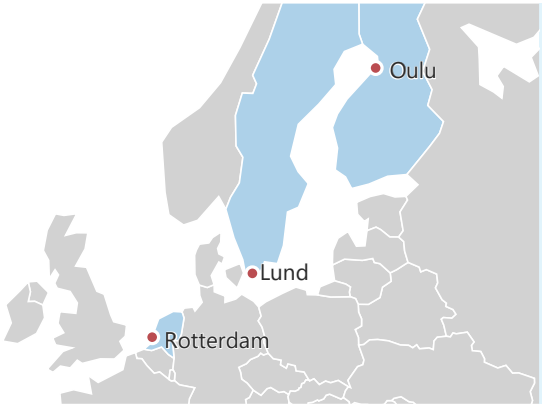
Call for research proposals in the area of Preclinical Phases of RMDs

There is a high interest in defining the earliest stages of Rheumatic and Musculoskeletal Diseases (RMDs). Early recognition of the initial phases of RMDs is important for scientists, clinicians and patients for gaining a better insight into the pathogenesis of these diseases and facilitating the development of timely interventions or even preventive approaches. In the last years it is increasingly recognized that characteristic molecular and cellular processes antedate the clinical phases of individual RMDs.

The call was launched in **2016**, and out of 20 letters of intent 4 projects were selected for funding:

- A prediction score for individuals at risk for Systemic Lupus Erythematosus (SLE) by integrating clinical, serologic and transcriptomic data
- Development of new tools for prediction and prevention of RA (PREDICT RA)
- Novel Treatment Targets in Early-stage Osteoarthritis
- ENVI-RA: Impact of ENVIronmental factors and gene-environment interaction in the development of Rheumatoid Arthritis

Novel treatment targets in early-stage OA



Project Lead

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Funding and Timeline

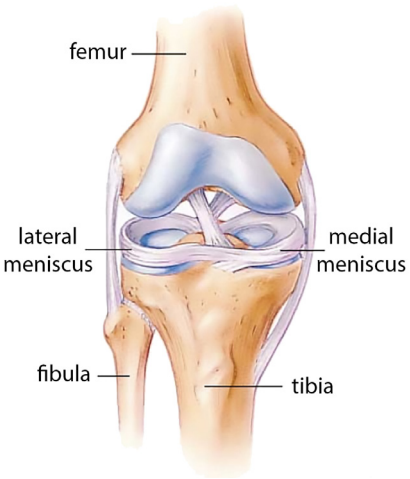
FOREUM research grant: EUR 600.000
Project duration: 2018–2020

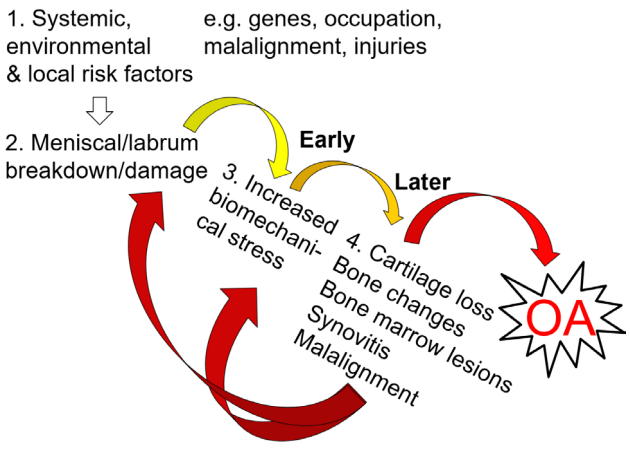
Project Url

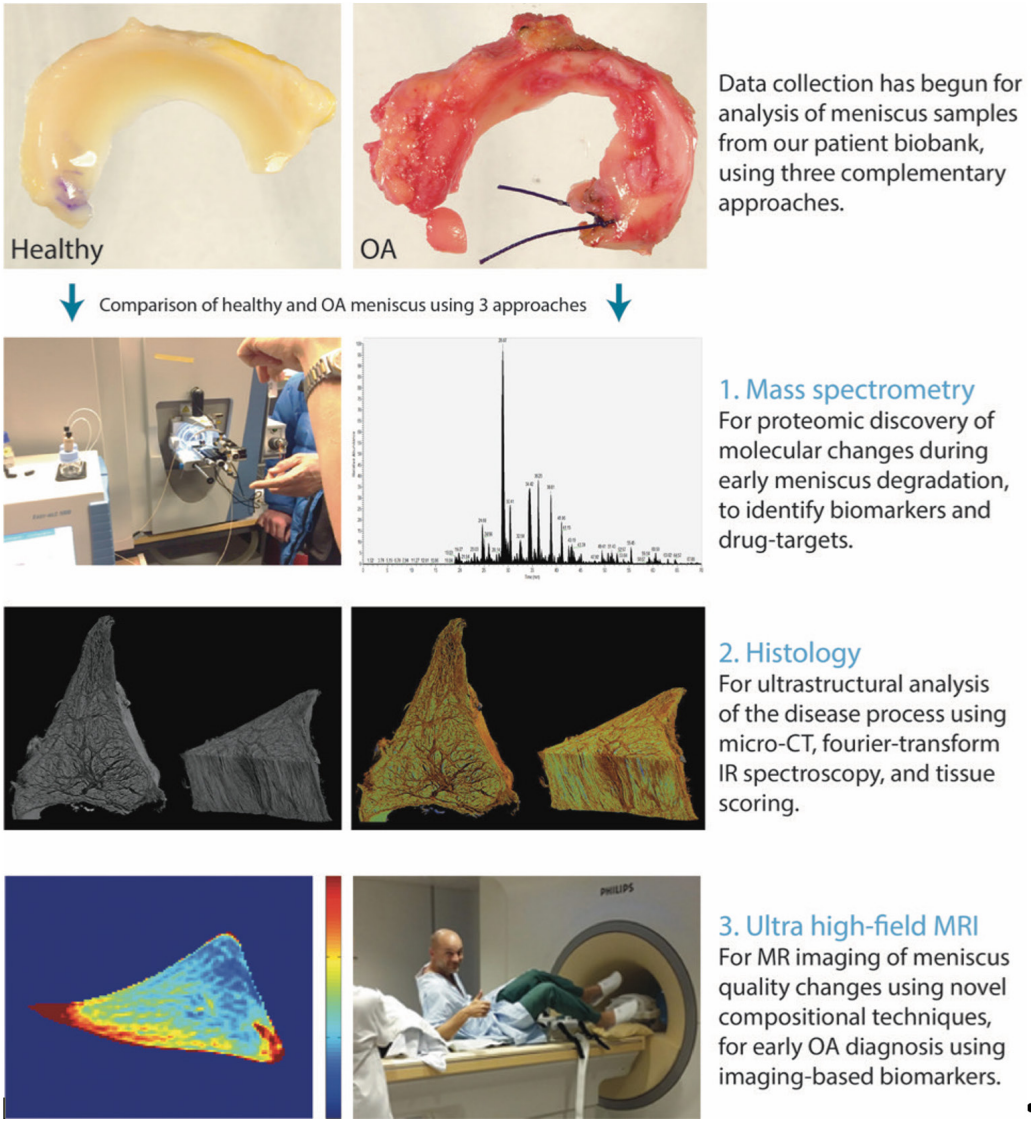
www.foreum.org/projects/?id=111

Concept

Osteoarthritis (OA) is a degenerative joint disease and a major cause of musculo-skeletal pain in the middle-aged and elderly. However, there is currently no disease modifying treatment for OA.
This research focuses on meniscal breakdown, one of the most common causes of OA. Our work shows that meniscus tears are most often part of a slowly developing degenerative disease, not usually the outcome of acute knee injury as previously considered. It was found that these early meniscus tears are strongly linked with the development of knee OA in the future. Detection and prevention of meniscal breakdown could therefore be a promising new target for early diagnosis and treatment of OA.







Final Results

Goals for the project's final report:

1. Report on a) differences between the proteomes in the joints of healthy donors vs. OA patients, and b) identification of OA biomarker candidates

Building on the previous work of characterise the proteomes of healthy human articular cartilage as well as the meniscus, the project team conducted proteomic analyses of the changes in the meniscus during OA. Comparing OA menisci with healthy menisci, it was found that OA menisci showed increased abundance of proteins involved in tissue matrix breakdown (e.g. MMP), but also of some inhibitors of breakdown (e.g. TIMP1). This suggests simultaneous activation of both catabolic (i.e. breaking down) and anabolic (i.e. building up) processes in the OA meniscus that warrants further study.

Additionally a study was conducted comparing the proteomes of the synovial fluid (the lubricating fluid in the knee) from healthy donors, early-stage OA patients, and late-stage OA patients. This

study shows a global increase in protein interplay in early OA, which is lost in late-stage OA. This novel finding suggests that the assessment of global proteomic activity may be a promising approach for early OA diagnosis in the future.

2. Report on histology and micro-CT imaging of the meniscus and possible associations with proteomic/MRI changes

A method was developed for 3D imaging of ex vivo tissue using micro-computed tomography (µCT), and compared structural features of healthy and OA menisci. Using 3D µCT imaging, we could visualise OA-related changes in surface morphology, collagen organization, and calcifications in the meniscus, similar to conventional histology. However, µCT offers the added benefit of 3D visualization over a larger tissue volume, to provide comprehensive knowledge of the changes in tissue structure and organization during meniscal degeneration in early OA.
Futhermore, an analysis of mineral crystal thickness in the cartilage/bone interface of healthy vs. OA knees using a nanometer-scale imaging approach called micro-focus small-angle X-ray scattering (µSAXS) was conducted. Using this technique, it was found that crystal thickness in calcified cartilage was greatest in late-stage OA knees, suggesting that articular cartilage may be stiffer in OA patients than in healthy subjects. Analyses of healthy and OA menisci using Raman spectroscopy, a technique that reveals biochemical changes in tissues that are injured or diseased were conducted. These studies offer insight into the microscale structural and molecular changes in knee tissue during OAs pathogenesis.

3. Findings from cross-sectional (baseline) 7T readings

Over the course of this project, the project team developed protocols to observe changes in the "quality" of meniscus tissue using state-of-the-art 7T MRI using ex vivo meniscus tissue and validated this approach by comparing the 7T MRI results with µCT and conventional histology analyses of the same tissue. Recruitment is now underway for long-term longitudinal imaging of knees of healthy volunteers and patients at risk for OA using our 7T MRI scanner. So far, 11 healthy volunteers and 1 patient at risk for OA were imaged.

Lay Summary

The work so far has enabled to characterise the protein composition of the healthy meniscus, and observe its changes during OA. Also the composition of synovial fluid, which is a lubricating fluid in the joint, between OA patients and healthy individuals were compared. The analysis shows changes in global protein co-expression profiles at different stages of OA, which warrants further study as a possible early molecular feature of OA progression.
Simultaneously, methods to observe structural changes in the "quality" of the meniscus, through MRI imaging of tissue samples extracted from patients undergoing knee-replacement surgery for OA, or from knee-healthy donors who are deceased were developed. These protocols were adapted to longitudinally image patients at risk for OA using an advanced MRI scanner. Over the coming years, this will allow the project team to observe the earliest tissue "quality" changes in patients during OA's development, which may lead to improved diagnostics for OA in the future.

Publications

– Proteomic characterization of the normal human medial meniscus body using data-independent acquisition mass spectrometry.

Folkesson E, Turkiewicz A, Rydén M, Hughes HV, Ali N, Tjörnstrand J, Önnerfjord P, Englund M. J Orthop Res. 2020;38(8):1735-1745
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- Proteomic comparison of osteoarthritic and reference human menisci using data-independent acquisition mass spectrometry. Folkesson E, Turkiewicz A, Ali N, Rydén M, Hughes HV, Tjörnstrand J, Önnerfjord P, Englund M. Osteoarthr Cartil. 2020;28(8):1092-1101.
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- Three-dimensional microstructure of human meniscus posterior horn in health and osteoarthritis.
Kestilä I, Folkesson E, Finnilä MA, Turkiewicz A, Önnerfjord P, Hughes V, Tjörnstrand J, Englund M, Saarakkala S. Osteoarthr Cartil. 2019;27(12):1790-1799.
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Olsson E, Folkesson E, Peterson P, Önnerfjord P, Tjörnstrand J, Hughes HV, Englund M, Svensson J. Osteoarthr Cartil. 2018;27(3):476-483
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- Differential protein expression in human knee articular cartilage and medial meniscus using two different proteomic methods: a pilot analysis.
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EULAR Abstracts

2019

- THU0415: Exploratory protein profiling of human synovial gluid from knee osteoarthritis
- FRI0509: 3D microstructure of intact and osteoarthritic human meniscus using micro-computed tomography

2020

- OP0184: Risk of comorbidities following incident clinician-diagnosed knee or hip osteoarthritis: a registry-based cohort study
http://scientific.sparx-ip.net/archiveeular/

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ENVI-RA: Impact of ENVIronmental factors and gene-environment interaction in the development of Rheumatoid Arthritis

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 100.000
Project duration: 2018–2021

Project Url

www.foreum.org/projects/?id=137

Concept

Rheumatoid arthritis (RA) is a complex di- sease in which environmental agents are thought to interact with genetic factors to trigger auto-immunity.

The contribution of genetic factors to RA susceptibility is well recognized. The heritability of anticitrullinated protein auto- antibody (ACPA)-positive and ACPA-negative RA implicates different genes [2]. To date, the main known genetic factoris HLA, in particular the HLA-DRB1-shared epitope (SE) alleles, that predispose much more strongly to ACPA. However, the concordance for RA between monozygotic twins is only 15.6%. Thus, environment plays a crucial role in the development of the disease as well.

Final Results

Achievements in the E3N cohort (including ~100.000 women):

- A study was performed to validate RA cases:
  This study enabled us to detect a large number of RA cases in a large general population prospective cohort of women:
  964 RA cases were validated, including 698 incident cases. This will allow investigating a large number of potential endogenous and exogenous risk factors of RA in women.
- Chronic diarrhea was identified as associated with an increased risk of developing RA in ever-smokers.
  These data fit with the multistep preclinical scheme of RA where interaction between different events, such as intestinal dysbiosis and smoking, occurs at an early stage to promote emergence of autoimmunity, followed years after by clinical disease.
- Some hormonal factors are associated with the risk of RA
  Early age at first pregnancy and early menopause were associated with an increased risk of RA, whereas RA was inversely associated with exposure to progestogen in perimenopause.
- Mediterranean diet was associated with a decreased risk of RA in ever-smoking women
  High adherence to a MD could reduce RA risk in ever-smoking women. Further studies are needed to confirm our findings.

Lay Summary

Various lifestyle and environmental factors to identify if they might increase the risk of RA.
From a previous work one of the cohort of this project, we identified passive smoking in childhood as being associated with an increased risk of RA, in future active smokers.
Analyses form this project provided interesting results on the following factors:

- The findings showed that transit disturbance, such as chronic diarrhoea, might also increase this risk.
- Hormonal factors were studied and early menopause was identified as being associated with an increased risk of RA in women, whereas a high lifetime exposure to oestrogen seems to decrease this risk.
- Also it was found that dietary factors such as adherence to Mediterranean diet (rich in vegetables, olive oils and omega 3) might protect for developing RA in non-smokers.

This project continues with new research focus.

Publications

- Nguyen Y, Salliot C, Gusto G, Descamps E, Mariette X, Boutron-Ruault MC, Seror R. Improving accuracy of self-reported diagnoses of rheumatoid arthritis in the French prospective E3N-EPIC cohort: a validation study. BMJ Open. 2019 Dec 16;9(12):e033536. doi: 10.1136/bmjopen-2019-033536. PMID: 31848174; PMCID: PMC6937120. https://bmjopen.bmj.com/content/bmjopen/9/12/e033536.full.pdf
- Salliot C, Nguyen Y, Gambaretti J, Gelot A, Mariette X, Boutron-Ruault MC, Seror R. THU0686 Early menopause and/or duration of menopausal hormonal treatment may increase the risk of rheumatoid arthritis in tobacco exposed women: results of the E3N cohort. Annals of the Rheumatic Diseases 2019;78:639-640. Doi: 10.1136/annrheumdis-2019-eular.6599 https://ard.bmj.com/content/78/Suppl_2/639.2
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- Nguyen Y, Salliot C, Gelot A, Gambaretti J, Mariette X, Boutron-Ruault MC, Seror R. Mediterranean Diet and Risk of Rheumatoid Arthritis: Findings From the French E3N-EPIC Cohort Study. Arthritis Rheumatol. 2020 Sep 9. doi: 10.1002/art.41487. Epub ahead of print. PMID: 32909390. https://onlinelibrary.wiley.com/doi/full/10.1002/art.41487
- Review article: Salliot C, Nguyen Y, Boutron-Ruault MC, Seror R. Environment and Lifestyle: Their Influence on the Risk of RA. J Clin Med. 2020 Sep 26;9(10):3109. doi: 10.3390/jcm9103109. PMID: 32993091; PMCID: PMC7601336. https://www.mdpi.com/2077-0383/9/10/3109/htm
- Salliot C, Nguyen Y, Gusto G, Gelot A, Gambaretti J, Mariette X, Boutron-Ruault MC, Seror R. Female hormonal exposures and risk of rheumatoid arthritis in the French E3N-EPIC cohort study. Rheumatology (Oxford). 2021 Feb 6:keab101. doi: 10.1093/rheumatology/keab101. Epub ahead of print. PMID: 33547777. https://pubmed.ncbi.nlm.nih.gov/33547777/

Project Team/Centres

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Development of new tools for prediction and prevention of RA (PREDICT RA)

Project Lead

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Funding and Timeline

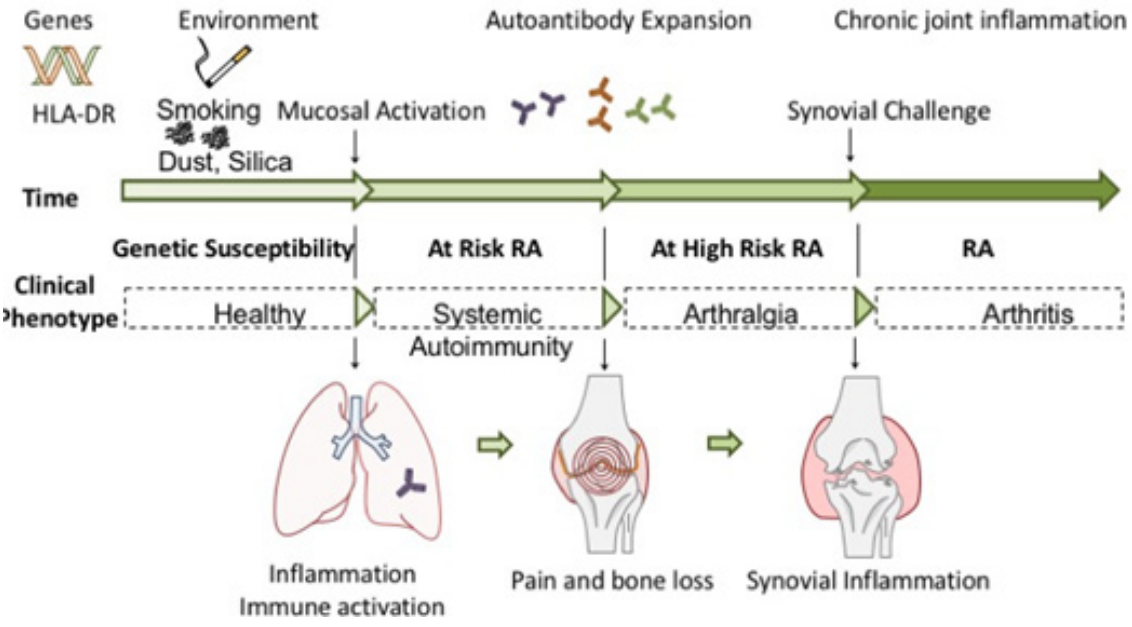
FOREUM research grant: EUR 300.000
Project duration: 2018–2021

Project Url

www.foreum.org/projects/?id=112

Concept

Rheumatoid Arthritis (RA) is such a disease where the abnormal body's reaction leads to formation of antibodies. We and others have shown that the lungs and the oral cavity (that are exposed to smoking and others pollutants) might be the starting point for the body's reactions in RA.
We are developing better tools to identify these persons, such as e-health web based questionnaires. We study how environmental factors interact with the body tissues (lungs and oral cavity) to give rise to disease-associated antibodies and how these antibodies contribute to pain and bone loss. This will allow each person to get more insights into the risk of developing RA and in what one can do self to minimise it.



Objectives

To characterize the mechanisms responsible for antibody production at mucosal sites (lung and oral mucosa) in order to identify novel mucosal biomarkers that predict RA development.

Interim Results

A common protocol for including individuals and collecting samples, harmonized between centers, have been worked out. So far we have included 39 subjects.

Patient Voice

A specific part of the budget (10%) is dedicated to facilitate patient partners participation to meetings and other research activities.
Patient research partners have given feedback and suggested changes have been integrated. Specifically, patient partners will be involved in developing tools for measuring patient relevant outcomes (pain), for improving recruitment (e-health tools to facilitate access to rheumatology units), for risk communication tools and for implementation of life-style changes (such as apps for quitting smoking and motivate for increased physical activity).

Publications

– K Eriksson, G Fei, A Lundmark, D Benchimol, L Lee, Y Hu, A Kats, S Saevarsdottir, A Catrina, B Klinge, A F. Andersson, L Klareskog, K Lundberg, L Jansson, T Yucel-Lindberg. Periodontal Health and Oral Microbiota in Patients with Rheumatoid Arthritis. Clin Med. 2019 May 8;8(5). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572048/
– Akilan Krishnamurthy, A. Jimmy Ytterberg, Meng Sun, Koji Sakuraba, Johanna Steen, Vijay Joshua, Nataliya K. Tarasova, Vivianne Malmström, Heidi Wähämaa, Bence Réthi and Anca I. Catrina. Citrullination Controls Dendritic Cell Transdifferentiation into Osteoclasts. J Immunol June 1, 2019, 202 (11) 3143-3150;
DOI: https://doi.org/10.4049/jimmunol.1800534
https://www.jimmunol.org/content/202/11/3143

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– D Courvoisier, Hôpitaux Universitaires de Genève, SWITZERLAND

A prediction score for individuals at risk for Systemic Lupus Erythematosus (SLE) by integrating clinical, serologic and transcriptomic data

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Funding and Timeline

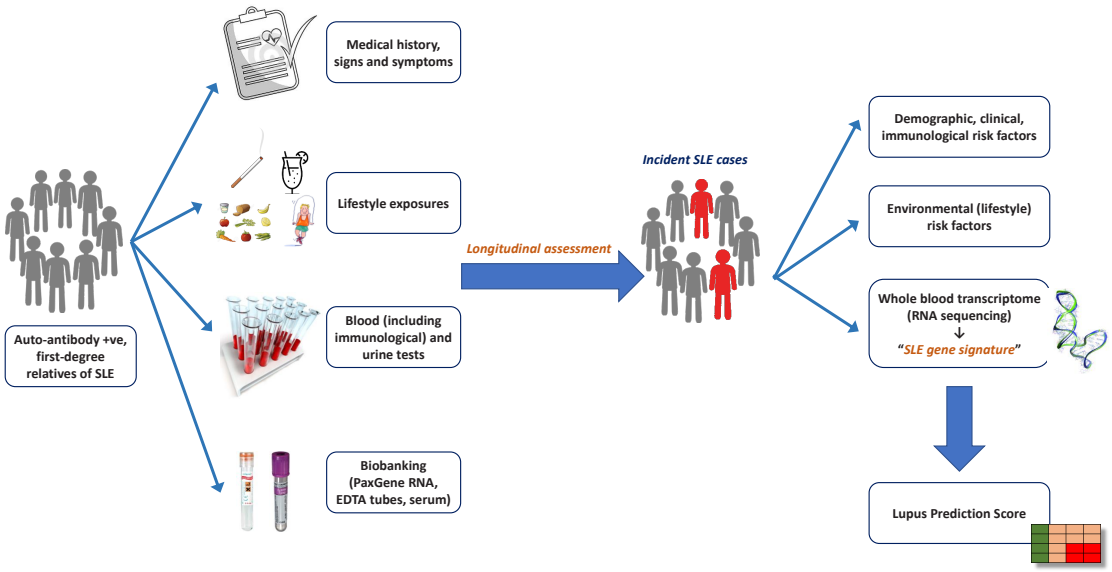
FOREUM research grant: EUR 400.000
Project duration: 2018–2021

Project Url

www.foreum.org/projects/?id=115

Concept

Systemic Lupus Erythematosus (SLE; «lupus») begins several years before the actual time of diagnosis, when a person has no or very mild symptoms but her/his immune cells start malfunctioning and produces antinuclear («ANAs») and other auto-antibodies (so called «preclinical lupus»). This gives an opportunity for planning preventive strategies which could potentially restore immune system function and delay (or even, prevent) lupus.



Objectives

To integrate demographic, family history, environmental (smoking, diet, exercise, alcohol use, working environment), clinical and serological data, with genotypes and whole-blood gene profiling towards developing a "lupus risk" prediction model.

Goals/Milestones

Year 1-2: Recruitment (inception cohort), biobanking
Year 1-5: Monitoring (inception cohort)
Year 3-5: RNA extraction, RNA-seq, bioinformatics
Year 3-5: Analysis of cohort data, prediction score

Interim Results

Among more than 400 screened individuals, 361 at-risk individuals have been enrolled in the cohort with complete demographic, clinical, serological data and biosampling. During follow-up of approximately 24 months, a total 43 individuals (12%) have progressed into classified SLE. Genome-wide RNA profiling at the time of enrolment of cases who eventually progressed or not to SLE is currently underway.

Final Results

The aim of the project is to define the subgroup of individuals who are at high risk for progression into SLE. For this, we established a multi-centre inception cohort of 298 individuals with mild or non-diagnostic symptoms and positive autoantibodies (ANA [anti-nuclear antibodies]), or first-degree relatives (FDRs) of SLE patients, monitored prospectively for multiple demographics, medical, lifestyle/environmental exposures, clinical data and use of medications. After an average 18 months, 12.4% of individuals have progressed into SLE. Blood transcriptome analysis is used to define a gene signature predictive of the transition from preSLE to SLE state, and integration with the abovementioned covariates will lead to a composite 'lupus prediction risk score'. In a complementary analysis, we are using the gene signatures of early established SLE and severe SLE (active nephritis) to define the underlying molecular aberrancies of step-wise progression from healthy state to mild/non-specific and clinical overt autoimmunity.

Lay Summary

Lupus exists in preclinical form (i.e., before it is clinically obvious) for a period of several months or even years, during which period serological abnormalities such as positive anti-nuclear antibodies (ANAs) may be detectable. However, not all individuals with positive ANA will develop lupus. In this project, we have monitored a large group of individuals with positive ANA or mild clinical features, to determine who are at high-risk to progress into lupus. After about 18 months of follow-up, about 12% of these individuals developed lupus. We are currently analysing their age, family and obstetrical history, smoking behaviour, physical activity and diet to determine what factors determine increased propensity for lupus. Importantly, we conjecture that much of this "predisposition" is reflected into changes (variations) in the genomic make-up (i.e., expression of genes) in the blood immune system, which we will assay in order to create a prognostic "score". These findings could be useful to provide personalized counselling and monitoring in people with positive ANAs or other signs and symptoms suggestive of lupus.

Patient Voice

The Arthritis Foundation of Crete and Lu- pus Europe participate in the consortium and have been involved in the discussions and the design of the study. Their representatives will participate in all consortium meetings where the study details will be finalized and the results will be presented and discussed.

In all phases, the patients' views will be incorporated as much as possible. Besides helping with patient recruitment and retention strategies (possible risk of the project), the Foundation will assist in interpretation and dissemination of the results.

Publications

- Suspected systemic rheumatic diseases in patients presenting with cytopenias. Nikolopoulos D, Adamichou C, Bertsias G. Best Pract Res Clin Rheumatol. 2019 Aug;33(4):101425. doi: 10.1016/j.berh.2019.06.007.
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  use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. Adamichou C, Nikolopoulos D, Genitsaridi I, Bortoluzzi A, Fanouriakis A, Papastefanakis E, Kalogiannaki E, Gergianaki I, Sidiropoulos P, Boumpas DT, Bertsias GK. Ann Rheum Dis. 2020 Feb;79(2):232-241. doi: 10.1136/annrheumdis-2019-216155.
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- An Update on the Diagnosis and Management of Lupus Nephritis. Kostopoulou M, Adamichou C, Bertsias G. Curr Rheumatol Rep. 2020 Jun 4;22(7):30. doi: 10.1007/s11926-020-00906-7.
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- Lupus or not? SLE Risk Probability Index (SLERPI):
  a simple, clinician-friendly machine learning-based model to assist the diagnosis of systemic lupus erythematosus. Adamichou C, Genitsaridi I, Nikolopoulos D, Nikoloudaki M, Repa A, Bortoluzzi A, Fanouriakis A, Sidiropoulos P, Boumpas DT, Bertsias GK. Ann Rheum Dis. 2021; doi: 10.1136/annrheumdis-2020-219069
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EULAR Abstracts

2020

- Comparative transcriptome analyses across tissues and species identify targetable genes for human Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN). E. Frangou, P. Garantziotis, M. Grigoriou, A. Banos, N. Panousis, E. Dermitzakis, G. Bertsias, D. Boumpas, A. Filia. (EULAR 2020, Poster Presentation THU0014).
- A multicenter "at-risk" cohort for the discovery of environmental, clinical and molecular predictors for the transition into systemic lupus erythematosus (SLE). C. Adamichou, D. Nikolopoulos,

M. Nikoloudaki, Z. Rahme, M. Fredi, A. Pieta, A. Repa, A. Parma, E. Kalogiannaki, N. Avgustidis, N. Kougkas, A. Banos, A. Eskitzis, A. Bortoluzzi, S. Jacobsen, P. Sidiropoulos, E. Dermitzakis, M. Mosca, L. Inês, L. Andreoli, A. Tincani, A. Fanouriakis, G. Bertsias. (EULAR 2020, Poster Presentation FRI0155).
http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

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- M Mosca, University of Pisa, ITALY
- L Inês, Centro Hospitalar E Universitario de Coimbra, PORTUGAL
- K Lerstroem, Lupus Europe, UNITED KINGDOM
- C Pamfil, University of Medicine and Pharmacy, ROMANIA
- S Jacobsen, Copenhagen University, DENMARK
- E Dermitzakis, University Hospitals of Geneva, SWITZERLAND
- A Fanouriakis, University Hospital, GREECE

2016

Call for research proposals in the area of Ageing in RMDs

Rheumatic Musculoskeletal Diseases (RMDs) are among the most important conditions affecting health at different stages of life. Whether young, middle-aged or senior, changes in the function of the musculoskeletal system but also the responsiveness of the immune system occur thereby impacting the clinical manifestations of RMDs. Since life expectancy continuously increases in Europe, the understanding of ageing, as a physiological process as well as a factor influencing RMDs, becomes increasingly important.

The call was launched in **2016**, and out of 15 letters of intent 2 projects were selected for funding:

- Does accelerated epigenetically defined ageing, including immune ageing, contribute to Rheumatoid Arthritis pathogenesis
- SEN-OA - Targeting senescent cells in osteoarthritis: an innovative therapeutic approach

SEN-OA – Targeting senescent cells in osteoarthritis: an innovative therapeutic approach

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 600.000
Project duration: 2018–2021

Project Url
www.foreum.org/projects/?id=139

Concept
The main risk factor for Osteoarthritis (OA) is ageing. An emerging concept for age-related diseases is that senescent cells accumulate with time and release SASP (senescence-associated secretory profile) products, which alter tissue functions. Accumulation of senescent cells during lifespan is believed to contribute to progressive tissue loss of functions. Specific elimination of these cells could prevent some age-associated diseases.

Objectives
We propose a multifaceted approach combining innovative biomedical senescence models, ageing animal studies, human sample analyses and screening for senescence-targeting compounds for clinical application to (i) decipher the role of ageing-associated senescence mechanisms in the appearance of OA and (ii) develop innovative treatments for OA patients. If successful, the project could lead to a first- in-man clinical trial.

Interim Results
– WP1. A movie dedicated to the presentation of the SEN-OA project has been made. A round table on the role of patients in research projects has been organized with one of the patient expert and Fondation Arthritis at the 1st French Congress on Regenerative Medicine and Biotherapies in Montpellier (October 2020)
– WP2. Several senescence markers have been validated by immunohistology on different articular samples from murine models and human with OA. A bio-collection of human OA tissues has been implemented.
– WP3. Direct modulation of p16INK4A was shown to partially protect mice from developing OA and a model of senescence in zebrafish was generated to investigate the impact of senolytics. Mesenchymal stromal cells and their derived extracellular vesicles can protect from senescence

induction in OA chondrocytes
– WP4. A preliminary screening was performed with a repurposing library to identify Senolytics and Pro-autophagy modulators in human chondrocytes. Validation of several candidates is ongoing.

Final Results

With the increasing evidence that many ageing-associated diseases such as osteoarthritis (OA) are associated with senescence, it was hypothesized that removing senescent cells from our organs could increase the lifespan. The SEN-OA project therefore aimed at evaluating whether senescence targeting might be a therapeutic strategy for OA.
We have detected a high number of senescent cells in the joint compartments, particularly in cartilage, that confirm that senescent cells accumulate with age and in severe OA grades. This was associated with the dysregulation of several targets that are responsible for tissue maintenance. We provided evidence that mesenchymal stromal cells and their extracellular vesicles can protect the cartilage cells to enter senescence and regulate the production of the components of the cartilage matrix. A number of molecules able to kill senescent cells and to improve OA symptoms have been identified and one of these, Fenofibrate, is now being tested in the clinics.

Lay Summary

With the increasing evidence that many ageing-associated diseases such as osteoarthritis (OA) are associated with cellular senescence, it was hypothesized that removing senescent cells from our body or organs could increase the healthspan (the length of time spent free of serious illness) and lifespan. The SEN-OA project therefore aimed at evaluating whether senescence targeting might be a therapeutic strategy for OA patients and at identifying novel compounds acting on senescence-associated processes.
We have detected a high number of senescent cells in the joint compartments, particularly in cartilage, using both human samples and animal models of OA that confirm that senescent cells accumulate with age and in the most severe OA grades. This was associated with the dysregulation of several emerging targets that are responsible for tissue maintenance and their modulation was sufficient to protect cartilage from damage. In the search of possible therapeutic options, we provided evidence that mesenchymal stromal cells and their extracellular vesicles can protect the cartilage cells to enter senescence and regulate the production of the components of the cartilage matrix. A number of molecules able to kill senescent cells and to improve OA symptoms have been identified and one of these, Fenofibrate, a repurposing molecule is now being tested in the clinics. Furthermore, a new chemical entities (NCE) screening effort was performed to identify novel senolytics to treat OA.
With 30 million Europeans who suffer from severe OA for whom there are no curative treatments, we have the hope to develop an innovative treatment for those patients.

Patient Voice

We have discussed the proposal with a patient group in Paris, they thought the idea novel and worthwhile. We gained their input to the lay summary. We will have two patient representatives to support the writing of our patient information sheets and to help communicate the findings of

the project. They will participate to the scientific advisory board. There are no obvious risks of the project to the patients. Technical risk is minimal as the assays involved are already carried out in our laboratories.

Publications

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- Delplace V, Boutet MA, Le Visage C, Maugars Y, Guicheux J, Vinatier C. Osteoarthritis: From upcoming treatments to treatments yet to come. Joint Bone Spine. 2021 Oct;88(5):105206. doi: 10.1016/j.jbspin.2021.105206. Epub 2021 May 4. PMID: 33962030.
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- Malaise O, Tachikart Y, Constantinides M, Mumme M, Ferreira-Lopez R, Noack S, Krettek C, Noël D, Wang J, Jorgensen C, Brondello JM. Mesenchymal stem cell senescence alleviates their intrinsic and seno-suppressive paracrine properties contributing to osteoarthritis development. Aging (Albany NY) 2019; 11(20): 9128-9146.

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- Nogueira-Recalde U, Lorenzo-Gómez I, Blanco FJ, Loza MI, Grassi D, Shirinsky V, Shirinsky I, Lotz M, Robbins PD, Domínguez E, Caramés B. Fibrates as drugs with senolytic and autophagic activity for osteoarthritis therapy. EBioMedicine 2019; 45: 588-605.
  https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(19)30430-X/fulltext
- Vinatier C, Domínguez E, Guicheux J, Caramés B. Role of the Inflammation-Autophagy-Senescence Integrative Network in Osteoarthritis. Front Physiol. 2018; 25; 9: 706.
  https://www.frontiersin.org/articles/10.3389/fphys.2018.00706/full

EULAR Abstracts

2021

- POS0375: Irene Lorenzo Gómez, Uxía Nogueira-Recalde, Natividad Oreiro, Jose A. Pinto-Tasende, Martin Lotz , Francisco J. Blanco, Beatriz Caramés. Chaperone-mediated Autophagy is a Hallmark of Joint Disease in Osteoarthritic Patients. 2021.
- POS0374: Boulestreau J, Maumus M, Rozier P, Jorgensen C, Noël D. Senescence did not alter the chondroprotective effect of extracellular vesicles from mesenchymal stromal cells. 2021 http://scientific.sparx-ip.net/archiveeular/

Abstracts to other meetings

2021

- M. Georget, N. Bon, C. Vignes, J. Lesoeur, C. Boyer, A. Defois, B. Bodic, G. Grimandi, J. Guicheux, C. Vinatier. In vitro and in vivo characterisation of senescence markers in osteoarthritis. 2021
- Boulestreau J, Maumus M, Rozier P, Jorgensen C, Noël D. Senescence did not alter the chondroprotective effect of extracellular vesicles from adipose mesenchymal stem cells in osteoarthritis. OARSI, 2021 (oral)
- Boulestreau J, Maumus M, Rozier P, Jorgensen C, Noël D. Senescence did not alter the chondroprotective effect of extracellular vesicles from mesenchymal stem cells. ISCT, 2021 (poster)
- Boulestreau J, Maumus M, Rozier P, Jorgensen C, Noël D. Senescence did not alter the chondroprotective effect of extracellular vesicles from adipose mesenchymal stem cells in osteoarthritis. ISEV, 2021 (oral)

Project Team/Centres

- D Noël, Université de Montpellier, FRANCE (lead)
- C Jorgensen, Université de Montpellier, FRANCE
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- P van der Kraan, Radboud UMC, THE NETHERLANDS

Does accelerated epigenetically defined ageing, including immune ageing, contribute to RA pathogenesis? Interaction in the development of RA

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 599.881
Project duration: 2018–2021

Project Url
www.foreum.org/projects/?id=138

Concept

Age is a major risk factor for rheumatoid arthritis (RA), yet we understand little of the role ageing processes play in RA pathogenesis. Why this matters is that if ageing processes are a driver for RA, then improved understanding of the mechanisms involved may reveal innovative approaches to prevention or early treatment of this disease.

Objectives

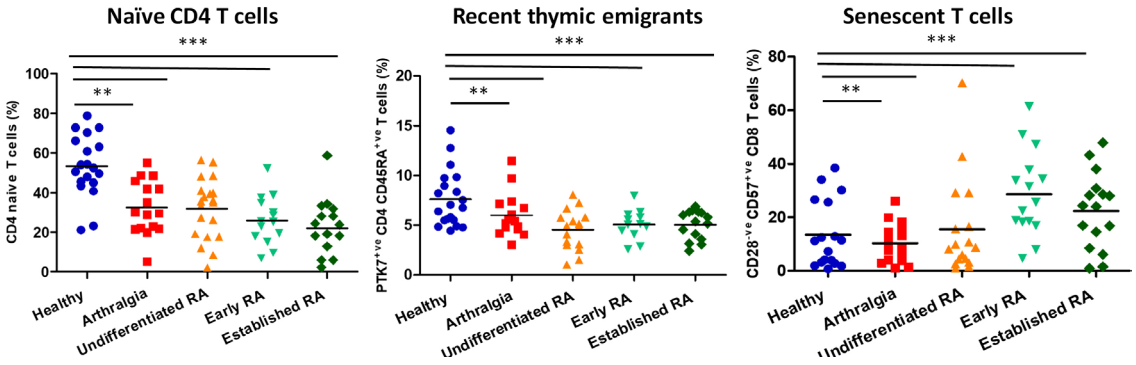
The group hypothesise that environmental factors such as smoking and genetic predisposition can cause premature ageing leading to an aged epigenome signature, driving immunesenescence and RA pathogenesis. DNA methylation at 350 specific sites, termed the epigenetic clock, has been identified as an indicator of biological age. The study will analyse existing data from patients with established RA and generate new data from very early RA cohorts across Europe to determine if the DNA methylation signature shows advanced ageing in RA patients and if this occurs in the earliest stages of the disease. Also immune phenotype at the various stages of disease development will be assessed to see if this occurs early or is a consequence of disease.

Goals/Milestones

M1 (mth 1): Kick off workshop to organise sample collection, re-distribution to analysis sites, standard operating procedures for sample collection, storage and shipping.
M2 (mth 3): PRPgroup established and first meeting held to establish role and working method.
M3 (mth 12): Analysis of existing DNAm data complete and manuscript submitted. 2ndworkshop held.
M4 (mth 24): Collection of new samples & distribution to analysis sites complete. 3rdworkshop held.
M5 (mth 30): Immune phenotyping complete and manuscript prepared.
M6 (mth 36): DNAm analysis and modelling complete and manuscript prepared. Final workshop held.
M7 (mth 36): Public dissemination strategy finalised with PRP.Budget:

Interim Results

The interim data show that innate immunity is not significantly affected in very early RA, there is an increase in regulatory monocytes but this occurs only once the disease is diagnosed. However for adaptive immunity thymic atrophy, reduction in naïve T cells and the increases in memory T cells all occur very early in disease pathogenesis and are likely contributing to disease development rather than being a cause. Early analysis of DNA methylation in patients newly diagnosed with RA showed acceleration of biological age of between 2 and 5 years, with the higher value seen in male patients. Analysis of samples from early RA patients has been delayed due to the pandemic but is now underway.



Final Results

Rheumatoid arthritis (RA) is more common with advancing age and the immune system of patients with RA show signs of ageing at an earlier age than healthy adults. This project had two objectives, to determine: 1. If those adults who develop RA are biologically older than those who do not; 2) Whether an aged immune system is a cause or consequence of RA. Results show that overall adults with RA are not biologically older than healthy adults. However, biological age was higher in RA patients of South Asian origin, though numbers were small and this finding needs confirmation. Through analysis of primary care data we also showed that a wide range of immune mediated inflammatory diseases, including RA, occur much earlier in non-white populations. For objective 2, the study found signs of an aged immune system in adults at risk of developing RA, namely those with arthralgia and undifferentiated arthritis.

Lay Summary

Rheumatoid arthritis (RA) is more common in old age and the immune system plays a role in causing the disease. In particular RA is associated with inflammation in the joints and with immune cells attacking tissues in the joint, called autoimmunity. As we age our immune system becomes more prone to inflammation and autoimmunity. This project set out to answer two questions: 1. Are those adults who develop RA biologically older than those who do not; 2) Is an aged immune system a cause or consequence of RA.

The project determined the biological age of twins, one who had RA and one who did not, by analysing their DNA. In general, adults with RA were not biologically older than healthy adults. However, RA patients of South Asian ethnicity were biologically older than healthy South Asian adults. The study also looked at how old patients were when they developed RA and found that non-white patients were approximately 7 years younger than white patients. These findings suggest that the disease may have some different causes in non-white populations.

For the second question, the results show that some signs of an aged immune system were seen in

adults at risk of developing RA, namely those with arthralgia and undifferentiated arthritis, and so this may be one cause of RA. These results are promising as there are studies that have identified drugs that can rejuvenate the immune system, this could be a new way to prevent or treat RA in its early stages.

Patient Voice

The project will include patient representatives at each site to support the writing of the patient information sheets and to help communicate the findings of the project. Close work with a patient group in Birmingham.

Publications

– Sharma-Oates A, Zemedikun DT, Kumar K, Reynolds JA, Jain A, Raza K, Williams JA, Bravo L, Cardoso VR, Gkoutos G, Nirantharakumar K, Lord JM. Early onset of immune-mediated diseases in minority ethnic groups in the UK. BMC Med. 2022 Oct 13;20(1):346. doi: 10.1186/s12916-022-02544-5. PMID: 36224602; PMCID: PMC9558944. https://pubmed.ncbi.nlm.nih.gov/36224602/

Project Team/Centres

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– A Pratt, University of Newcastle, UNITED KINGDOM
– L Padyukov, University of Birmingham, UNITED KINGDOM
– L Mirbahai, University of Birmingham, UNITED KINGDOM
– A van der Helm-van Mil, UMC Leiden, THE NETHERLANDS
– S W Jones, University of Birmingham, UNITED KINGDOM
– N Duggal, University of Birmingham, UNITED KINGDOM

2017

Call for research proposals in the area of Stratified Medicine in RMDs

Stratified medicine approaches are based on the concept that different subgroups (often referred to as "endotypes" or "pathotypes") exist within a single disease entity. There is a substantial level of heterogeneity within individual Rheumatic and Musculoskeletal Diseases (RMDs) suggesting that stratified medicine approaches are not only feasible but will become an essential part of a more specific and better management of these diseases.

The call was launched in **2017**, and out of 24 letters of intent 2 projects were selected for funding:

- Stratified Medicine in primary Sjögren's syndrome
- START: Molecular stratification of patients with giant cell arteritis to tailor glucocorticoid therapy

Stratified medicine in primary Sjögren's syndrome

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600.000
Project duration: 2018–2023

Project Url

www.foreum.org/projects/?id=141

Concept

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease that can cause severe disability and even mortality with joint swelling, sensitivity, loss of motion and synovial tissue damage. JIA is one of the most common inflammatory joint disease.
Chronicity in autoimmune diseases depends on the balance between pro-inflammatory and anti-inflammatory responses. One of the main factors in achieving this equilibrium is T-cell co-inhibitor receptors, which are highly expressed by exhausted-T-cells.
Previous studies revealed that T cells play an important and central role in the pathogenesis of especially the oligoarticular and polyarticular forms of the disease. We aim to define the role of T cell co-inhibitory receptors (co-IRs) for predicting the outcome of JIA and try to find a novel therapeutic target molecule.

Objectives

- To evaluate soluble levels and cell surface expressions of co-IRs in synovial fluid and peripheral blood of JIA patients
- To design an ex-vivo disease model and perform functional analysis
- To examine similarities and differences between different JIA subtypes
- To define a prognostic biomarker among co-IRs
- To explore novel therapeutic target molecule

Goals/Milestones

WP1 month 1-6: Patient recruitment for the pilot study
WP2 month 6-12: Orientation of laboratory environment, getting familiar with the relevant lab techniques, examination of PBMC and SFMC samples obtained from JIA patients at Aarhus University
WP3 month 13-24: Reporting the results of the pilot study & Establishing similar study setup at Hacettepe University
WP4 month 25-36: Study a larger JIA cohort and other autoimmune diseases at Hacettepe University

Interim Results

A pilot study including 14 oligoarticular JIA patients was held in Denmark. We have designed an ex-vivo arthritis model using co-cultures of fibroblasts and PBMC/SFMCs. We suggest that LAG-3 may have a potential role at the pathogenesis and its effect on PBMCs may be a potential therapeutic target for the treatment of oligoarticular JIA. Based on this, a larger cohort of different JIA subtypes will be studied.

Final Results

This is the first study showing the role of co-inhibitory receptors (checkpoint proteins) in the pathogenesis of JIA. Both the soluble levels and the surface expressions of these co-IRs are higher atsynovium which is the site of inflammation in JIA. Co-cultures of autologous fibroblasts and PBMCs/SFMCs may serve as an important ex-vivoarthritis modelfor JIA. Polyarticular JIA patients had a different coIR profile, having more CTLA-4, PD-1 and 4-1BB in their plasma than the other subtypes of JIA. Lag-3 is a central immune receptor in the oligoarticular JIA pathogenesis and LAG-3 agonists mightbe a novel therapeutic option for oligoarticular JIA patients.

Lay Summary

In this project we aimed to investigate the role of checkpoint proteins, also known as co-inhibitory receptors (co-IRs), in the pathogenesis of childhood arthritis (juvenile idiopathic arthritis (JIA)). These molecules were found to be higher in the synovium which is the site of inflammation in JIA patients. We have shown that LAG-3 is an important molecule in the pathogenesis of oligoarticular JIA. We have shown that LAG3 agonists might be a novel therapeutic option for oligoarticular JIA patients in the future. Furthermore, during this study, we designed a novel ex-vivo arthritis models for JIA and performed our functional analysis with this model.We also analysed the co-inhibitory receptor profiles in different JIA subtypes, showing that patients who have a polyarticular course have a unique pattern with elevated CTLA-4, PD-1 and 4-1BB, which was different from the other forms of JIA. This is the first study analysing these proteins in childhood arthritis and is hoped to lead to more work in the relevant area.

Patient Voice

Patient participation is very important to define the unmet needs from the patient perspective. We have a mother of systemic JIA patient as Patient/Parent Research Partner, who had valuable input in identifying the research questions and in the design of the study.

Publications

– Sag E, Demir S, Aspari M, Nielsen MA, Skejø C, Hvid M, Turhan E, Bilginer Y, Greisen S, Ozen S, Deleuran B. Juvenile idiopathic arthritis: lymphocyte activation gene-3 is a central immune receptor in children with oligoarticular subtypes. Pediatr Res. 2021 May 24. doi: 10.1038/s41390-021-01588-2. Epub ahead of print. PMID: 34031570
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https://www.nature.com/articles/s41390-021-01636-x

EULAR Abstracts

2019
OP0152 : Oligoarticular Juvenile Idiopathic Arthritis does not show signs of T-cell exhaustion, in spite of increased expression of co-inhibitory receptors
http://scientific.sparx-ip.net/archiveeular/

Paediatric Rheumatology European Society PReS Abstracts

ABS-1140: Lag-3 is a central immune receptor in oligoarticular Juvenile Idiopathic Arthritis

Project Team/Centres

– E Sag, Hacettepe University, TURKEY (lead)
– S Ozen, Hacettepe University, TURKEY
– B Deleuran, Aarhus University, DENMARK

START – Molecular stratification of patients with giant cell arteritis to tailor glucocorticoid and tocilizumab therapy

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600.000
Project duration: 2018–2023

Project Url

www.foreum.org/projects/?id=142

Concept

To provide tools to select the likely most effective therapy for each patient with giant cell arteritis (GCA) right from the time of diagnosis.

Objectives

- Identification of biomarkers in temporal artery biopsies (TABs) whose quantification may allow to predict at diagnosis patients' response to glucocorticoids (GCs) and tocilizumab (TCZ).
- Stratification of GCA patients according to molecular signatures in TABs and correlation of such signatures to the clinical characteristics of patients.

Goals/Milestones

Month 12: Ppatient recruitment for the glucocorticoid study
Month 18: Patient recruitment for the tocilizumab study
Month 30: Completion of patients follow up for the tocilizumab study
Month 33: Definition of predictors of response to therapy
Month 36: Completion of patient recruitment
Month 40: Completion of RNA, protein and DNA methylation profiling in TABs
Month 46: Definition of molecular signatures associated to clinical characteristics
Month 54: Completion of patients follow up, definition of predictors of response to therapy, validation of the candidate biomarkers and signatures

Interim Results

An electronic CRF by the SMARTY Web platform of AUSL-IRCCS was created to securely collect clinical data. 28 patients were recruited:
24 in the GC arm and 4 in the GC + TCZ arm. We analyzed with RNA sequencing and DNA methylation 8 TABs from patients who responded to GC therapy versus 8 TABs from patients who developed relapses during GC therapy. No differentially expressed genes emerged between the two groups while 211 CpGs were found to be differentially methylated (FDR < 0.05 and $\Delta\beta > 0.15$). LIRE

organized an informative event on GCA and polymialgia rheumatica in collaboration with FEP and Instituto de Investigación Sanitaria del Hospital Universitario de La Princesa. AMRER disseminated the project in the news bulletin of the association.

Patient Voice

One Italian (AMRER) and two Spanish (FEP and LIRE) associations of patients are involved as patient research partners (PRPs). The design of the project and the burden for patients have been discussed with the PRPs integrating their feedback. PRPs raised awareness about the disease in the respective associations, prepared leaflets about the disease and the research project and are disseminating information in the association social media.

Publications

EULAR Abstracts

2020

– SAT0338:
  Contrast-enhanced ultrasonography in the evaluation of myositis
  http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

– N Pipitone, Azienda Unità Sanitaria Locale, ITALY (lead)
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– F Ciccia, Università della Campania Vanvitelli, ITALY
– R Alessandro, University of Palermo, ITALY
– S Fontana, University of Palermo, ITALY
– M Gonzalez-Gay, Hospital Universitario Marqués de Valdecilla, SPAIN
– S Castaneda, Hospital La Princesa, SPAIN
– J Martin, Institute of Parasitology and Biomedicine López-Neyra, SPAIN
– P Liò, University of Cambridge, UNITED KINGDOM
– D Saadoun, Pitie-Salpetriere Hospital, FRANCE
– D Conti, Associazione Malati Reumatici Emilia Romagna, ITALY
– J Baquero, Foro Español de Pacientes, SPAIN
– V Romero, Liga Reumatologica Española, SPAIN
– L Carmona, Instituto de Salud Musculoesquelética, SPAIN

2018

Call for international exchange 3-year fellowships

FOREUM is committed to funding and promoting scientific research into rheumatic and musculoskeletal diseases (RMD) and has a goal to foster links between rheumatology units in different countries. Consistent with these goals is the establishment of a call for international exchange fellowships that have the specific objective of facilitating the development of research capacity and training high-caliber applicants in RMD research.

The first call for a 3-year fellowship was launched in **2018**, and out of 10 letters of intent 3 projects were selected for funding:

- Crosstalk of metabolic and epigenetic pathways in systemic sclerosis
- Applicability of standardized ultrasound examination to estimate disease activity in combination with JADAS and inflammation markers in JIA patients
- The effect of T cell exhaustion profiles of synovial fluid and peripheral blood from juvenile idiopathic arthritis patients on disease pathogenesis and prognosis

Applicability of standardized ultrasound examination to estimate disease activity in combination with JADAS and inflammation markers in JIA patients

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 125.000
Project duration: 2019–2023

Project Url

www.foreum.org/projects/?id=156

Concept

This multicenter, international longitudinal study will recruit JIA patients (according to ILAR classification criteria) with active disease according to JADAS 10 and 27 scoring prior starting recommended treatment. All JIA relevant data (demographics, duration, disease activity, medication usage and treatment efficacy) will be collected and parent/guardian written consent obtained. At enrolment and during predefined scheduled follow up visits (at 3 months up to 12 months) all JIA patients will be clinically evaluated by JADAS 10 and 27 scoring, examined by ultrasound gray-scale (GS) and Power Doppler (PD) in (44 joints) using OMERACT synovitis scoring system by an expert in pediatric ultrasound. At each visit blood samples will be obtained for evaluation of inflammatory markers (such as cytokines, chemokines and S100A8, S100A9 and S100A12). In the case of disease worsening, the same parameters will be performed as unscheduled visit.

Objectives

- to establish minimal corset of representative joints to be assessed by clinical examination and ultrasound to be used as outcome tool in JIA
- to investigate if joint findings correlate with the panel of laboratory inflammation markers
- to evaluate sensitivity and predictive value of the multi-biomarker panel (clinical examination of the joints, ultrasound and inflammatory biomarkers) in JIA patients
- to test if multi-biomarker panel could be applied in every day clinical practice to predict response to treatment and outcome tool in JIA
- to improve possibility to achieve optimized personalized tailored treatment

Goals/Milestones

Month 0-3: Ethics Committees Approval, ICF and CRF preparation, organization of web based ultrasound calibration exercise
Month 0-12: Active enrolment of the patients (to be extended if necessary)
Month 12-18: Longitudinal phase of the study and midterm analysis
Month 18-24: Termination of the follow up phase
Month 24-27: Shipment of the blood samples and analysis
Month 27-36: Statistical analysis and publications

Interim Results

- Obtained Ethics Comittee approvals: home center (Niš, Serbia) and host center (Genoa, Italy) / participating centers: France, Greece, Turkey, Italy (Milano), Denmark, and Germany / Rome Italy still in process
- Prepared Daisy Study Webportal (built up PRINTO platform for data collection from the Pharmachild registry with study material of importance for investigators:
  1. Instructions for Ultrasonographers / Ultrasound Educative Modules / Pathological Ped MSUS Athlas / Test for Ultrasonographers
  2. Study Protocol
  3. Laboratory Instructions and Lab Kits
- Activated participating centers: France, Turkey, Greece / in preparation Italy (Milano), Denmark and Germany
- 34 patients recruited (17 Servia, 5 Italy, 5 France, 6 Turkey, 1 Lithuania)

Patient Voice

Patient participation from local patient organizations will be crucial to explore which questions of interest have the greatest impact on the patient disease outcomes and treatment response. Planned is to include patients organizations representatives from each participating center and give them possibility to ask all questions important for their future perspectives. Patients feedback will be used to create a brochure with all disease aspects that patients want to know. This will help JIA patients and their families to better understand disease course and treatment strategies. The project results will also be presented during World Arthritis day. All of this information will be available on patients organization website and will be shared via other available social media channels.

Publications

– D. Lazarevic, J. Vojinovic, C. Malattia , L. Rossi-Semerano , B. Sozeri, M. Tsinti, et al. Internal consistency and interrater reliability in musculoskeletal ultrasound in children. Pediatric Rheumatology 2022, 20(Suppl 2):P204Proceedings of the 28th European Paediatric Rheumatology Congress (PReS 2022) : Prague, Czech Republic. 20-23 September 2022. Pediatr Rheumatol Online J. 2022 Sep 7;20(Suppl 2):75.
https://ped-rheum.biomedcentral.com/articles/10.1186/s12969-022-00729-z

Project Team/Centres

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– S Magni Manzoni, Roma Ospedale Pediatrico Bambino Gesu, ITALY
– L Rossi, CeRéMAIA, Bicêtre (Hôpital Bicêtre AP-HP), FRANCE
– B Sözeri, Umraniye Education and Research Hospital, TURKEY
– T Herlin, Aarhus University, DENMARK
– E Tsitsami, Aghia Sophia Children's Hospital, GREECE
– D Windschall, St. Josef-Stift Sendenhorst, GERMANY
– C Host, Aarhus University, DENMARK
– A Snipaitiene, Hospital of health sciences Kauno Klinicos, LITHUANIA
– L Bukovac, Children's Hospital Srebrnjak, CROATIA

Effect of T-cell exhaustion profiles of synovial fluid and peripheral blood from JIA patients on disease pathogenesis and prognosis

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 150.000
Project duration: 2018–2021

Project Url
www.foreum.org/projects/?id=153

Concept

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease that can cause severe disability and even mortality with joint swelling, sensitivity, loss of motion and synovial tissue damage. JIA is one of the most common inflammatory joint disease.
Chronicity in autoimmune diseases depends on the balance between pro-inflammatory and anti-inflammatory responses. One of the main factors in achieving this equilibrium is T-cell co-inhibitor receptors, which are highly expressed by exhausted-T-cells.
Previous studies revealed that T cells play an important and central role in the pathogenesis of especially the oligoarticular and polyarticular forms of the disease. We aim to define the role of T cell co-inhibitory receptors (co-IRs) for predicting the outcome of JIA and try to find a novel therapeutic target molecule.

Objectives

- To evaluate soluble levels and cell surface expressions of co-IRs in synovial fluid and peripheral blood of JIA patients
- To design an ex-vivo disease model and perform functional analysis
- To examine similarities and differences between different JIA subtypes
- To define a prognostic biomarker among co-IRs
- To explore novel therapeutic target molecule

Goals/Milestones

WP1 month 1-6: Patient recruitment for the pilot study
WP2 month 6-12: Orientation of laboratory environment, getting familiar with the relevant lab techniques, examination of PBMC and SFMC samples obtained from JIA patients at Aarhus University
WP3 month 13-24: Reporting the results of the pilot study & Establishing similar study setup at Hacettepe University
WP4 month 25-36: Study a larger JIA cohort and other autoimmune diseases at Hacettepe University

Interim Results

A pilot study including 14 oligoarticular JIA patients was held in Denmark. We have designed an ex-vivo arthritis model using co-cultures of fibroblasts and PBMC/SFMCs. We suggest that LAG-3 may have a potential role at the pathogenesis and its effect on PBMCs may be a potential therapeutic target for the treatment of oligoarticular JIA. Based on this, a larger cohort of different JIA subtypes will be studied.

Final Results

This is the first study showing the role of co-inhibitory receptors (checkpoint proteins) in the pathogenesis of JIA. Both the soluble levels and the surface expressions of these co-IRs are higher atsynovium which is the site of inflammation in JIA. Co-cultures of autologous fibroblasts and PBMCs/SFMCs may serve as an important ex-vivoarthritis modelfor JIA. Polyarticular JIA patients had a different coIR profile, having more CTLA-4, PD-1 and 4-1BB in their plasma than the other subtypes of JIA. Lag-3 is a central immune receptor in the oligoarticular JIA pathogenesis and LAG-3 agonists mightbe a novel therapeutic option for oligoarticular JIA patients.

Lay Summary

In this project we aimed to investigate the role of checkpoint proteins, also known as co-inhibitory receptors (co-IRs), in the pathogenesis of childhood arthritis (juvenile idiopathic arthritis (JIA)). These molecules were found to be higher in the synovium which is the site of inflammation in JIA patients. We have shown that LAG-3 is an important molecule in the pathogenesis of oligoarticular JIA. We have shown that LAG3 agonists might be a novel therapeutic option for oligoarticular JIA patients in the future. Furthermore, during this study, we designed a novel ex-vivo arthritis models for JIA and performed our functional analysis with this model.We also analysed the co-inhibitory receptor profiles in different JIA subtypes, showing that patients who have a polyarticular course have a unique pattern with elevated CTLA-4, PD-1 and 4-1BB, which was different from the other forms of JIA. This is the first study analysing these proteins in childhood arthritis and is hoped to lead to more work in the relevant area.

Patient Voice

Patient participation is very important to define the unmet needs from the patient perspective. We have a mother of systemic JIA patient as Patient/Parent Research Partner, who had valuable input in identifying the research questions and in the design of the study.

Publications

– Sag E, Demir S, Aspari M, Nielsen MA, Skejø C, Hvid M, Turhan E, Bilginer Y, Greisen S, Ozen S, Deleuran B. Juvenile idiopathic arthritis: lymphocyte activation gene-3 is a central immune receptor in children with oligoarticular subtypes. Pediatr Res. 2021 May 24. doi: 10.1038/s41390-021-01588-2. Epub ahead of print. PMID: 34031570
https://www.nature.com/articles/s41390-021-01588-2.epdf?sharing_token=l_MXb9fLST8-iRut-fLx6xdRgN0jAjWel9jnR3ZoTv0Otgk8m2U1TuiGJXrz6m8uVEbTLEivQprW3AmsIe1-_zjwnfudKz-JGqAfQ87xGjjw0BhKwS24iaOzxaI1JrJM2qKhOSLc8dLzrl1oJWsXPxUJ6UlHWpVO04nOD-3kIwyE-c%3D

– Sag, E. ECI Biocommentary:
Erdal Sag. Pediatr Res 90, 711 (2021).
PMID:34175892
https://doi.org/10.1038/s41390-021-01636-x
https://www.nature.com/articles/s41390-021-01636-x

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Paediatric Rheumatology European Society PReS Abstracts
ABS-1140: Lag-3 is a central immune receptor in oligoarticular Juvenile Idiopathic Arthritis

Project Team/Centres
– E Sag, Hacettepe University, TURKEY (lead)
– S Ozen, Hacettepe University, TURKEY
– B Deleuran, Aarhus University, DENMARK

Crosstalk of metabolic and epigenetic pathways in systemic sclerosis (SSc)

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 150.000
Project duration: 2018–2021

Project Url

www.foreum.org/projects/?id=155

Concept

Targeting metabolic pathways in systemic sclerosis (SSc) could represents a promising new treatment strategy in SSc.

Objectives

The aim is to explore dysregulation of metabolic pathways in SSc and determine, whether metabolic substrates, such as aKG, influence the pro-fibrotic activities of SSc fibroblasts. Targeting metabolic pathways might halt fibrosis in SSc with direct implications for drug discovery in SSc

Goals/Milestones

WP1: Determine metabolic dysregulation present in fibrotic SSc skin
WP2: Identify possible metabolic intermediates to interfere with profibrotic activation in SSc
WP3: Determine the effects of metabolic treatment on profibrotic activation of dermal fibroblasts
WP4: Extend analysis on fibrotic human skin
WP5: Present new data at international meetings
WP6: Submit a manuscript to a high impact journal

Interim Results

The in vitro analyses showed that dm-aKG can efficiently inhibit profibrotic and proinflammatory responses of skin fibroblasts by interfering with the TGFβ-induced myofibroblast differentiation/function, indicating its strong ability to halt fibrotic activation of dermal fibroblasts.

Final Results

The project aimed to investigate metabolic dysregulations and its effect on development of skin fibrosis in systemic sclerosis (SSc). We have identified dimethyl-alpha ketoglutarate (dm-akg) as a potential suppressor of myofibroblast activation in SSc. Our extensive in vitro analyses showed that dm-akg can efficiently inhibit profibrotic and proinflammatory responses of skin fibroblasts by interfering with the TGFβ-induced myofibroblast differentiation (alpha-smooth muscle protein,

cytoskeleton organization, secretion of the extracellular matrix proteins) and function (contraction, migration, invasion, proliferation). Further scRNAseq analysis of ex-vivo treated SSc skin tissues explants identified fibroblasts as the main cell target of dm-akg within skin tissue with predominant transcriptomic effect on suppression of fibrotic and inflammatory pathways. Thus, our results strongly suggest that dm-akg might be a novel repressor of pathogenic myofibroblast reprogramming and skin fibrosis in SSc.

Lay Summary

Metabolic dysregulation lies at the core of fibrotic diseases, such as systemic sclerosis, and its modulation might be directly involved in development of fibrosis. In our project we have identified an important cell metabolite analogue, dimethyl alpha-ketoglutarate (dm-akg) as a potential novel suppressor of extracellular matrix deposition in systemic sclerosis. Our in vitro and ex vivo analysis revealed its strong effect on suppression of profibrotic and inflammatory responses in human dermal fibroblasts and in fibrotic skin tissue. Thus, dm-akg represent a potential novel anti-fibrotic compound for treatment of skin fibrosis and additional testing is needed to determine its in vivo efficacy and exact mechanism of action, leading to development of more specific and stable analogs.

Patient Voice

Patients with SSc will be involved in the preparation of informed consent forms and communicating our research findings to public. We will promote the EULAR's initiative 'Patients research partners'. This will establish long-term partnerships between rheumatologists, researchers and patients in Slovenia. Patients will actively participate in the development of research projects.

Publications

ACR 2019 Poster: The Metabolic Intermediate Alpha-Ketoglutarate Suppresses the TGF beta-driven Profibrotic Responses of Dermal Fibroblasts

16th International Workshop on Scleroderma Research 2019, Poster and Oral presentation: Metabolic intermediate alpha-ketoglutarate attenuates TGFB-driven responses of dermal fibroblasts

ACR 2021 Poster: Metabolic Intermediate Dimethyl-Alpha-Ketoglutarate Is a Novel Repressor of Pathogenic Myofibroblast Reprogramming and Skin Fibrosis in Systemic Sclerosis

EULAR Abstracts

2020

- SAT0292: Integrative transcriptomic and functional analysis reveals a role of dimethyl-α-ketoglutarate in TGFβ-driven cytoskeleton regulation and myofibroblast differentiation http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

- B Burja, University Medical Centre Ljubljana, SLOVENIA (lead)
- M Tomšič, University Medical Centre Ljubljana, SLOVENIA
- K Lakota, University Medical Centre Ljubljana, SLOVENIA
- O Distler, University of Zurich, SWITZERLAND
- M Frank-Bertoncelj, University of Zurich, SWITZERLAND

2018

Call for research proposals in the area of Comorbidities

RMDs usually occur in conjunction with other diseases (comorbidities). Comorbidities may affect the natural course of the RMD, determine the overall state of the patient and influence treatment decisions. Traditionally, RMDs are seen as isolated diseases and one does not account for comorbidities. However, in real life, not least due to the ageing population, co-morbidities become increasingly important. Comorbidities develop independently from the respective RMD, although sometimes the underlying RMD may increase the risk for certain comorbidities.

The call was launched in **2018**, and out of 24 letters of intent 2 projects were selected for funding:

- Immunometabolites to stratify Systemic Lupus Erythematosus patients at high risk of cardiovascular diseases (IMSLE)
- Comorbidities in osteoarthritis
- Burden and impact of co-morbidity and frailty in patients with RMDs in Europe: a multi-national analysis of big healthcare data

Immune mediators and metabolites to stratify SLE patients at high risk of cardio vascular diseases (IMSLE)

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 595.000
Project duration: 2019–2022

Project Url
www.foreum.org/projects/?id=158

Concept

Accelerated atherosclerosis is an established complication of systemic autoimmune diseases, particularly SLE. Young female patients with SLE are more likely to develop myocardial infarction than matched healthy controls, and CVD is nowadays one of the most common causes of death (27%) in lupus patients. While traditional CV risk factors cannot explain such increased CV morbidity associated with SLE, common disease factors shared between SLE, atherosclerosis and treatment exposure may be of outmost importance in this process. 3 findings of particular interest were found that could link SLE pathogenesis and atherosclerosis-associated immune dysregulation:
1/ specific immunometabolites (circulating nucleotide-derived metabolites) which are increased in the circualtion of SLE patients 2/ OX40L as an important costimulatory molecule implicated in follicular helper T cell (Tfh) activation in SLE 3/ Immune complexes-activated platelets sustain aberrant immune response in SLE and block immunosuppressive functions of regulatory T cells (Tregs). Exploring these interconnected pathways in SLE patients together with traditional and other well-established disease-related factors, might lead to a better stratification of CV risk in SLE.

Objectives

The general objective of this study is to investigate the accuracy, predictive value and utility of immunological disease-related biomarkers in stratifying CV risk in patients with SLE.

Goals/Milestones

MS1: Ethical approval of the protocol (D1a) and signing off the dissemination plan (D1b)
MS2: End of patients' recruitment (D2:
Final recruitment report)
MS3: End of central biobanking of the included patients (D3:
Final biobanking report)
MS4: Cross sectional lab and statistical analyses (D4:
Intermediate statistical report)

MS5: End of patients' recruitment (D5:
Final follow-up report)
MS6: Longitudinal lab and statistical analyses (D6:
Final statistical report)

Patient Voice

Patients had already participated in the grant preparation phase, helping the research team to identify and prioritize key research topics and objectives. Then, they helped us in the study protocol elaboration especially to provide complementary views on ethical considerations that are inherent to certain aspects of the research plan.
We would like to include them in the data analysis to improve the ability of the research team to design a more focused analysis and to contextualize conclusions.

Project Team/Centres

- P Duffau, CHU of Bordeaux, FRANCE (lead)
- P Blanco, University Hospital Bordeaux, FRANCE
- B Faustin, University Hospital Bordeaux, FRANCE
- C Richez, University Hospital Bordeaux, FRANCE
- T Martin, University Hospital Strasbourg, FRANCE
- R Voll, Albert Ludwig University Freiburg, GERMANY

Comorbidities in Osteoarthritis

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600.000
Project duration: 2019–2022

Project Url

www.foreum.org/projects/?id=159

Concept

Osteoarthritis (OA) is the most common form of arthritis and a major cause of disability in older people. The prevalence of OA increases in the past 20 years(1). However, little has been done into its burden such as comorbidities. Our recent systematic review has found that people with OA are more likely to have other diseases, especially stroke, peptic ulcer, hypertension and depression(2). Whether these comorbidities just co-exist with, share common risk factors with or are causes or consequences of OA remains unknown.

Objectives

This project aims to examine:

- prevalence, incidence and associations and time sequence of comorbidities in OA;
- common clusters and impact of comorbidities on patient health states;
- association between commonly used OA drugs such as non-steroidal anti-inflammatory (NSAIDs) and comorbidities;
- early biomarkers and mechanistic pathways between OA and the comorbidities;
- consistency of OA comorbidities and clusters across countries.

Five work packages (WP) will be performed for these five objectives. Four national registration databases in the UK, Netherlands, Sweden and Spain will be used for WP1-3. Two cohort study databases (the UK Biobank and the Rotterdam study) will be used for WP4. Finally, data from different countries will be meta-analysed (WP5) to examine the consistency between countries and to pool results together as appropriate.

So far, UK and Sweden have been able to produce some results on the comorbidities associated with OA.

Swedish database studied the association with 18 conditions. UK database examined the association with 49 conditions before and after the diagnosis of OA. Besides, the clusters of comorbidities were explored among OA and matched controls using UK database.

Goals/Milestones

Months 0-6: data extraction, cohort development, case/control matching, data cleaning, coding and validation
Months 7-24: complete WP1-3
Months 25-36: complete WP4-5

Interim Results

In Sweden, people with physician-diagnosed knee or hip OA were more likely to develop depression, cardiovascular diseases, back pain, and osteoporosis than people without OA.
In the UK, people with physician diagnosed OA were more likely to develop multimorbidity (≥2 other diseases). The hazard ratio was 1.34, (95% CI 1.82-1.41) between OA and non-OA after adjusting for age, gender, BMI, smoking status and alcohol consumption.
Leading comorbidities were fibromyalgia, rheumatoid arthritis, liver diseases, sleep problems, ankylosing spondylitis, dementia, heart failure, osteoporosis, anaemia, and peripheral vascular diseases.
In the OA group five clusters were identified including relatively healthy (18%), 'cardiovascular/ musculoskeletal ' (12.3%), metabolic syndrome (28.2%), 'pain and psychological (9.1%), and 'musculoskeletal' (32.4%). The non-OA group had similar patterns except that the 'pain+ psychological' cluster was replaced by 'thyroid and psychological'.

Patient Voice

Three patient research partners (PRPs) are involved in the project since we applied for this project. They have actively participated in the meetings and shared their views on the list of conditions to be studied, possible ways of disseminations and the challenges they face because of the comorbidities.

Publications

– S. Swain, C. Coupland, C. Mallen, CF. Kuo, A. Sarmanova, S.M.A. Bierma-Zeinstra, M. Englund, D. Prieto-Alhambra, M. Doherty, W. Zhang. Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting. Rheumatology, Volume 60, Issue 9, September 2021, Pages 4327–4339, https://doi.org/10.1093/rheumatology/keab067 https://academic.oup.com/rheumatology/article/60/9/4327/6121906?login=false
– A. Dell'Isola, K. Pihl, A. Turkiewicz, V. Hughes, W. Zhang, S. Bierma-Zeinstra, D. Prieto-Alhambra, M. Englund. Risk of comorbidities following physician-diagnosed knee or hip osteoarthritis: a register-based cohort study. Arthritis Care Res (Hoboken). 2021 Jun 4. doi: 10.1002/acr.24717. Epub ahead of print. PMID: 34086422. http://pubmed.ncbi.nlm.nih.gov/34086422/
– A. Dell'Isola, A.Turkiewicz, W. Zhang, A. Kiadaliri, S. Bierma-Zeinstra, J. Runhaar, D. Prieto-Alhambra, M. Englund. Does osteoarthritis modify the association between NSAID use and risk of comorbidities and adverse events?, Osteoarthritis and Cartilage Open, Volume 4, Issue 2, 2022, 100253, ISSN 2665-9131 http://www.sciencedirect.com/science/article/pii/S2665913122000218?via%3Dihub

– S. Swain, C. Coupland, V. Strauss, C. Mallen, C.F. Kuo, A. Sarmanova, S.M.A. Bierma-Zeinstra, M. Englund, D. Prieto-Alhambra, M. Doherty, W. Zhang, Clustering of comorbidities and associated outcomes in people with osteoarthritis - A UK Clinical Practice Research Datalink study, Osteoarthritis and Cartilage, 2022, ISSN 1063-4584
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– S, Kamps A, Runhaar J, Dell'Isola A, Turkiewicz A, Robinson D, et al. Comorbidities in osteoarthritis (ComOA): a combined cross-sectional, case–control and cohort study using large electronic health records in four European countries. BMJ Open. 2022;12(4):e052816.
https://pure.eur.nl/en/publications/comorbidities-in-osteoarthritis-comoa-a-combined-cross-sectional-
– S, Fernandes GS, Sarmanova A, Valdes AM, Walsh DA, Coupland C, et al. Comorbidities and use of analgesics in people with knee pain: a study in the Nottingham Knee Pain and Health in the Community (KPIC) cohort. Rheumatology Advances in Practice. 2022.
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– A, Turkiewicz A, Zhang W, Bierma-Zeinstra S, Runhaar J, Prieto-Alhambra D, et al. The association between preexisting conditions and osteoarthritis development in peripheral joints:
A population based nested case-control study. Osteoarthritis and Cartilage Open. 2022 2022/06/01/;4(2):100265.
https://portal.research.lu.se/en/publications/the-association-between-preexisting-conditions-and-osteoarthritis
– S, Sarmanova A, Coupland C, Doherty M, Zhang W. Comorbidities in Osteoarthritis:
A Systematic Review and Meta-Analysis of Observational Studies. Arthritis Care Res (Hoboken). 2020 Jul;72(7):991-1000.
https://pubmed.ncbi.nlm.nih.gov/31207113/

Conference Papers

– Andrea Dell'Isola, Aleksandra Turkiewicz, Subhashisa Swain, Weiya Zhang, Sita Bierma-Zeinstra, Jos Runhaar, Daniel Prieto-Alhambra, Martin Englund, The association between different comorbidities and osteoarthritis development in peripheral joints:
a population based nested case-control study. (OARSI 2022)
– A. Kamps, J. Runhaar, M. de Wilde, M.A.J. de Ridder, J. van der Lei, S. Swain, W. Zhang, D. Prieto-Alhambra, M. Englund, E.I.T de Schepper, S.M.A. Bierma-Zeinstra. Prevalence of comorbidity among incident osteoarthritis patients and matched controls". (Orally presented at NAPCRG 2021 & OARSI 2022)
– Pineda Moncusi M.; Strauss, V.; Robinson, D.; Prieto-Alhambra, D. and Khalid, S. (2022). Unsupervised Learning to Understand Patterns of Comorbidity in 633,330 Patients Diagnosed with Osteoarthritis. In Proceedings of the 15th International Joint Conference on Biomedical Engineering Systems and Technologies - Volume 3:
BIOINFORMATICS, ISBN 978-989-758-552-4, ISSN 2184-4305, pages 121-129. (BIOSTEC 2022)
– Pineda Moncusi M.; Strauss, V.; Robinson, D.; Prieto-Alhambra, D. and Khalid, S. (2022). Unsupervised Learning to Understand Patterns of Comorbidity in 633,330 Patients Diagnosed with Osteoarthritis. BIOINFORMATICS - 13th International Conference on Bioinformatics Models, Methods and Algorithms. Oral Communication #10 (Feb 12th 2022). (BSM, 2022)

EULAR Abstracts

2020

– OPO184:
  Risk of comorbidities following incident clinician-diagnosed knee or hip osteoarthritis: a registry-based cohort study.
  K. Pihl, A. Turkiewicz, V. Hughes, W. Zhang, S. M. A. Bierma-Zeinstra, D. Prieto-Alhambra, M. Englund.
– OPO074:
  Multimorbidity clusters, determinants and trajectories in Osteoarthritis in the UK: findings from the Clinical Practice Research Datalink
  S. Swain , C. Coupland , V. Strauss , C. Mallen , C. F. Kuo , A. Sarmanova , M.Doherty , W. Zhang.
  http://scientific.sparx-ip.net/archiveeular/

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Burden and impact of co-morbidity and frailty in patients with RMDs in Europe: a multi-national analysis of big healthcare data

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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2019–2022

Project Url
www.foreum.org/projects/?id=180

Concept
The Observational and Medical Outcomes Partnerships (OMOP) common data model (CDM) provides a framework for standardising observational health data. Multi-database studies can then be performed without a need to pool patient-level data across network sites, and with only aggregate results shared.
In this project we are mapping data from biologic registries to the OMOP CDM. This will then allow for an assessment of comorbidity in people with severe RA in Europe, and provide the basis for further collaborative projects.

Objectives
To map national biologic registry data collected from different European countries to the OMOP CDM. In particular, five biologic registries are currently being mapped to the OMOP CDM: 1) the Czech biologics register (ATTRA), 2) Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas (BIOBADASER), 3) British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA), 4) German biologics register 'Rheumatoid arthritis observation of biologic therapy' (RABBIT), and 5) Swiss register 'Swiss Clinical Quality Management in Rheumatic Diseases' (SCQM).
Subsequently, to summarise the available data on comorbidities across these registries.

Interim Results
A total of 64,901 individuals are included in the 5 registries being mapped to the OMOP CDM. The number of unique baseline conditions being mapped range from 17 in BSRBR-RA to 108 in RABBIT, while the number of baseline medications range from 26 in ATTRA to 802 in BSRBR-RA. Those registries which captured more comorbidities or medications generally allowed for these to be inputted as free text.
Mapping biologic registry data to the OMOP CDM is feasible. The adoption of the OMOP CDM will facilitate collaboration across registries, and allow for multi-database studies which include data from both biologic registries and other sources of health data which have been mapped to the CDM.

Final Results

Biologic/rheumatology registries from 5 countries were mapped to the OMOP Common Data Model. Such data is the beginning to enable future multinational federated collaborations (i.e. with no transfer of patient-level data). We run quality control checks, including conformity, plausibility, and completeness. The resulting data are available for future collaboration and distributed network analyses beyond our work/research.
Second, we created an analytical package to assess the presence of comorbidities at each of the registries. Enabled by the use of the same CDM, the same analytical code run across sites, with only aggregated results shared between partners. Two key learnings are: 1) there is great heterogeneity in the recording of comorbidities in biologic registries across Europe; and 2) comorbidities are very common amongst patients with RA included in biologic registries. More work needs to be done to harmonise the information on comorbidity contained in European biologic registries.

Lay Summary

We speculated that by curating data to a common data model, we would be able to analyse the presence of comorbidities (concomitant conditions) amongst people with Rheumatoid Arthritis registered in existing biologic registries across Europe. We processed data accordingly in collaboration with colleagues from Czechia, Germany, Spain, Switzerland, and the UK.
After doing so, we looked at comorbidities, and learned that such information is recorded in very different ways in the different databases. More work is therefore needed to harmonise biologic registries data to enable future collaboration on the association between comorbidity and patient-relevant outcomes.

Patient Voice

Patient research partners are being involved as research partners throughout this project.

Publications

– Burn, E. & Kearsley-Fleet, Lianne & Hyrich, K. & Schäfer, Martin & Huschek, Doreen & Strangfeld, Anja & Zavada, J. & Lagová, M. & Courvoisier, Delphine & Tellenbach, Christoph & Lauper, Kim & Sánchez-Piedra, C. & Montero, Nohelia & Sánchez Costa, Jesús & prieto-alhambra, Daniel. (2020). OP0285 TOWARDS IMPLEMENTING THE OMOP CDM ACROSS FIVE EUROPEAN BIOLOGIC REGISTRIES. Annals of the Rheumatic Diseases. 79. 177.2-178. 10.1136/annrheumdis-2020-eular.3303.
https://ard.bmj.com/content/79/Suppl_1/177.2
– Kearsley-Fleet, Lianne & Hyrich, K. & Schäfer, Martin & Huschek, Doreen & Strangfeld, Anja & Zavada, J. & Lagová, M. & Courvoisier, Delphine & Tellenbach, Christoph & Lauper, Kim & Sánchez-Piedra, C. & Montero, Nohelia & Sánchez Costa, Jesús & prieto-alhambra, Daniel & Burn, E.. (2021). OP0105 FEASIBILITY AND USEFULNESS OF MAPPING BIOLOGIC REGISTRIES TO A COMMON DATA MODEL: ILLUSTRATION USING COMORBIDITIES. Annals of the Rheumatic Diseases. 80. 58.2-59. 10.1136/annrheumdis-2021-eular.888.
https://ard.bmj.com/content/80/Suppl_1/58.2

Project Team/Centres

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2018

Call for international exchange 1-year fellowships

FOREUM is committed to funding and promoting scientific research into rheumatic and musculoskeletal diseases (RMD) and has a goal to foster links between rheumatology units in different countries. Consistent with these goals is the establishment of a call for international exchange fellowships that have the specific objective of facilitating the development of research capacity and training high-caliber applicants in RMD research.

The first call for a 1-year fellowship was launched in **2018** and out of 5 letters of intent 4 projects were selected for funding:

- T cell-fibroblast interactive cell atlas in systemic sclerosis: Role of T cell exhaustion in tissue fibrosis
- Incidence and outcome of cardiovascular disease in patients with inflammatory joint diseases
- Epigenetic regulation by DAMPs underlying trained immunity in health and disease
- Exploring disease control and treatment response in ankylosing spondylitis versus non-radiographical axial spondylarthritis

T cell-fibroblast interactive cell atlas in systemic sclerosis: Role of T cell exhaustion in tissue fibrosis

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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2019–2020

Project Url
www.foreum.org/projects/?id=168

Concept
In recent years, accumulating evidence suggests that exhausted T cells (Tex) are of paramount importance for the maintenance of immunological self-tolerance and immune homeostasis. Tex are characterized by high expression of co-inhibitory receptors (CiR), and their key role is supported by the worsening of autoimmune diseases after depletion, or inhibition of, co-inhibitory molecules in mice, as well as in man. The purpose of this project was to examine T cell exhaustion and the role of Co inhibitory receptors(CiRs) in the outcome of systemic sclerosis.

Final Results
Projects implemented :
ELISA analysis of soluble CiRs. Analysis of extracellular expression of CiRs in by diseased T cells through flowcytometry. Different sub groups of PBMC's including T and B cells were analysed for their expression of CiR's and compared to healthy controls. Functional studies were carried out on SSc PBMC's by blocking/stimulating PD1 and LAG 3 . The results from these experiments are promising.

Lay Summary
The experimental nature of this research proposal limited the potential contribution of patient research partners. However, A project taskforce was setup at Aarhus University based on EULAR recommendations during the course of this project.
Coinhibitory receptors are molecules that regulate the functions of several immune cells and help to maintain a homeostatic balance. The functionality of these receptors can be utilized to regulate and or stabilize autoimmune responses in rheumatic diseases.

Publications

EULAR Abstracts

2020

– AB0151:
  Preliminary results show an increased expression of coinhibitory receptors in Systemic Sclerosis
  http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

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– S Greisen, Stinne Greisen Department of Biomedicine, Aarhus University, DENMARK
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Incidence and outcome of cardiovascular disease in patients with inflammatory joint diseases

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Funding and Timeline
FOREUM reserach grant: EUR 50.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=169

Concept
Patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) have a 1.5- to 2-fold increased risk of cardiovascular disease (CVD) compared to the general population. To be able to prevent CVD in patients with inflammatory joint diseases (IJD), it is of great importance to provide up-to-date evidence on the prevalence of CVD and the effect of medication on CVD outcome. The project is conducted within the Norwegian Cardio-Rheuma register, which is a nationwide register linkage study with data on the whole Norwegian population and all patients with RA, PsA and AS from 2008 – 2017, as well as similar Finnish register data.

Objectives
- To explore contemporary incidence and prevalence of RA, PsA and AS in Norway
- To evaluate all-cause and cause-specific mortality in patients with RA, AS and PsA compared to the general population
- To study prevalence, incidence and outcome of CVDs in IJDs compared to the general population
- To compare the risk of CVD among users and non-users of biologic disease-modifying antirheumatic drugs in patients with IJD
- To explore sex differences in CVD event rates in patients with IJD compared to the general population
- To compare the use of secondary preventive medication in patients with IJD and general population controls after acute coronary syndrome (ACS)
- To study similar research questions among Finnish IJD patients based on Finnish register data

The results from this project may facilitate the establishment of CVD prevention recommendations/guidelines specifically developed for patients with IJD.

Goals/Milestones
- October 2020:
  Linkage of data across registers
- November 2020 - February 2021:

Preparation of the Norwegian Cardio-Rheuma register database and initial analyses
– March - October 2021:
Statistical analyses, preparation of first manuscripts and their submission to international peer-reviewed journals

Interim Results

The register-based incidence estimates of RA and PsA in Norway are slightly higher than in previous Norwegian studies, and it was found that risk of RA and PsA was higher among persons with lower education level. Even in the 2010s, Norwegian RA patients suffer from excess mortality compared to the general population. In contrast, mortality among PsA patients was similar to the general population, which may relate to an overall milder disease course and/or improved treatment. In addition to effective suppression of disease activity, our findings warrant further attention to co-morbidity prevention in RA.
Among Finnish RA patients, long-term outcomes after myocardial infarction (MI) compared to the general population are impaired. Glucocorticoid use before MI is associated with higher mortality and recurrent MI. Secondary prevention of CVD among RA patients should be prioritized.

Final Results

Our register-based estimates of RA and PsA incidence in Norway were 42/100,000 person-years and 26/100,000 person-years, respectively. The incidence of RA and PsA was higher among persons with lower education level. Even in the 2010s, Norwegian RA patients suffer from excess all-cause and cardiovascular mortality compared to the general population. In contrast, mortality among PsA patients was similar to the general population. In our Finnish register-linkage study, long-term outcomes after myocardial infarction among patients with RA were impaired compared to the general population. In an international audit exploring cardiovascular disease risk assessment and management among patients with RA in 19 countries, we revealed that although cardiovascular disease and its risk factors were more common among RA patients with diabetes mellitus compared to those without, lipid goals were more frequently obtained among RA patients with diabetes. All in all, our findings warrant more attention to cardiovascular disease prevention in RA patients.

Lay Summary

The goal of this post-doctoral research project was to study the epidemiology of inflammatory joint diseases and related cardiovascular diseases within the Norwegian Cardio-Rheuma Register, which is a newly-established register-linkage study combining data from Norwegian nationwide registers on the entire Norwegian adult population ≥18 yearsbetween 2008and 2017. During this FOREUM-funded post doc year, we have shown that over 1.5% of the Norwegian adult population have RA, PsA or axSpA. Approximately 42 and 26 persons are diagnosed with RA and PsA, respectively, each year in a population of 100,000 adult Norwegians. Even in the 2010s, Norwegian RA patients but not PsA patients had a higher risk of death compared to the general population. The most common causes of death in were cardiovascular disease, malignancies and respiratory disease, and patients with RA had increased risk of death from all of these causes.In a Finnish registry-linkage study, we showed that Finnish RA patients who have suffered a myocardial infarction have a higher risk of death, a new myocardial infarction, and revascularization compared to well-matched non-RA patients. In an international audit among RA patients in 19 countries, we revealed that although cardiovascular disease and its risk factors were more common among

RA patients with diabetes mellitus compared to those without, lipid goals were more frequently obtained among RA patients with diabetes. Our findings warrant more attention to cardiovascular disease prevention in RA.

Patient Voice

Two patient representatives, one from the patient user council of Diakonhjemmet hospital and one from the National Association of Rheumatology, are involved in all stages of the project. The aim is to have regular meetings and communication with the patient representatives to include them in the development of protocol writing, choice of outcome measures, final analyses and presentation and dissemination of results. The project group will actively seek to disseminate results from the projects to patients through lay summaries and presentations at patient organization meetings.

Publications

- Kerola, A. M., Sexton, J., Wibetoe, G., Rollefstad, S., Crowson, C. S., Mars, N., Kazemi, A., Haavardsholm, E. A., Kvien, T. K., Semb, A. G. (2021). Incidence, sociodemographic factors and treatment penetration of rheumatoid arthritis and psoriatic arthritis in Norway. Seminars in Arthritis and Rheumatism, 51(5), p. 1081-1088. doi: 10.1016/j.semarthrit.2021.08.006 https://doi.org/10.1016/j.semarthrit.2021.08.006
- Palomäki A*, Kerola AM*, Malmberg M, Rautava P, Kytö V. Patients with rheumatoid arthritis have impaired long-term outcomes after myocardial infarction - a nationwide case-control registry study. Rheumatology (Oxford). 2021 Mar 1:keab204. doi: 10.1093/rheumatology/keab204. Epub ahead of print. PMID: 33667301 *shared first authorship https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keab204/6154670
- Semb AG, Rollefstad S, Ikdahl E, Wibetoe G, Sexton J, Crowson C, van Riel P, Kitas G, Graham I, Rantapää-Dahlqvist S, Karpouzas GA, Myasoedova E, Gonzalez-Gay MA, Sfikakis PP, Tektonidou MGG, Lazarini A, Vassilopoulos D, Kuriya B, Hitchon C, Stoenoiu MS, Durez P, Pascual-Ramos V, Galarza-Delgado DA, Faggiano P, Misra DP, Borg AA, Mu R, Mirrakhimov EM, Gheta D, Douglas K, Agarwal V, Myasoedova S, Krougly L, Valentinovna Popkova T, Tuchyňová A, Tomcik M, Vrablik M, Lastuvka J, Horak P, Medkova HK, Kerola AM; SURF-RA collaborators. Diabetes mellitus and cardiovascular risk management in patients with rheumatoid arthritis: an international audit. RMD Open 2021; 7:e001724. doi: 10.1136/rmdopen-2021-001724 https://rmdopen.bmj.com/content/7/2/e001724
- Kerola, A. M., Rollefstad, S., & Semb, A. G. (2021). Atherosclerotic Cardiovascular Disease in Rheumatoid Arthritis: Impact of Inflammation and Antirheumatic Treatment. European cardiology, 16, e18. https://doi.org/10.15420/ecr.2020.44 https://doi.org/10.15420/ecr.2020.44
- Kerola AM, Palomäki A, Rautava P, Nuotio M, Kytö V. (2021). Sex Differences in Cardiovascular Outcomes of Older Adults after Myocardial Infarction. Journal of the American Heart Association. doi: 10.1161/JAHA.121.022883. https://www.ahajournals.org/doi/pdf/10.1161/JAHA.121.022883

– Kerola AM, Kazemi A, Rollefstad S, Lillegraven S, Sexton J, Wibetoe G, Haavardsholm EA, Kvien TK, Semb AG. All-cause and cause-specific mortality in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: a nationwide registry study. Rheumatology (Oxford). 2022 Apr 4:keac210. doi: 10.1093/rheumatology/keac210. Epub ahead of print. https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac210/6563184?login=false
– Kerola AM, Rollefstad S, Kazemi A, Wibetoe G, Sexton J, Mars NJ, Kauppi M, Kvien TK, Haavardsholm EA, Semb AG (2022) Psoriatic arthritis, axial spondyloarthritis and rheumatoid arthritis in Norway:
nationwide prevalence and use of biologic agents, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2021.1997436
https://www.tandfonline.com/doi/full/10.1080/03009742.2021.1997436?scroll=top&needAccess=true
https://doi.org/10.15420/ecr.2020.44

2021
– POS0029 Incidence and treatment penetration of rheumatoid arthritis in Norway – a nationwide register linkage study
– POS1041 Prevalence, incidence and antirheumatic drug use in psoriatic arthritis (PsA) in Norway

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Epigenetic regulation by DAMPs underlying trained immunity in health and disease

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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2019–2020

Project Url
www.foreum.org/projects/?id=170

Concept
Trained immunity is a process of innate immune memory in which a primary stimulus, such as β-glucan, enhances the response of monocytes upon nonspecific re-stimulation. During trained immunity, an epigenetic reprogramming of monocytes is observed, characterized by histone methylation marks in pro-inflammatory genes and an increased production of TNFa and IL-6. In humans, apart from the protection from re-infection, this process might lead in the long-term to the development and/or persistence of chronic inflammatory conditions. The hypothesis that trained immunity contributes to the initiation and perpetuation of the inflammatory response in rheumatoid arthritis (RA) has not been investigated so far.

Objectives
In the current proposal, we aim to better investigate pathogen-associated and damage-associated molecular pattern (PAMP and DAMP, respectively)-induced trained immunity in healthy individuals and RA patients. The association of epigenetic modifications with transcriptomic data will identify gene promoters, enhancers and transcription factor motifs possibly involved in trained immunity. Gene silencing will give more insights into their function. By targeting specific mechanisms of trained immunity on either molecular, protein or epigenetic level, novel therapeutic approaches could be developed.

Goals/Milestones
– The characterization of the innate immune memory process in healthy human monocytes (month 1-4)
– The investigation of the innate immune memory process in RA (month 4-9)
– The analysis of trascriptomic and epigenetic changes leading to innate immune memory (month 6-12)

Interim Results
Citrullinated vimentin induces epigenetic modifications and metabolic changes in monocytes, probably through a STING and TBK1-dependent activation, resulting in enhanced cytokine and chemokine production upon restimulation. Inhibition of the STING signaling pathway may be a novel therapeutic target for myeloid activation in RA.

Final Results

Citrullinated vimentin, which functions as damage-associated pattern in rheumatoid arthritis, seems to induce trained immunity in vitro in healthy individuals, thereby promoting chronic inflammation. The monocytes undergo epigenetic modifications and metabolic changes, resulting in functional reprogramming and enhanced release of cytokines and chemokines upon restimulation. The differentiation to an invasive macrophage with proinflammatory signature turns the monocytes to a decisive player in the pathogenesis of rheumatoid arthritis. By targeting the specific mechanisms of trained immunity on either molecular, protein or epigenetic level, novel therapeutic approaches could be developed.

Lay Summary

The ability of monocytes to develop adaptive features and provide long-term protection against pathogenic reinfection is termed "trained immunity". The cells undergo a transcriptional, metabolic and functional reprogramming toward a pre-activated state. Since citrullinated vimentin plays an important role in the pathogenesis of rheumatoid arthritis, we hypothesized that it functions as damage associated pattern and induces innate immune memory, thereby promoting chronic inflammation. We showed that citrullinated vimentin induces epigenetic modifications and metabolic changes in monocytes, probably through a STING and TBK1-dependent pathway, resulting in functional reprogramming and enhanced release of cytokines and chemokines upon restimulation. Our data suggest that citrullinated vimentin induces the differentiation to an invasive macrophage with proinflammatory signature that constitutes a decisive player in the pathogenesis of rheumatoid arthritis. By targeting the specific mechanisms of trained immunity on either molecular, protein or epigenetic level, novel therapeutic approaches could be developed.

Patient Voice

For this laboratory project, based on novel technologies, patients have not been directly involved in the design of the experiments, however peripheral blood from the patients will be collected and analyzed.

The development of novel potential therapeutic targets and strategies will clearly benefit the patients.

Publications

– POS0368: itrullination induces epigenetic memory of the innate immune system. Laskari K, Sabu S, Distler O, Karouzakis E, Neidhart M. Annals of the Rheumatic Diseases 2021;80: 414. DOI: 10.1136/annrheumdis-2021-eular.3302 https://ard.bmj.com/content/80/Suppl_1/414.1

Project Team/Centres

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Exploring treatment response in AS versus non-radiographic axSpA

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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2019–2020

Project Url
www.foreum.org/projects/?id=171

Concept

Ankylosing spondylitis (AS) is the severe, end stage phenotype of axial spondyloarthritis (axSpA), which also comprises an earlier, undifferentiated state, referred to as non-radiographic axSpA. Although biologics have revolutionized the management of patients with axSpA, there are limited data evaluating the treatment response between subjects with AS and nr-axSpA. Controversy remains as to whether nr-axSpA represents a milder form with biologic DMARD (bDMARD) treatment restrictions still in place in many countries.

Final Results

The two main objectives were:

- To examine the baseline characteristics in axSpA patients in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) according to radiographic status.
- To explore treatment response to bDMARDs at 1 year as well as drug survival according to radiographic status (nr-axSpA vs r-axSpA)

Baseline characteristics were available for 1,145 patients. Those with r-axSpA were more likely to be male, were older, and had longer disease duration.
Follow-up ASDAS at 1 year was available in 290 patients. Two thirds of the patients achieved ASDAS low disease state at one year regardless of radiographic status (nr-axSpA: 64.2% vs r-axSpA: 66.1, Diff: -1.9%, 95% CI -13.7 to 9.8). Further, no significant differences were seen between the groups in attaining ASDAS CII (nr-axSpA: 50.7% vs r-axSpA: 44.7%, Diff: 6.0%, 95% CI -7.8 to 19.8%) or MI (nr-axSpA: 20% vs r-axSpA: 18.7%, Diff: 1.3%, 95% CI -9.7 to 12.3%).
Although there appeared to be some differences in the baseline characteristics when exploring this cohort, according to radiographic status, which are likely related to the natural history of the disease; the level of biologic response was comparable between the groups supporting the concept of axSpA as a single disease entity.

Lay Summary

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects mainly the spine. Ankylosing spondylitis (or radiographic axSpA) is the most severe form of axSpA with an earlier stage called nonradiographic axSpA (nr-axSpA) that may not show as full blown structural changes of sacroiliitis in a simple radiograph, much the same as rheumatoid arthritis may not be identifiable on xrays of hands and feet despite giving pain and stiffness in these joints. This is why it is sometimes difficult for axSpA to be diagnosed, particularly when the disease has not been present for too long. Some argue that nr-axSpA is a milder form of axSpA, although there is evidence that patients suffering from nr-axSpA may have the same symptoms and disease
burden than those affected by radiographic axSpA (r-axSpA). In some countries, there are still treatment restrictions in nr-axSpA and not all patients can benefit from biological therapies.
In order to understand the possible differences between nr and r-axSpA/AS, a study was designed to describe the baseline characteristics, biologic treatment response and treatment retention (drug survival) of axSpA patients in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS). A total of 1,145 axSpA patients were included in this analysis. It was found that there was a higher male prevalence, older age and longer disease duration in the r-axSpA subgroup, however a similar percentage of patients (nr-axSpA: 64.2% vs r-axSpA: 66.1) achieved a state of low disease as measured by ASDAS (disease activity score for axSpA) after 1 year treatment with biologic drugs regardless of their sub-group classification (ie nr versus r-axSpA/AS). Further, drug retention was similar for both subgroups, even when adjusted for sex, age, baseline ASDAS, smoking status, disease duration, HLA-B27 and prescribed biologic.
In conclusion, this study showed that the level of biologic response and drug survival was comparable between nr-axSpA and r-axSpA in this cohort. These results add evidence that nr-axSpA and r-axSpA should be treated with the same treatment strategies, guaranteeing the access to biologic treatments to all patients with axSpA who may need them.

Publications

Michelena X, Zhao SS, Dubash S, Dean LE, Jones GT, Marzo-Ortega H. Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the BSRBR-AS registry. Rheumatology (Oxford). 2021 Jan 27:keab070. doi: 10.1093/rheumatology/keab070. Epub ahead of print. PMID: 33502476

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EULAR Abstracts

2020

- FRI0287: Biologic drug response does not appear related to radiographic status in axial Spondyloarthritis: data from the BSRBR-AS registry
  http://scientific.sparx-ip.net/archiveeular/

Project Team/Centres

- X Michelena Vegas, Hospital Universitari de Bellvitge, SPAIN (lead)
- J M Nolla Solé, Hospital Universitari de Bellvitge, SPAIN
- H Marzo-Ortega, University of Leeds, UNITED KINGDOM

2019

Call for research proposals in the area of Innovative Medicine

This program was designed as an open research call seeking for the best and most visionary approaches to better understand RMDs and to improve the life of patients with RMDs.

As such, the call was not limited to a specific disease within the RMD spectrum but rather intended to target fundamentally new concepts that have potential to gain concept-changing insights into RMDs. Rapid improvements in molecular biotechnology, imaging and computer sciences have started to influence todays' medicine in so far unprecedented manner.

The call was launched in **2019**, and out of 32 letters of intent 2 projects were selected for funding:

- ROR2 blockade for cartilage regeneration and pain relief in osteoarthritis
- The Gestalt of Early Arthritis in Europe: Beyond Expert Opinion alone

ROR2 blockade for cartilage regeneration and pain relief in OA

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 599.862
Project duration: 2019–2022

Project Url
www.foreum.org/projects/?id=165

Concept
Osteoarthritis is due to loss of cartilage in the joints. Without cartilage, patients struggle with walking, climbing stairs and taking a bath. Pain killers help initially, but when the cartilage is destroyed, a joint replacement is the only remedy that can return patients to some degree of independence, but not to full function. Joint replacements have a finite life and revision surgery to replace them is complex, making them sub-optimal especially for the growing number of younger patients with osteoarthritis.
The project team discovered that blocking a specific receptor called ROR2 on the surface of cartilage cells induces cartilage regeneration and sustained pain relief in mice with osteoarthritis. Additionally, it has been shown that this approach also works on human cartilage.
We hope to develop a first-in-kind disease modifying drug that will slow progression or even revert cartilage breakdown and, at the same time, treat pain for patients with osteoarthritis.

Objectives
The formulation that we developed is effective with intra-articular injections every 5 days, which is too frequent to be tolerated by patients. We intend to develop ROR2 blockade which can be delivered systemically – for instance with subcutaneous, self-administered injections - or intra-articularly not more often than every 3 months. Such formulations would be amenable to enter clinical practice.
This research also aims to validate ROR2-dependent biomarkers for patient selection and rapid efficacy assessment.

Goals/Milestones
- Aim 1: Generate and validate a humanized monoclonal blocking antibody to ROR2
- Aim 2: Stabilize siRNA for longer-term delivery
- Aim 3: Identify biomarkers for patient selection and assessment of efficacy

Interim Results

More than 20 siRNA modifications were generated so far which are being tested for efficacy and durability of the effect.

The ROR2 gene was deleted specifically in the joints of mice with osteoarthritis and currently it is being assessed if this intervention has protected them from cartilage breakdown.

Patient Voice

Patients with arthritis have helped identify priorities of the study and have helped the research team to understand what would be acceptable in terms of frequency of injections, thereby effectively setting the goals of the project.

Throughout this project, patients are being consulted. Patient input has included their views upon local injections that would require visits to a doctor versus systemic injections they could take by themselves, balancing the duration of a dose (needing less frequent injections) versus reversibility in case of non-tolerability. This led to important insights, including that patients with polyarthritis have different needs from patients with a single affected joint. Finally, we have discussed with patients their willingness for samples to be taken to assess suitability for a ROR2-blocking treatment, and to monitor effectiveness of the drug engaging with the target throughout a course of treatment.

Publications

– Thorup, A.-S. et al. ROR2 blockade as a therapy for osteoarthritis. Science Translational Medicine 12, (2020) DOI: 10.1126/scitranslmed.aax3063
https://stm.sciencemag.org/content/12/561/eaax3063
– Nalesso, G. et al. Calcium calmodulin kinase II activity is required for cartilage homeostasis in osteoarthritis. Scientific Reports 11, 5682 (2021) PMCID: PMC7952598 DOI: 10.1038/s41598-021-82067-w
https://www.nature.com/articles/s41598-021-82067-w
– Thorup, A.-S., Dell'Accio, F. & Eldridge, S. E. Lessons from joint development for cartilage repair in the clinic. Dev. Dyn. (2020) doi:10.1002/dvdy.228. DOI: 10.1002/dvdy.228
https://anatomypubs.onlinelibrary.wiley.com/doi/10.1002/dvdy.228
– Eldridge, S. E. et al. Agrin induces long-term osteochondral regeneration by supporting repair morphogenesis. Science Translational Medicine 12, (2020). DOI: 10.1126/scitranslmed.aax9086
https://stm.sciencemag.org/content/12/559/eaax9086

EULAR Abstracts

2021

OPO200: Blocking ROR2 improves cartilage integrity and provides pain relief in osteoarthritis

Project Team/Centres

– F dell'Accio, Queen Mary University of London, UNITED KINGDOM (lead)
– A S Thorup, Queen Mary University London, UNITED KINGDOM
– S Lohmander, University of Lund, SWEDEN
– J C Bertrand, Otto-von-Guericke-Universität, GERMANY

The Gestalt of Early Arthritis in Europe: Beyond expert opinion alone

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 226.186
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=167

Concept
Research in rheumatology has successfully focused on early diagnosis and early intervention, resulting in reduced burden of disease. However, the 'early aggressive' approach may also have 'side effects': overdiagnosis/overtreatment. Disentangling early arthritis (EA) patients with a 'full blown disease' prognosis and those who may fare a milder course or even go into spontaneous remission is a real challenge at presentation. Expert-based classification criteria have been revised to capture these early patients better but suffer from circularity. We propose an analytical, non-expert-based, approach that allows us to gain a more unbiased insight into the concept of EA, by investigating EA's 'latent constructs' (latent class analysis) and how these constructs change over time (latent transition analysis).

Objectives
- To identify the latent EA phenotypes by using an analytical technique that circumvents expert opinion.
- To assess if (and how) EA patients change latent phenotypes over time.
- To assess if there are prognostic dissimilarities between different latent EA phenotypes.
- To assess how the 2010 EULAR-ACR RA classification criteria capture the latent EA phenotypes.

Goals/Milestones
Task 1: Database extraction and management (year 1 and 2)
Task 2: Data analysis and interpretation (year 1, 2 and 3)
Task 3: Abstract presentation (EULAR and PARE) (year 3)
Task 4: Mansurcript writing (year 3)
Task 5: Smartphone app. design and evaluation (year 3)

Patient Voice
A patients' advisory group (PAG) consisting of 3 experienced patient research partners will be involved in all steps of the project, including study concept, data interpretation and participation

in meetings. The study Principal Investigator (PI) and the Study Coordinator (SC), will work as the bridge between the PAG and the remaining collaborators. Members of the PAG will present the project main findings in the PARE conference with close support by the PI and SC, and their contribution recognized by authorship in publications.

Project Team/Centres

- R Landewé, University of Amsterdam, THE NETHERLANDS (lead)
- D van Schaardenburg, University of Amsterdan, NETHERLANDS
- A van der Helm-van Mil, UMC Leiden, THE NETHERLANDS
- S Ramiro, Leiden University, THE NETHERLANDS
- S Bergstra, Leiden University, THE NETHERLANDS
- B Combe, University of Montpellier, FRANCE
- A Sepriano, Nova Medical School, PORTUGAL
- M de Wit, PARE, THE NETHERLANDS
- E Frazão Mateus, PARE, PORTUGAL
- A Kent, PARE, UNITED KINGDOM
- B T van Dijk, Leiden University Medical Centre, THE NETHERLANDS

2019

Call for career research grants

FOREUM is committed to promote the best talents in the field of rheumatic and musculoskeletal diseases (RMD). Consistent with these goals FOREUM issued a new call that aims to fund excellent young researchers promoting innovative ideas and supporting high quality research projects covering basic and clinical science projects related to RMDs. Scientific excellence is the key eligibility criterion for this career research grant initiative, which aims to foster independent science and intends to develop new research leaders in the field.

The first call was launched in **2019**, and out of 58 letters of intent 4 projects were selected for funding:

- Leveraging genetic and epigenetic evidence in spondyloarthritis to predict disease severity and to discover new drug targets
- The role of immune effector fibroblast subsets in treatment refractory rheumatoid arthritis
- The role of the intervertebral disc cartilage catabolites in Modic type 1 changes
- Trends and factors associated with prescription opioid utilisation, dependence and deaths in patients with musculoskeletal conditions

Uncover the genetic basis of Spondyloarthritis to predict disease severity and to discover new drug targets

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=172

Concept
SpA is a chronic inflammatory rheumatic disease. Reliable diagnosis and prognosis biomarkers are lacking and there is a need for new treatments. Given the strong genetic background of spondyloarthritis with more than 50 genetic factors of susceptibility already identified, use of genetic data is an appealing approach to better understand the disease pathogeny and to improve its management. The possibility to identify groups of patients with similar clinical and genetic characteristics might be the first step toward precision of medicine and help to propose more tailored treatment strategies.

Objectives
The main objective is to translate the results of genomics studies in spondyloarthritis into clinical benefits. In particular we aim at identifying genetic factors associated with disease severity and at discovering new treatment targets.

Goals/Milestones
Milestone 1: identification of genetic factors associated with disease severity (year 1-3)
Milestone 2: identification of new treatment targets through a genetics-led approach (year 2-3)
Milestone 3: dissemination of the findings (year 2-3)

Patient Voice
This study involves established patient cohorts and translational research. It is difficult to include patients at this stage into the design of the study. We have however approached two patient representatives who agreed to help us writing our patient information sheets and communicating our results.

Project Team/Centres
– F Costantino, Université Versailles Saint-Quentin, FRANCE (lead)
– M Breban, Université Versailles Saint-Quentin, FRANCE

The role of immune effector fibroblast subsets in treatment refractory RA

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=173

Concept

Fibroblasts are cells which form the lining of the joint. During inflammation these cells expand in number and exist as several distinct subtypes that have different roles in driving inflammation and damage depending on where these cells are located in the lining tissue. We have shown that the presence of certain subtypes of fibroblast within the joint lining is critical in determining the severity and persistence of inflammation. What is not known, is how the proportion, and type of fibroblasts within the joint lining relates to treatment response, treatment failure and the development of refractory disease.

Objectives

To determine the role of specific subtypes of synovial fibroblasts (cells which form the lining of the joint) in the development of treatment refractory disease.

Goals/Milestones

WP1: Fibroblast heterogeneity in refractory disease
WP2: Mouse in vivo studies
Dissemination activities: @ EWRR, EULAR, ACR

Patient Voice

Patient participants within the Birmingham Rheumatology Research Patient Partnership (R2P2) have participated in the designing of the clinical studies within this project and will continue to do so and provide feedback on their experiences of synovial biopsy during the course of the project so we can identify ways to improve their experience. Findings of the study will be presented and discussed with the group to we can consider the implications for patients. The team will be involved in the dissemination of the research outputs from all aspects of the proposal to patient groups and the wider public and in the publication of the study results.

Publications

– - Ilya Korsunsky, Kevin Wei, Mathilde Pohin, ..., Christopher D. Buckley, Michael B. Brenner, Soumya Raychaudhuri. Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases. Med (N Y). 2022 May 26; S2666-6340(22)00184-2. doi: 10.1016/j.medj.2022.05.002. Online ahead of print https://www.sciencedirect.com/science/article/pii/S2666634022001842

Project Team/Centres

– A Croft, University of Birmingham, UNITED KINGDOM (lead)
– C Buckley, University of Birmingham, UNITED KINGDOM

The role of the intervertebral disc cartilage catabolites in Modic type 1 changes

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=174

Concept
Inflammation and scarring of the vertebral bone marrow are often seen in patients with chronic low back pain on MRI. These changes are called Modic type 1 changes (MC1). They occur adjacent to a degenerated intervertebral disc. In most cases disc degeneration does not cause pain. In contrast, MC1 are in most cases a source of pain.

Objectives
The aim is to identify molecules that cause inflammation and scarring of vertebral bone marrow, processes that contribute to chronic low back pain. Once these molecules are identified and understood how they cause inflammation and scarring of the bone marrow, different drugs that stop this undesired painful reaction in the bone marrow will be tested.

Goals/Milestones
M1 12 mts: Identified ECM-derived DAMPs and dysregulated pathways
M2 24 mts: Most relevant ECM-derived DAMPs identified causing MC1-like changes in-vitro
M3 36 mts: Inhibitors tested to inhibit MC1-like changes by ECM-DAMPs in-vitro
M4 40 mts: Last manuscript submitted. Project completed.

Patient Voice
A supervising committee with patient representatives from local low back pain organizations and a few key opinion leaders will be formed. This committee has the goal to control the translational direction of the project from the very beginning and to help communicate the findings of the project.

Project Team/Centres
– S Dudli, University of Zurich, SWITZERLAND (lead)
– O Distler, University of Zurich, SWITZERLAND

Trends and factors associated with prescription opioid utilisation, dependence and deaths in patients with musculoskeletal conditions

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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=175

Concept

Rising opioid use has been associated with an alarming rise in opioid-related harms, dependence and mortality in North America. However, fewer data are available in Europe. RMDs are one of the most common indications for prescribing opioids. These patients may already be at high-risk of opioid-relatedmorbidity/mortality due to multimorbidity, immunosuppression and polypharmacy.

Objectives

In new opioid users with the following RMDs:
rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, osteoarthritis and fibromyalgia to:

- Characterise national UK opioid prescribing trends between 2006-2019
- Evaluate trends in hospital admissions associated with opioid-related prescriptions, dependence and mortality
- Identify individual, prescribing, demographic and contextual risk factors that predispose to opioid-dependence and mortality
- Predict opioid-related mortality risk to enable a stratified approach to prescribing in clinical care

Goals/Milestones

Month 6: Obtain linked data, prepare datasetsfor analysis, characterise study population including subpopulations for each condition using established algorithms
Month 12: Describe national opioid prescribing trends between 2006-19 for each condition
Month 18: Prepare and analyse data on hospital admissions related to opioids, opioid-related dependence and opioid-related mortality
Month 24: Complete analysis using multi-statemodel to assess individual, prescribing and contextual risk factors that predispose to opioid-dependence and mortality
Month 30: completed by month 36:
Complete analysis using ML to identify individual and subgroup risk of death
Months 7-36: Submit publications and final dissemination of results

Patient Voice

This project has been informed and revised as per recommendations from our Research User Group, a group of lay individuals with a musculoskeletal condition. Two patient partners will be involved in all phases of the research to improve the relevance, quality and validity. One has been prescribed a number of opioids for osteoarthritis and experienced a range of opioid-related harms. The other has fibromyalgia and is also affiliated with Versus Arthritis and Fibromyalgia Action UK. Having experienced both the benefits and harms of opioids personally, they are well-informed and passionate about the outlined work. They will attend relevant meetings, help with the interpretation of results and disseminate findings by tailoring key messages to patients and stakeholders including patient pain organisations.

Project Team/Centres

– M Jani, University of Manchester, UNITED KINGDOM (lead)
– B Birlie Yimer, University of Manchester, UNITED KINGDOM
– W Dixon, University of Manchester, UNITED KINGDOM
– D Jenkins, University of Manchester, UNITED KINGDOM
– M Lunt, University of Manchester, UNITED KINGDOM
– N Peek, University of Manchester, UNITED KINGDOM
– E Archer, University of Manchester, UNITED KINGDOM
– C Lowe, University of Manchester, UNITED KINGDOM

2019

Call for research proposals in the area of Sex- and Gender Issues in RMDs

Many Rheumatic Musculoskeletal Diseases (RMDs) show gender differences with respect to their prevalence, clinical manifestation and disease course. Furthermore, sex hormones and other sex-dependent mediators are known to differentially affect the cells of the immune system as well as the musculoskeletal system, thereby affecting the pathogenesis of RMDs. In addition, sex- and or gender-related issues may affect treatment decisions and the general management of RMDs. To date, little is known about the mechanisms of how sex and gender influence RMDs.

The call was launched in **2019**, and out of 29 letters of intent 3 projects were selected for funding:

- Exploring the X-linked determinant implicated in the female susceptibility to rheumatic diseases
- Validation of sex-dependent molecular pain mechanisms in osteoarthritis
- Genetic variants associated with Sjögren's syndrome leading to differential gene expression in males and females and functional impact on the immune system

Exploring the X-linked determinant implicated in the female susceptibility to rheumatic diseases

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Funding and Timeline
FOREUM research grant: EUR 600.000
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=176

Concept
The incidence of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) is markedly increased in women. Both sex hormones and X chromosomes might contribute to this sex bias. The dosage of X-linked genes is equilibrated between men and women due to the inactivation of one X chromosome (XCI) in female cells. However, XCI is incomplete, leading to increased expression of some X-linked genes.

Objectives
It will be investigated whether higher levels of TLR7 expression, arising from the escape of X-chromosome inactivation (XCI) are linked to increased risk of developing autoimmunity specifically in women. This will be achieved by exploring the relevance of TLR7 XCl escape to the pathophysiology of SLE and SSc by assessing the functions of key human immune cell subsets implicated in disease development, in relationship to the dose of TLR7 (one copy or two copies) expressed in each cell subset.

Goals/Milestones
Year 1 and 2: Collect PBMCs from patients
Year 1 and 2: Provide functional relationship between TLR7 biallelism and ABC development, sex-bias in TLR7-responsiveness using cells from healthy donors.
Year 2 and 3: Provide the first proof of concept regarding the clinical associations between ABC cells, monocytes and pDC in relationship to XCI-escape of TLR7 genes and frequency of monoallelic vs biallelic cells in SLE and SSc patients.
Year 1-3: Functional relationship between Tlr7 biallelism, ABC development and SLE pathogenesis in a mouse model of spontaneous lupus.

Patient Voice
Representative of the Swiss SLE (Lupus-Suisse.ch) and SSc (sclerodermie.ch) patient organizations have reviewed the present proposal and have provided a feedback. It is foreseen that the results

will be discussed annually with these representative and upon completion, the study results will be presented at meetings of interested patients' organizations.

Publications

- Cenac C, Ducatez M, Guéry JC. Hydroxychloroquine inhibits proteolytic processing of endogenous TLR7 protein in human primary plasmacytoid dendritic cells. European Journal of Immunology 2022 52(1): 54-61. doi: 10.1002/eji.202149361. PMID: 34580855 https://onlinelibrary.wiley.com/doi/epdf/10.1002/eji.202149361
- Youness A, Miquel CH, and Guéry JC. Escape from X chromosome inactivation and the female predominance in autoimmune diseases. International Journal of Molecular Sciences 2021 23;22(3): 1114. doi: 10.3390/ijms22031114. https://www.mdpi.com/1422-0067/22/3/1114/htm
- Miquel CH, Youness A, Guéry JC. Prédominance féminine des maladies auto-immunes: les lymphocytes ont-ils un sexe? Revue du rhumatisme 2021 88: 3-7. https://www.sciencedirect.com/science/article/abs/pii/S1878622720301235?via%3Dihub
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- Heparin-Independent and Heparin-Dependent Anti-CXCL4 Antibodies Have a Reciprocal Expression in a Systemic Sclerosis Patients' Cohort. Palazzo R, Stefanantoni K, Cadar M, Butera A, Riccieri V, Lande R, Frasca L. Antibodies (Basel). 2022 Dec 15;11(4):77. doi: 10.3390/antib11040077. PMID: 36546902 https://pubmed.ncbi.nlm.nih.gov/36546902/
- Miquel CH, Faz-Lopez B, and Guéry JC. Influence of X chromosome in sex-biased autoimmune diseases. J. Autoimmun. 2023 Jan 12:102992. doi: 10.1016/j.jaut.2023.102992. Online ahead of print. PMID: 36641351. https://pubmed.ncbi.nlm.nih.gov/36641351/
- Chizzolini C, Hughes S., Ribi C. Pourquoi le LES touche-t'il préférentiellement les femmes ? Magazine Lupus 2020 N°1: p6-10. http://www.lupus-suisse.ch

Project Team/Centres

- J Guéry, University of Toulouse, FRANCE (lead)
- S Hugues, University of Geneva, SWITZERLAND
- L Frasca, Istituto Superiore di Sanità, ITALY

Validation of sex-dependent molecular pain mechanisms in OA

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 594.222
Project duration: 2020–2023

Project Url
www.foreum.org/projects/?id=177

Concept
The patient pain experience in OA is highly variable and this is particularly apparent when comparing males with females. Identification of molecular mechanisms that underly sexdependent differences could provide personalised approaches to patient care.

Objectives
Through recent collaboration, three potential pathways were identified that might explain sexdependent differences in arthritis pain. These include:
(i) 5 neurotrophins exclusively upregulated in female joints at the time of late OA pain behaviour (ii) evidence for increased complement pathway activation in female arthritis, and (iii) sex-dependent differences in the inflammatory cell profiles within the dorsal root ganglion. In this proposal we will explore these pathways in mice as they develop OA pain behaviour, and then test the sex-dependence and correlation with pain outcomes of candidate molecules in two large patient cohorts.

Goals/Milestones
- Steer from the patient groups regarding the project approach and outcomes.
- Creation of an agreed molecular panel (46 genes) to test over the OA time course.
- Confirm regulation of identified neurotrophins in female compared with male mice exhibiting pain behaviour
- Determine the time course of this regulation with relation to development of pain and the tissue of origin
- Determine whether there are sex-dependent changes in complementthatalso associatewith pain
- Determine whether inflammatory changes (including complement) in DRG occur in surgically induced OA and whether these exhibit sex-dependence
- Determine whether moleculesvalidated in the mouseexhibit sex-dependence in human OA tissues from multiple highly phenotyped cohortsand how this relates to reported pain

Patient Voice

Through the Centre for Osteoarthritis Pathogenesis Versus Arthritis regular "Research Showcase" days are being hold in which patients are being invited to hear about planned studies and to provide their feedback on (i) the importance of the study (ii) the proposed approach and (iii) how they think the results should be disseminated.

Project Team/Centres

- T Vincent, University of Oxford, UNITED KINGDOM (lead)
- C Svensson, Karolinska Institutet, SWEDEN
- N Eijkelkamp, Utrecht University, NETHERLANDS

Sjögren's syndrome leading to differential gene expression in males and females and functional impact on the immune system

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600.000
Project duration: 2020–2023

Project Url

www.foreum.org/projects/?id=178

Concept

The majority of rheumatic diseases are more common in women than in men. Primary Sjögren's syndrome has among the highest observed female-to-male ratios, and approximately nine out of ten patients with this chronic inflammatory condition are women. This sex-bias remains poorly understood, even though female sex is the strongest known risk factor for Sjögren's syndrome

Objectives

There is no difference in the frequency of the SS-associated genetic polymorphisms between womenand men in the general population, yet there is a much higher likelihood for the diseases to develop in women carrying these SNPs compared to men. We therefore hypothesize that the context "female sex" influences the functional impact of the genetic polymorphisms associated with SS differently than the context "male sex".

Goals/Milestones

Year 1: SNP selection and comprehensive identification of their sex-influenced eQTLs
Year 2 and 3: Sex-influenced transcription factor enrichment to identified gene regions defined
Year 1-3: Gene and pathway confirmation in experimental models
Year 2 and 3: Verification of genes and related pathways in patient-derived tissues
Year 3: Based on data from 1-4, propose at least onetarget or pathway suitable forsex-tailoredpersonalized medicine

Patient Voice

Patient partners trained through the Swedish Rheumatism Association will participate in both projectdesign and during the study. The patient partners will be part of the steering group and participate indiscussions on the results and making the most of potential findings. The patient partners will also beinvolved in the communication with patients and society, including the writing of a plain languagesummary of the project and main findings.

Publications

– Thorlacius, G.E., Björk, A. & Wahren-Herlenius, M. Genetics and epigenetics of primary Sjögren syndrome: implications for future therapies. Nat Rev Rheumatol (2023). https://doi.org/10.1038/s41584-023-00932-6 https://www.nature.com/articles/s41584-023-00932-6.epdf?sharing_token=0auZN-3V10Nhw9JlpoJWqsNRgN0jAjWel9jnR3ZoTv0MYghUeQ8r2k88zofKGinZ0wg8HkkAuACmz-cO4s_-WqbTqxOTxjNsLjUijZ8dMLV3MBLtUA5H0P_XiZfzMVggbaer3NVHmOZ_8lMSKxW-FJ6qrVSfDH8qll7th4pzieaV9o%3D

Project Team/Centres

– M Wahren-Herlenius, Karolinska Institute, SWEDEN (lead)
– R Jonsson, University of Bergen, NORWAY
– S Appel, University of Bergen, NORWAY
– V Kuchroo, Harvard Medical School, UNITED STATES

2019

Call for international exchange 1-year fellowships

FOREUM is committed to funding and promoting scientific research into rheumatic and musculoskeletal diseases (RMD) and has a goal to foster links between rheumatology units in different countries. Consistent with these goals is the establishment of a call for international exchange fellowships that have the specific objective of facilitating the development of research capacity and training high-caliber applicants in RMD research.

The second call for a 1-year fellowship was launched in **2019** and out of 11 letters of intent 4 projects were selected for funding:

- Exploring the added value of densitometric and quantitative analysis chest CT scans to differentiate class I and class III pulmonary hypertension (PH) in Systemic Sclerosis
- A new therapeutic strategy for inhibiting pro-inflammatory macrophages in pre-clinical models of rheumatoid arthritis: using antagomir-155 encapsulated in pegylated liposomes
- Tissue profiling of the Th17 gene activity in ankylosing spondylitis
- Investigating patient related outcomes as tools for predicting disease in individuals at risk for developing arthritis

Exploring the added value of lung densitometric and texture analysis of chest CT scans in the characterization of pre-capillary Pulmonary Hypertension (PH) in Systemic Sclerosis

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=185

Concept

The proposed project aims at better differentiating clusters of pre-capillary pulmonary hypertension (PH) in systemic sclerosis (SSc) patients, using radiomics automated computer technology for the quantification of the extent and the severity of lung fibrosis. The aim is to create clusters of SSc-PH patients, in the context of possible coexisting lung fibrosis, to really define prognosis and treatment impact.

Objectives

- To assess whether chest HRCT parameters using novel high throughput image analysis tools have predictive potential to distinguish between Group 1 and 3 PH.
- To define data-based clinical groups based on functional and radiological parameters including Lung Densitometry and Lung Texture Analysis to identify different groups of pre-capillary PH and compare discovered groups with the old classification in terms of survival and treatment options.

Goals/Milestones

- Patients identification (suitable patients with available CT images)
- Evaluation of feasibility of available chest CT scans with post-processing image software programs (LD/LTA)
- Post-processing CT scan analysis
- Clinical data collection
- Data analyses and results interpretation
- Manuscript preparation, abstract submission, presentations
- Starting June 2020, publications expected at end of 2021
- Final Results

We showed that an automatic quantification of pulmonary fibrosis and pulmonary vessels is as good as the visual assessment combined with functional decline in identifying group 3 SSc-PH. In addition, the combination of functional impairment and automated radiomic estimation of pulmonary fibrosis and lung vessels was statistically superior to the current practice in achieving the

same aim. This may help to homogenize the repeatability of patients' assessments and perform specific studies, such as testing medications, which are a big unmet need in particular in patients with pulmonary hypertension and extensive pulmonary fibrosis. These studies should always take into consideration the quantification of radiological and functional involvementrelated to ILD and its patterns. Our cluster analysis showed that the different impact on survival might be possibly related to differences in these of variables, more that on hemodynamic features.

Lay Summary

The current practice to identify if pre-capillary pulmonary hypertension in systemic sclerosis mostly relates to lung tissue disease or to "pure" vascular disease, relies on the functional respiratory assessments and the visual estimation of pulmonary fibrosis extent on high-resolution chest CT. Reproducibility issues affect both assessments, in particular the latter that also relies on local expertise. We showed that an automatic quantification of pulmonary fibrosis and pulmonary vessels is as good as the visual assessment combined with functional decline. In addition, the combination of functional impairment and automated radiomic estimation of pulmonary fibrosis and lung vessels was superior to the current practice. This may homogenize the repeatability of patients' assessments. This is also in line with the results of our cluster analysis, in which the groups of pre-capillary pulmonary hypertension associated with systemic sclerosis represent different extents of radiological and functional involvements due to pulmonary fibrosis. These parameters, together with the pulmonary hypertension features, should therefore be taken into account when performing studies and testing medications, which are a high unmet need in this cohort. Certain groups may, probably, benefit from a more vascular-oriented treatment regimen while other from an anti-fibrosis targeting schema, or very likely the combination of both.

Patient Voice

The study should provide a novel, automated classification workflow that will allow to classify patients into groups. Such classification, if shown significant by survival analysis, will allow for early detection of patients as high risks from those of lower risk. But at this stage, given the observational nature of the study, no direct patient involvement is requested, except for patient consent to data analysis if locally required. If the project will be successful, patients will be involved in multi-centric studies to validate the results and in future Randomised Clinical Trials (RCTs), as both active participant and as part of scientific advisory boards.

Project Team/Centres

- C Bruni, University of Florence, ITALY (lead)
- O Distler, University of Zurich, SWITZERLAND
- M Matucci Cerinic, University of Florence, ITALY

A new therapeutic strategy for inhibiting pro-inflammatory macrophages in pre-clinical models of rheumatoid arthritis: using antagomir-155 encapsulated in pegylated liposomes

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=186

Concept

In RA patients, an increased expression of miR-155 in monocytes/macrophages could be responsible for impaired maturation of monocytes into M2 anti-inflammatory macrophages. Our aim is to assess if the defect of M2 polarization and the impact of miR-155 and others microRNA in this defect are present in 2 pre-clinical models of RA: the CIA and STIA mice.

Objectives

To demonstrate in mice model of rheumatoid arthritis (RA) that microRNA could be responsible of polarization of monocytes in pro-inflammatory macrophages in order to find a new safe treatment of RA specific of these cells.

Goals/Milestones

- First phase, validate new miR by classical PCR and study in vitro the effect of RA monocytestransfection on M2 polarization.
- Second phase, study in vivo on CIA and STIA mice monocytes polarization in M2 macrophages as compared to wild type mice.
- Third phase, determine in vivo on CIA and STIA mice monocytes polarization in M2 macrophages with or without injection of PEG-liposomes containing antagomiR-control or 155 and off-target" effect of injection of PEG-liposomes containing antagomiR-155 in other immunes cells.

Final Results

We found that an increased expression of miR-155 in monocytes/macrophages was responsible for the impaired differentiation of monocytes in anti-inflammatory macrophages. We have identified 7 microRNAs that differentiate monocytes of RA patients from those of healthy. Unfortunately, we could not confirm implication of new miR, except miR-155.
Also, we demonstrated that miR-155-driven defect of anti-inflammatory macrophage differentiation was also present in 2 pre-clinical models of RA: serum-transfer-arthritis (STA) and collagen-induce-arthritis (CIA) mice. We validated the therapeutic strategy using antagomiR-155 encapsulated in PEG-liposomes for decreasing arthritis incidence and paw volume-size in CIA and STA. Moreover, PEG-liposomes were specific of monocytes and had no impact on other immune cells. Finally, we demonstrated a restoration of monocytes polarization in M2 macrophages in bone-marrow-derived-macrophages but also in mice synovial tissue.

Lay Summary

Monocytes-macrophages are key players in the pathogenesis of Rheumatoid Arthritis (RA). An up-regulation of miR-155 expression has been shown in RA synovial macrophages, fibroblasts, peripheral blood and synovial fluid CD14+ monocytes. Our group has demonstrated epigenetic mechanism driving preferential differentiation of RA monocyte into pro-inflammatory macrophages published in The Journal of Immunology (Paoletti A et al J Immunol. 2019 Oct 1;203(7):1766-1775).
We found that an increased expression of miR-155 in monocytes/macrophages was responsible for the impaired differentiation of monocytes in anti-inflammatory macrophages.
We have identified 7 microRNAs, that differentiate monocytes of RA patients from those of healthy. Unfortunately, we could not confirm implication of new miR, except miR-155. Based on this and robust evidence of the pathogenic role of miR-155 in experimental and clinical arthritis, we proposed to test the therapeutic utility of targeting miR-155 in arthritis.
This program research achieved 2 important goals:

- We demonstrated that miR-155-driven defect of anti-inflammatory macrophage differentiation was also present in 2 pre-clinical models of RA: serum-transfer-arthritis (STA) and collagen-induce-arthritis (CIA) mice
- We validated the therapeutic strategy using antagomiR-155 encapsulated in PEG-liposomes as compared to systemic delivery for decreasing arthritis incidence in CIA and STA mice. Moreover, PEG-liposomes were specific of monocytes and had no impact on other immune cells.

Finally, injection of PEG-liposome containing antagomiR-155 with a small amount of antagomiR, we demonstrated a decrease of arthritis incidence, and a restoration of monocytes polarization in M2 macrophages in bone-marrow-derided-macrophages but also in mice synovial tissue.
Overall, this research program contributed to a better understanding of the abnormalities of monocytes–macrophages in pathophysiology of RA. miR-155 inhibition is already in phase II in hematological malignancies with an apparent good safety profile. We confirm efficacy and specificity of antagomiR-155 encapsulated in PEG-liposomes in pre-clinical models of RA, with this approach specifically addressed to monocytes/macrophages could emerge as a novel and possible treatment for RA patients.

Patient Voice

microRNA inhibition by another molecule is already in progress in some cancer with an apparent good safety profile. If we confirm efficacy and specificity of our treatment in mice models of arthritis, this approach could emerge as a novel and possible treatment for rheumatoid arthritis patients. Moreover our therapeutic strategy uses a new way for addressing the possible new drug directly in the macrophages infiltrating the joints and thus, should be devoid of side effects

Project Team/Centres

- A Paoletti, Paris-Saclay University, FRANCE (lead)
- X Mariette, Hôpitaux Universitaire Paris-Sud, FRANCE
- I McInnes, University of Glasgow, UNITED KINGDOM
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Tissue Profiling of the Th17 Gene Activity in AS

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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=187

Concept
Ankylosing Spondylitis (AS) is a chronic immune-mediated disease that affects various musculo-skeletal structures and extra-articular organs, such as the skin, the gut and the eye. In AS, Th17 cells drive inflammation and tissue damage. Although targeting Th17 cells represents an effective treatment strategy, over half of patients fail to respond, and this class of drugs does not provides benefit on the AS-associated colitis. The plan is to perform single cell sequencing of Th17 cells from blood and 3 common sites of AS inflammation:
peripheral joint, gut mucosa and psoriatic skin.

Objectives
Ankylosing Spondylitis (AS) is a chronic rheumatic disease, in which an altered immune system causes excessive inflammation in the joints, the spine, the skin and the gut. Immune cells are able to adapt to the surroundings by switching their genes on and off, and this makes the available medications not always effective on all the organ manifestations of AS. The aim of this research is to provide an in depth study of a class of immune cells called Th17, isolated from the blood and the organs of AS patients, using a novel high-resolution technology called single cell sequencing. This technique is able to show how these cells modulate their genome during a disease flare in each organ, and to reveal novel targets for effective treatments for AS.

Goals/Milestones
- 6 months sample processing and RNA sequencing in batches. Incl. 4 months for patient recruitment and sample collection.
- 6 months of computational analysis.

Patient Voice

For the initial gene sequencing, 9 patients, 3 for each of 3 typical manifestation of the disease (joint, intestine, skin) will be recruited. AS is a severe, debilitating condition, typically diagnosed before the age of 40, which carries life-long impact. There is also considerable need for new, more effective drugs, because a number of patients do not respond to the available treatments, which are often very expensive.

Project Team/Centres

– D Simone, Università della Campania Vanvitelli, ITALY (lead)
– F Ciccia, Università della Campania Vanvitelli, ITALY

Investigating patient related outcomes as tools for predicting disease in individuals at risk for developing arthritis

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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=188

Concept
According to the concept that rheumatoid arthritis (RA) develops across different phases long before the onset of clinical arthritis, studies for better characterisation and monitoring of risk factors for RA are of high importance. This kind of studies require the enrolment of individuals at risk for developing RA that are longitudinally and prospectively followed up. Dataset of clinical, patient-reported and laboratory / immunological variables will be used for clarifying the symptom burden of people at-risk, evaluate the relevance of PROs in monitoring and/or predicting RA development.

Objectives
- evaluate the symptom burden in a specified group of people at high risk ('at-risk") for developing rheumatoid arthritis (RA)
- test the ability of patient-reported outcomes (PROs) as prediction tools for the development of RA in at-risk individuals
- analyze the usefulness of PROs to adequately mirror changes of symptoms in monitoring of at-risk individuals

Goals/Milestones
- A comparative evaluation on disease/symptom burden between symptomatic at-risk individuals and patients with early RA.
- Evaluation report on the appropriate use of standard PROs and newly designed PROs for monitoring of at-risk individuals.
- Proposal of a prediction model to develop RA emphasizing PROs as prediction candidates.
- Validation concept of the retrieved results in data of the at-risk register of the MUV (register starting enrolling in spring 2020 to monitor people with arthralgia at-risk for RA).

Final Results
People with rheumatoid arthritis (RA) should receive targeted DMARD treatment as early as possible. How to manage people at potential risk to develop RA is less clear.

The at-risk project explores characteristics of individuals at-risk to develop RA to improve risk stratification and provide the earliest clinical care possible.
We aimed to assess the symptom burden by patient-reported outcomes in individuals at-risk included into this program at the Karolinska Institutet. These individuals were ACPA positive with musculoskeletal complaints without signs of clinical or subclinical arthritis at inclusion. These were match to incident early RA patients from the Stockholm region registered in the Swedish Rheumatology Quality register.
– Individuals at risk for RA report less symptom burden than early diagnosed RA patients.
– However, these differences only range around minimal clinically important differences
– No differences at inclusion between progressors towards arthritis and non-progressors, but progressors worsen and non-progressors partwise improve over time.

These data stress the need for medical attention and incorporation of PROs in assessment and risk stratification of at-risk individuals.

Lay Summary

Rheumatoid arthritis (RA) is a rheumatic chronic inflammatory disease that impacts function, health-related quality of life (HrQoL) and work participation. It is needed to offer treatment for RA as early as possible to restore HrQoL. This research aimed at understanding how and which symptoms individuals perceive before a potential onset of RA. Certain blood markers, like antibodies in combination with discomfort and problems with joints and muscles (musculoskeletal symptoms) indicate a higher risk to develop RA in the future. The burden of symptoms of individuals at-risk was unclear and how this would compare to patients, that have just been diagnosed with RA. Several patient-reported outcomes exist, that help measuring these symptoms. We used data of a structured at-risk for RA program in Stockholm and routine data of patients with RA, that have been in care in the Stockholm region between 2015 and 2020. We found that symptom burden of patients with RA at time of diagnosis is higher than for at-risk individuals at inclusion in this program. The difference in the measured scores is however smaller than expected in between RA patients and at-risk individuals and ranges around a limit that we know from different studies is around the threshold for detecting a difference between two measurements that might not just be erratic. Symptoms are similar between those that further-on develop arthritis and those that don't. However, people that don't develop arthritis improve in pain, fatigue and the global estimation of health, but those developing arthritis get worse over time. This means that at-risk individuals are in need for medical attention and that monitoring of patient-reported outcomes over time helps in better characterising the risk of an individual to develop RA.

Patient Voice

The results of this study will provide a better characterisation of the restrictions in life and symptom burden in people with joint pain at-risk for RA. It will provide a comprehensive overview of the ability of clinical and patient-reported outcomes in monitoring at-risk individuals and to detect symptom changes due to interventions. This will ultimately lead to earlier diagnosis, access to treatment and more profound evidence-based information on the risk for developing RA.

Publications

– Studenic P, Karlfeldt S, Alunno A. The past, present and future of e-health in Rheumatology. Joint Bone Spine. 2021 Jul;88(4): 105163. DOI: 10.1016/j.jbspin.2021.105163. Epub 2021 Feb 19. PMID:

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– Studenic, P, and Radner, H. "Back to Basics: Prioritizing Communication as a Key Instrument in Managing Rheumatoid Arthritis." Journal of rheumatology 49.2 (2022): 123–125. DOI: 10.3899/jrheum.210984. https://www.jrheum.org/content/jrheum/early/2021/09/26/jrheum.210984.full.pdf
– Van Hoovels, Studenic, P., Sieghart, D., Steiner, G., Bossuyt, X., & Rönnelid, J. (2022). Impact of autoimmune serology test results on RA classification and diagnosis. Journal of Translational Autoimmunity (Online), 5, 100142–100142. https://doi.org/10.1016/j.jtauto.2022.100142 http://Van Hoovels, Studenic, P., Sieghart, D., Steiner, G., Bossuyt, X., & Rönnelid, J. (2022). Impact of autoimmune serology test results on RA classification and diagnosis. Journal of Translational Autoimmunity (Online), 5, 100142–100142. https://doi.org/10.1016/j.jtauto.2022.100142
– Studenic P, Hensvold A, Kleyer A, van der Helm-van Mil A, Pratt AG, Sieghart D, Krönke G, Williams R, de Souza S, Karlfeldt S, Johannesson M, Krogh NS, Klareskog L and Catrina AI (2022) Prospective Studies on the Risk of Rheumatoid Arthritis: The European Risk RA Registry. Front. Med. 9:824501. doi: 10.3389/fmed.2022.824501 https://www.frontiersin.org/articles/10.3389/fmed.2022.824501/full#h14

Abstracts

– Symptoms characteristics of seropositive individuals at-risk for developing rheumatoid arthritis are versatile and comparable to those in people with early rheumatoid arthritis. P. Studenic, A. Circiumaru, D. Aletaha, K. Chatzidionysiou, A. Hensvold, A. Catrina. DOI: 10.1136/annrheumdis-2021-eular.3884 https://ard.bmj.com/content/annrheumdis/80/Suppl_1/1005.3.full.pdf
– Studenic P, Circiumaru A, Aletaha D, Chatzidionysiou K, Catrina A, Haj Hensvold A. Symptom Burden in Anti-citrullinated Protein Antibody Positive Individuals At-risk for Rheumatoid Arthritis Is Changing over Time and Comparable to Patients with Early Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). https://acrabstracts.org/abstract/symptom-burden-in-anti-citrullinated-protein-antibody-positive-individuals-at-risk-for-rheumatoid-arthritis-is-changing-over-time-and-comparable-to-patients-with-early-rheumatoid-arthritis/

EULAR Poster

2021:
POS1441: Symptoms characteristics of seropositive individuals at-risk for developing rheumatoid arthritis are versatile and comparable to those in people with early rheumatoid arthritis. P. Studenic, A. Circiumaru, D. Aletaha, K. Chatzidionysiou, A. Hensvold, A. Catrina

Project Team/Centres

– P Studenic, Medical University of Vienna (MUV), AUSTRIA (lead)
– D Aletaha, Medical University of Vienna (MUV), AUSTRIA
– A H Hensvold, Karolinska Institutet, SWEDEN
– A Chatzidionysiou, Karolinska Institutet, SWEDEN

2020

Call for Career Research Grants

FOREUM is committed to promote the best talents in the field of rheumatic and musculoskeletal diseases (RMD). Consistent with these goals FOREUM issued a new call that aims to fund excellent young researchers promoting innovative ideas and supporting high quality research projects covering basic and clinical science projects related to RMDs. Scientific excellence is the key eligibility criterion for this career research grant initiative, which aims to foster independent science and intends to develop new research leaders in the field.

The second call was launched in **2020**, and out of 70 letters of intent 5 projects were selected for funding:

- Role of trained immunity in the pathogenesis and treatment of Still's disease
- Uncovering musculoskeletal pain susceptibility profiles since childhood
- Understanding barriers and facilitators to effective disease-management in Rheumatoid Arthritis to prevent refractory disease. A Mixed-Methods study with a focus on social determinants of treatment outcomes
- PMR research on disease mechanisms in Synovium (PROMIS)
- A new concept of ANCA-Associated Vasculitis (ANCA)

Role of Trained Immunity in the pathogenesis and treatment of Still's disease

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=189

Concept

Aim of this study is to determine the role of Trained Immunity in the pathogenesis of Still's disease, and the therapeutic potential of inhibiting this mechanism for the treatment of this condition. Several factors are ideally aligned to achieve these ambitious research goals:
a large cohort of patients with Still's disease, an optimal experimental platform, and a synergistic enterprise with world-leading experts in the field.

Objectives

In order to test the hypotheses the following aims are proposed:
– AIM 1: to determine epigenetic and immunometabolic features of TI in SD monocytes.
– AIM 2: to determine the therapeutic potential of inhibiting TI for the treatment of SD.

Goals/Milestones

– Month 12: identification of functional and epigenetic features of TI in SD monocytes.
– Month 24: identification of immunometabolic features of TI in SD monocytes.
– Month 30: evaluation of TI as a predictor of clinical outcomes in SD.
– Month 36: Identification of strategies effectively inhibiting TI for the treatment of SD.

Patient Voice

This study is important to many patients with AOSD and SJIA, and many already volunteered to donate samples. In collaboration with AMRI (a non-profit patient organisation with investment in SD) there is a strong engagement of patients in the research process.
Regular updates on research findings, instructions on research strategies based on patients' insight, and development for shared initiatives for effective dissemination of findings to societal stakeholders will be provided.

Publications

- Ferrero E, Villa A, Stefanoni D, Nemkov T, D'Alessandro A, Tengesdal I, Belloni D, Molteni R, Vergani B, De Luca G, Grassini G, Cangi MG, Dagna L, Doglioni C, Cavalli G, Ferrarini M. Immunometabolic activation of macrophages leads to cytokine production in the pathogenesis of KRAS-mutated histiocytosis.. Rheumatology (Oxford). 2022 Apr 11;61(4):e93-e96. doi: 10.1093/rheumatology/keab869.PMID: 34919661 https://pubmed.ncbi.nlm.nih.gov/34919661/
- Molteni R, Biavasco R, Stefanoni D, Nemkov T, Domínguez-Andrés J, Arts RJ, Merelli I, Mazza D, Zambrano S, Panigada M, Cantoni E, Tengesdal IW, Maksud P, Piras F, Cesana D, Cassina L, Distefano G, Loffreda A, Gnani D, De Luca G, Tomelleri A, Campochiaro C, Joosten LAB, Dinarello CA, Kajaste-Rudnitski A, Haroche J, Cardaci S, Cenci S, Dagna L, Doglioni C, Ferrarini M, Ferrero E, Boletta A, D'Alessandro A, Montini E, Netea MG, Cavalli G. Oncogene-induced maladaptive activation of trained immunity in the pathogenesis and treatment of Erdheim-Chester disease. Blood. 2021 Oct 28;138(17):1554-1569. doi: 10.1182/blood.2020009594.PMID: 34077954 https://pubmed.ncbi.nlm.nih.gov/34077954/
- Cavalli G, Tengesdal IW, Gresnigt M, Nemkov T, Arts RJW, Domínguez-Andrés J, Molteni R, Stefanoni D, Cantoni E, Cassina L, Giugliano S, Schraa K, Mills TS, Pietras EM, Eisenmensser EZ, Dagna L, Boletta A, D'Alessandro A, Joosten LAB, Netea MG, Dinarello CA. The anti-inflammatory cytokine interleukin-37 is an inhibitor of trained immunity. Cell Reports. 2021 Apr 6;35(1):108955. doi: 10.1016/j.celrep.2021.108955.PMID: 33826894 https://pubmed.ncbi.nlm.nih.gov/33826894/

Project Team/Centres

- G Cavalli, IRCCS San Raffaele Hospital, ITALY (lead)
- M Netea, Radboud University, THE NETHERLANDS
- A Ravelli, Ospedale Pediatrico Giannina Gaslini, ITALY

Uncovering musculoskeletal pain susceptibility profiles since childhood by bringing together population and clinical cohorts

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=190

Concept

This study bridges population-based and clinical cohorts to investigate early markers of adverse musculoskeletal pain trajectories. The project examines the ways that children and their caregivers use to describe the child's pain experience, and to assesses which early features are the most useful to predict whether children are going to develop later musculoskeletal pain, including in the absence of a medical condition that can biologically account for pain.

Objectives

- to identify accurate predictors of non-specific musculoskeletal pain at age 16 years, among a wide set of pain-related traits collected since birth
- to assess whether experimental pain response is altered before the onset of non-specific musculoskeletal pain
- to develop an interactive graphical tool to quantify the long-term explicit memory of pain, and to compare the experiences described by adolescents with non-specific musculoskeletal pain to those of adolescents with diagnosed juvenile idiopathic arthritis.

Goals/Milestones

- M1: Data collection protocol designed
- M2: Online software developed and pilot-tested
- M3: Data collection completed from G21 and JIA chohorts
- M4: Interim data analysis report
- M5: Research papers prepared
- M6: Dissemination of first results in scientific and society-oriented events

Patient Voice

The individual pain trajectories will be of added-value in describing subjective impact of pain, as an addition to other well-established patient-reported outcomes. In the long term it is expected that the results will be useful to

- inform health professionals on how to identify children at higher risk of musculoskeletal pain in the absence of an identifiable disease
- provide parents with a set of alerts to signal that specialized help should be sought.

Project Team/Centres

- R Lucas, Universidade do Porto, PORTUGAL (lead)
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- A Rocha, INESC TEC, PORTUGAL
- M J Santos, Portuguese Society of Rheumatology, PORTUGAL
- E Frazão Mateus, PARE, PORTUGAL
- C Cooper, University of Southampton, UNITED KINGDOM
- L Carmona, Instituto de Salud Musculoesquelética, SPAIN
- G Goncalves, INESC TEC, PORTUGAL

Understanding barriers and facilitators to effective disease-management in Rheumatoid Arthritis to prevent refractory disease

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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2022–2025

Project Url
www.foreum.org/projects/?id=191

Concept

There is a pressing need to understand the social dimensions that add to disease burden in rheumatoid arthritis (RA) and potential synergistic interactions with biological parameters of disease, such as level of inflammation. The overarching aim of this study is to gather in-depth information on social determinants that drive refractory disease in RA, which could be used alongside 'traditional' disease management (i.e. drug therapy), to inform resource allocation and service redesign in line with national standards.

Objectives

– To identify the most relevant social determinants of treatment outcomes in RA.
– To quantify the proportion of refractory RA attributable to social determinants.

Goals/Milestones

– Month 3-6: ethics application and data access (Phase IIa) approvals
– Month 12: Completion of qualitative study and questionnaire design for Phase IIa
– Month 30: Cross-sectional survey data collection
– Month 36: Data analysis, final reports/publications and dissemination

Patient Voice

This study will provide a deep understanding into non-biological, social factors that drive active disease. This way, the study will provide evidence on how to best combine health and social resources to improve the care pathway of patients with RA, ensuring fair and equal access to all.

Project Team/Centres

– E Nikiphorou, King's College London, UNITED KINGDOM (lead)
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– M Buch, University of Manchester, UNITED KINGDOM

PMR Research On Disease Mechanisms In Synovium (PROMIS)

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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=192

Concept
The 'PMR Research on Disease Mechanisms In Synovium' (PROMIS) project is dedicated to unravelling the pathobiology of PMR. Ultrasound-guided synovial biopsies will be obtained from the subacromial-subdeltoid bursa of patients with PMR. A combination of immunohistochemistry and single-cell RNA sequencing will be applied to gain unprecedented insight into the synovial pathobiology of PMR.

Objectives
The overarching aim of the PROMIS project is to identify synovial targets for treatment in PMR.
- To identify immunological targets for already existing therapies in PMR synovium.
- To identify senescent cells in PMR synovium as potential targets for treatment.
- To determine cellular heterogeneity and networks in PMR synovium on a molecular level.

Goals/Milestones
- Start of the project March 2021
- Collection of biopsies from 15 patients at mid-term report and 30 patients at final report.
- Results on Study Aim 1 and Study Aim 2 available for 10 patients at the mid-term report.
- Final results on Study Aim 1, Study Aim 2 and Study Aim 3 available at the final report.
- Publication of results in the top 5 peer-reviewed journals in the field of rheumatology.
- Interim report to patients' organisation (Vasculitis Stichting).
- Dissemination of results via conferences (EULAR, International GCA/PMR Workshops)

Patient Voice
Half of patients with PMR are currently 'sentenced' to prolonged use of glucocorticoids and frequently develop complications caused by this treatment. This project will accelerate the introduction of existing, targeted therapies (i.e. already used for other diseases) for patients with PMR by providing a clear rationale for such therapies. The ultimate goal of the study is to make long-term glucocorticoid therapy obsolete and to improve the patients' well-being.

Publications

- Jiemy WF, Zhang A, Boots AMH, Heeringa P, Sandovici M, Diepstra A, Hein S, Dasgupta B, Brouwer E, van der Geest KS. Expression of interleukin-6 in synovial tissue of patients with polymyalgia rheumatica. Ann Rheum Dis. 2023 Mar;82(3):440-442. doi: 10.1136/ard-2022-222873. Epub 2022 Aug 12. PMID: 35961758.
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- Reitsema RD, Jiemy WF, Wekema L, Boots AMH, Heeringa P, Huitema MG, Abdulahad WH, van Sleen Y, Sandovici M, Roozendaal C, Diepstra A, Kwee T, Dasgupta B, Brouwer E, van der Geest KSM. Contribution of pathogenic T helper 1 and 17 cells to bursitis and tenosynovitis in polymyalgia rheumatica. Front Immunol. 2022 Aug 11;13:943574. doi: 10.3389/fimmu.2022.943574. PMID: 36032100; PMCID: PMC9402989.
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- van der Geest KSM, Sandovici M, Nienhuis PH, Slart RHJA, Heeringa P, Brouwer E, Jiemy WF. Novel PET Imaging of Inflammatory Targets and Cells for the Diagnosis and Monitoring of Giant Cell Arteritis and Polymyalgia Rheumatica. Front Med (Lausanne). 2022 Jun 6;9:902155. doi: 10.3389/fmed.2022.902155. PMID: 35733858; PMCID: PMC9207253
  https://www.frontiersin.org/articles/10.3389/fmed.2022.902155/full

Meeting presentations:

- Dutch Society for Rheumatology Annual Meeting, 2021. Characterization of synovial fluid T cell in Polymyalgia Rheumatica:
  implication of Th1 and Tc1 responses. Oral presentation.
- ACR Convergence, 2021. Characterization of synovial fluid T cell in Polymyalgia Rheumatica: implication of Th1 and Tc1 effector memory profiles. Poster presentation, Abstract no. 1407.
- EULAR Annual Congress, 2022. Proinflammatory monocytes and macrophages in synovial fluid and bursal tissue of patients with polymyalgia rheumatica:
  potent producers of IL-6 and GM-CSF. Oral presentation, Abstract no. 4396.
- Dutch Society for Rheumatology Annual Meeting, 2022. Proinflammatory monocytes and macrophages in synovial fluid and bursal tissue of patients with polymyalgia rheumatica:
  potent producers of IL-6 and GM-CSF. Poster presentation.

Project Team/Centres

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A New Concept of ANCA-Associated Vasculitis (ANCA)

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=193

Concept
The potentially life-threatening disease anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO). Despite decades of research, the trigger that initially breaks tolerance and causes ANCA-production remains unknown. This project will provide crucial insight into AAV-pathogenesis that can subsequently be used to develop more effective treatments e.g. by eradicating S. aureus or tolerizing the involved antigen-specific immune cells.

Objectives
This project proposes a novel hypothesis regarding the onset of autoimmunity in AAV: tolerance to PR3 and MPO is broken through complex formation with the S. aureus proteins Eap and SPIN, enabling ANCA B cells to present S. aureus peptides and recruit the help of S. aureus-specific T cells. It aims to investigate this hypothesis by focusing on the following three objectives:

- To delineate whether ANCA can bind their target epitopes on PR3 and MPO when these are in complex with Eap and SPIN
- To identify ANCA-specific B cells, isolate and immortalize them, thereby generating ANCA B cell lines. These B cell lines will be used to:
- Elucidate whether ANCA B cells can phagocytose and present PR3/Eap and MPO/SPIN complexes to S. aureus specific-T cells.

Goals/Milestones
The metrics and milestones to measure the success are the products of the different aims:

- Aim 1. For sufficient support of the hypothesis, the majority (>50%) of sera from AAV-patients should still recognize PR3 and MPO when they are in complex with Eap and SPIN respectively.
- Aim 2. In light of the challenging techniques involved in generating immortalized antigen-specific B cell lines, the aim will be to produce anti-PR3 and anti-MPO B cell lines from at least three different patients.

– Aim 3. Stimulation of T cells by immortalized B cells with Eap-PR3 or SPIN-MPO-complexes should lead to considerably more pronounced T and B cell activation (measures of T and B cell activation being at least twice as high) compared to stimulation with PR3 or MPO only.

Patient Voice

This project will provide crucial insight into AAV-pathogenesis that can subsequently be used to develop more effective treatments. If S. aureus indeed triggers vasculitis as described above, then eradicating this bacterium could prevent onset of disease (e.g. in genetically at-risk family members), and in patients with established disease, it could diminish debilitating disease flares. Furthermore, it would allow the development of tolerizing therapies aimed at inhibiting the T cells reacting to Eap and SPIN that form the starting point of the disease.

Publications

– Scherer, H.U., van der Woude, D. & Toes, R.E.M. From risk to chronicity: evolution of autoreactive B cell and antibody responses in rheumatoid arthritis. Nat Rev Rheumatol 18, 371–383 (2022).
https://doi.org/10.1038/s41584-022-00786-4
https://rdcu.be/cQV6Z

Project Team/Centres

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2020

Special Call for research proposals in the area of COVID-19 in RMDs

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan leading to a cluster of respiratory infections. The disease caused by SARS-CoV-2 (coronavirus disease 2019, COVID-19) rapidly spreads worldwide. Patients with Rheumatic Musculoskeletal Diseases (RMDs) may be at particular risk for COVID-19 as they show an intrinsically higher risk for infections. In addition, many of the treatments used for RMDs, such as glucocorticoids or disease modifying anti-rheumatic drugs have the potential to increase infection risk. Therefore, a better mechanistic understanding and clinical knowledge on the impact of COVID-19 in RMD patients is urgently needed

The call was launched in **2020**, and out of 35 full proposals 5 projects were selected for funding:

- In-depth analysis of immunological, genetic and clinical aspects of the thrombo-inflammatory disorder triggered by SARS-CoV-2 and their correlation with autoinflammatory/systemic rheumatic diseases
- The impact of COVID-19 and national COVID-19 policies on people with rheumatic diseases; the CORE (COVID-19 in rheumatic diseases) project
- Telomere length in COVID-19: Biological aging and susceptibility to severe disease
- Deciphering a specific signature of the immunosenescence induced in COVID-19+ patients versus rheumatoid arthritis patients
- Assessing the impact of COVID-19 on Rheumatic and Musculoskeletal Disorders in primary care: an observational study of UK national primary care electronic health records

Whole Genome Sequencing in thrombo-inflammatory disorders triggered by SARS-CoV-2: machine learning applied to extensive immunological, genetic, and clinical datasets and implications for systemic rheumatic diseases

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Funding and Timeline
FOREUM research grant: EUR 100.000
Project duration: 2021–2022

Project Url
www.foreum.org/projects/?id=194

Concept
While the majority of coronavirus disease 2019 patients develop a mild disease, up to 20% become severely ill, with a severe interstitial pneumonia with high levels of acute phase mediators (cytokine storm) and other complications. There is a lack of knowledge on the role of individual genetic variability in conferring differential viral susceptibility, response to treatments, and severity of disease. This study aims at addressing this question, to identify factors predictive for the different evolution of the disease.

Objectives
The project aims at:
- retrieving all the possible genetic information, by whole genome sequencing, from a heterogeneous set of individuals, affected by autoinflammatory/rheumatic and COVID-19 diseases, showing different disease severity (e.g. requiring versus non requiring hospitalization)
- preliminary data achieved on complement activation and its role in COVID-19 will be confirmed in a larger series of patients with mild, moderate, severe, and critical disease and in serial samples from patients during the follow-up

Goals/Milestones
- 6 months: selection of patients and shipment of samples for WGS at IIT or another identified provider
- 18 months: WGS data elaboration, genetic analysis and deep learning approaches applied
- 21 months: data on complement activation
- 24 months: drawing conclusions, dissemination of results, publications

Final Results

After performing Whole Genome Sequencing in 200 Covid19 patients, stratified on disease severity (100 each with mild and severe symptoms), response to therapies and presence of co-morbidities, genetic, clinical, and laboratory datasets underwent biased and unbiased burden tests for rare pathogenic variants, in addition to machine learning (ML) and genome-wide association (GWAS) analyses for common predisposing or protecting variants

ML confirmed CRP as the major factor discriminating patient status and showed that IL18 variants accumulation correlates with mild patients, thus reflecting a protective role of this cytokine with respect to severe Covid19. GWAS confirmed presence of more variants than expected by chance in the IL18 gene, in addition to replicate the already known involvement of SLC6A20/LZTFL1 SNP rs35081325 in severe versus mild Covid19

Finally, functional tests revealed a role of the complement activation through increased levels of C5a and C5b9 levels, found to be predictive for adverse outcomes

Lay Summary

To clarify the pathogenic mechanisms inducing either a severe outcome or mild disease in patients affected with Covid-19, in the past 2 years we have collected, in the Reggio Emilia Hospital Unit (UO2), a large set of whole blood and serum/plasma samples from 100 Covid-19patients who did not require hospitalization (mild symptoms) and 100 Covid-19 patients who were hospitalized (severe symptoms). DNA samples thus extracted were transferred to the IIT Unit (Genoa, Italy – UO4) where they have been subjected to Whole Genome Sequencing (WGS). Primary data analysis, variants calling and further genomic, statistical and AI analyses have been carried out in the IIT and IGG Units (Genoa, Italy – UO1).

Clinical, laboratory and genetic datasets underwent i) search and analysis of rare variants, possibly responsible for congenital conditions able to modulate the response to the SARS-CoV-2 infection, ii) machine learning, an artificial intelligence approach, to identify relevant biological markers and molecular signatures, iii) a genome wide association study (GWAS) to identify common variant possibly responsible for increased or decreased susceptibility to severe Covid-19. To this end, patients were grouped based on disease severity, response to the therapies, presence of pre-existing morbidities, such as rheumatologic chronic diseases, and familial clustering.

Functional tests focusing on the complement activation were carried out in 97 patients (54 mild and 43 severe disease) (Istituto Auxologico, Milan, Italy – UO3). The disease severity was associated with therapy independent increased levels of C5a and C5b9 levels suggesting that complement activation products may be predictive for the negative outcome.

Patient Voice

Matching the two proposed approaches (WGS and ML in parallel to an experimental study) is novel and going to be relevant to gain insights into pathogenic mechanisms playing a role in the onset and progression of COVID-19. This will provide novel biomarkers and original tools to recognize and treat more effectively both COVID-19 and rheumatic disorders, paving the way to personalized medicine interventions. The identification of genetic markers associated with COVID-19 severity will allow, a priori, to inform those subjects at higher risk of developing complications when infected with SARS-CoV-2. This knowledge will allow to plan interventions in those individuals (e.g. vaccination, preventive drugs / behaviours) to decrease the burden of COVID-19.

Publications

– Meroni PL, Croci S, Lonati PA, Pregnolato F, Spaggiari L, Besutti G, Bonacini M, Ferrigno I, Rossi A, Hetland G, Hollan I, Cugno M, Tedesco F, Borghi MO, Salvarani C. Complement activation predicts negative outcomes in COVID-19:
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Project Team/Centres

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Telomere length in COVID-19: Biological aging and susceptibility to severe disease

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Funding and Timeline
FOREUM research grant: EUR 75.000
Project duration: 2021–2022

Project Url
www.foreum.org/projects/?id=195

Concept
COVID-19 is are characterized by acute lung inflammatory disease and a strong systemic inflammatory response, termed “cytokine storm” that partially resembles other situations such as macrophage activation and autoinflammatory syndromes or CART therapy. The project investigates on the hypothesis that biological ageing and TS may be mechanistically linked to hyperinflammatory responses, and propose to investigate telomere shortening (TS) as a risk factor for severe disease and for long-term morbidity after recovery from acute COVID-19.

Objectives
The objective of the project is to better understand the relationship between ageing, previous chronic diseases (vascular, hypertension, diabetes) and the severity of COVID-19, through the study of a well-known process associated with aging:
telomere shortening (TS).

Goals/Milestones
- Collection of 1st DNA sample from COVID biobank and TL determination.
- Revision of clinical and lab variables from electronic records of the hospitalization and completion of database.
- Analysis of correlations TL and clinical data and report.
- Collection of 2nd DNA sample where available along follow-up.
- Analysis of basal/follow-up TL changes in a subset of patients with available samples.
- Analysis of correlations of TL with clinical evolution at 18 months and report.

Final Results

We analysed telomere length (TL) by qPCR in 251 patients hospitalized for COVID-19 in the first months of the pandemics and in an age matched healthy cohort (n = 169). After discharge, 144 COVID-19 survivors were followed-up for persistent COVID-19 manifestations. A second TL determination was performed in a group of 63 patients 1 year later and compared with baseline TL. Hospitalized COVID-19 patients had a decreased age-adjusted TL compared to the reference group. No differences in TL were observed in patients with different COVID-19 outcomes). In 144 patients, followed for a median of 8 months, post-COVID manifestations were not associated with shorter TL. Persistence of lung radiographic abnormalities was associated with shorter TL. In patients with a second TL determination, further telomere shortening was observed in 35%, and these patients had suffered a more severe disease.
Shorter TL is associated with COVID-19 hospitalization and delayed resolution of lung involvement.

Lay Summary

Aging is an important contributor to the development and progression of numerous inflammatory diseases such as rheumatic, vascular and infectious diseases. During the COVID pandemic it was observed that age was the most important factor of poor prognosis, such that older patients more frequently suffered a more severe disease characterized by greater pulmonary and systemic inflammation, and complications that led to higher mortality.
The degree of biological aging depends on chronological age but also on multiple factors such as healthy habits, previous diseases etc. Biological aging can be measured indirectly by measuring in blood cells the shortening of the terminal ends of the chromosomes called telomeres, which occurs parallel to cellular aging. It is thought that biological age has a greater influence on health or disease than chronological age.
To better understand the relationship between biological age and the severity of inflammation, we analyzed the length of telomeres in relation to the different evolution of hospitalized COVID-19 patients, and with other clinical characteristics such as the degree of inflammation, or delayed resolution of persistent symptoms or lung lesions.
The results confirmed a relationship between telomere shortening (older biological age) and the need for hospitalization for COVID. However, once hospitalized, the patients did not evolve more seriously in relation to this factor, but rather in relation to chronological age and other factors. We also observed a relationship between telomere shortening and a slower resolution of lung inflammation.
These observations support a relationship between age, biological aging, and inflammatory disease more complex than expected, which deserves further studies to better interpret its involvement in different forms of inflammatory disease.

Patient Voice

Not immediate individual benefits expected. Future patients with COVID-19, or with future similar viral diseases could benefit.

Publications

– Retuerto M, Lledó A, Fernandez-Varas B, Guerrero-López R, Usategui A, Lalueza A, García-García R, Mancebo E, Paz-Artal E, Sastre L, Perona R, Pablos JL. Shorter telomere length is associated with COVID-19 hospitalization and with persistence of radiographic lung abnormalities. Immun Ageing. 2022 Aug 22;19(1):38. doi: 10.1186/s12979-022-00294-9. PMID: 35996190; PMCID: PMC9394033.
https://pubmed.ncbi.nlm.nih.gov/35996190/

Project Team/Centres

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The impact of COVID-19 and national COVID-19 policies on people with rheumatic diseases; the CORE (COVID-19 in rheumatic diseases) project

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 100.000
Project duration: 2021–2022

Project Url

www.foreum.org/projects/?id=196

Concept

The aims of the CORE (COVID-19 in rheumatic diseases) project are to determine the impact of the pandemic on health care utilization for the most frequent RMDs (incl. rheumatoid arthritis (RA), spondyloarthritis (SpA), and osteoarthritis (OA). It will also assess the impact of different national COVID-19 lockdown policies on RMD patients' healthcare utilisation in comparison with the reference population.

Objectives

- To estimate the effect of the COVID-19 pandemic (as a natural experiment) on healthcare utilisation (access to treatments including surgeries, prescribed drugs, etc.) in individuals with and without RMDs
- To assess the impact of pandemic lockdown restrictions and social distancing on hospitalisation/ mortality due to COVID-19 in RMD patients.

Goals/Milestones

- Data cleaning / analysis and data retrieval
- Abstract / Publication

Interim Results

EULAR Abstract

2021

- AB0678:
  Rates of surgical procedures of the knee and hip during the "first wave" of covid 19 in Sweden.
  Dell'isola A, Kiadaliri A, Turkiewicz A, et al; Annals of the Rheumatic Diseases 2021;80
  Go to EULAR Abstract Archive

Final Results

In this project, we examined the impact of the COVID 19 pandemic on patients which rheumatic diseases, using population-wide data from Norway, Sweden, and the Netherlands. Our studies have found that both diagnosis and treatment of osteoarthritis (OA) were severely reduced due to the pandemic. However, important care for severe OA (for instance hip and knee replacement surgeries) were offered at rates close to normal towards later stages of the pandemic, implying that crucial treatment for severe OA can be provided during a pandemic when suitable measures are taken. We also found that strict lockdown in Norway was associated with reduced risk of hospitalization and (to a lesser extent) death due to COVID-19 among patients with rheumatic diseases, compared to neighbouring Sweden where no lockdown was enforced.

Lay Summary

We aimed to understand the impact of the COVID-19 pandemic on people with rheumatic diseases. Using healthcare data from the Netherlands, Sweden and Norway, we found that the first wave of the pandemic was associated with greatly reduced in-person healthcare consultations, although remote consultations increased somewhat. In Sweden, we found that hip and knee replacement surgeries were greatly reduced in the first wave of the pandemic. However, in the second wave of the pandemic, the rates of these surgeries were nearly back to normal, offering hope that care for severe disease can be provided during a pandemic alongside suitable measures to contain the spread of infection. We also studied the risks faced by people with rheumatic diseases when exposed to COVID-19 infection, as well as the impact of country-specific policies on this vulnerable patient population's health outcomes. Comparing Norway, which implemented strict lockdowns, with neighbouring Sweden, which implemented only recommendations for social distancing, we found that hospitalizations due to COVID-19 were largely reduced in Norway among patients with rheumatic diseases, compared to Sweden. This confirms the effect of strict lockdown on healthcare outcomes, in particular among older persons with rheumatic diseases, who are at higher risk of COVID-19 complications.

Patient Voice

In the absence of a vaccine, protecting vulnerable individuals is the only strategy to reduce the impact of the deadly COVID-19 virus. The CORE project will provide the necessary knowledge to develop precise protection strategies for people with rheumatic disease and, in the eventuality of a vaccine, will help healthcare systems to prioritise people at higher risk. Altogether, this project will provide knowledge that will be immediately useful and will support future efforts against COVID-19 and similar pandemics.

Publications

– Ali Kiadaliri, Karin Magnusson, Aleksandra Turkiewicz, Andrea Dell'Isola, Jos Runhaar, Sita Bierma-Zeinstra, Martin Englund, Impact of the first wave of the COVID-19 pandemic on healthcare use in osteoarthritis: A population register-based study in Sweden, Osteoarthritis and Cartilage Open, Volume 4, Issue 2, 2022, 100252, ISSN 2665-9131, https://doi.org/10.1016/j.ocarto.2022.100252. https://www.sciencedirect.com/science/article/pii/S2665913122000206?via%3Dihub
– Dell'Isola A, Kiadaliri A, Turkiewicz A, Hughes V, Magnusson K, Runhaar J, Bierma-Zeinstra S, Englund M. The impact of first and second wave of COVID-19 on knee and hip surgeries in Sweden. J

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- Velek P, de Schepper, E, Schiphof D, Evert van Spil W, Englund M, Magnusson K, Kiadaliri A, Dell'Isola A, Licher S, Bierma-Zeinstra S, Runhaar J. Changes to consultations and diagnosis of osteoarthritis in primary care during the COVID-19 pandemic. Osteoarthritis Cartilage. 22023 Mar 5;S1063-4584(23)00699-4. doi:
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https://portal.research.lu.se/en/publications/changes-to-consultations-and-diagnosis-of-osteoarthritis-in-prima
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- Kiadaliri A, Turkiewicz A, Magnusson K, Methi F, Dell'Isola A, Runhaar J, Bierma-Zeinstra S, Englund M. Pandemic lockdown restrictions and COVID-19 hospitalization and deaths in patients with rheumatic and musculoskeletal diseases. Preprint from Research Square, 12 Aug 2022 DOI:
10.21203/rs.3.rs-1584534/v1 PPR:
PPR531340
https://europepmc.org/article/PPR/PPR531340

Project Team/Centres

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Deciphering a specific signature of the immunosenescence induced in COVID-19+ patients versus rheumatoid arthritis patients

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Funding and Timeline
FOREUM research grant: EUR 75.000
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=197

Concept
Immune aging or immunosenescence is characterized by a loss of T cell clonal diversity and a contraction of naïve T cells with proliferative capacity associated with the functional impairment of many others immune cells as well as a chronic low degree of inflammation. It is not clear today if the association of COVID-19 disease severity with age is mainly related with the immunosenescence of infected patients. To better understand the immunological mechanisms involved in SARS-Cov-2 pathophysiology, this project aims at comparing the immunosenescence patterns observed during RA, aging and SARS-Cov-2 infected patients in order to design improved therapeutic interventions.

Objectives
- Determine the senescence immunophenotyping in COVID-19+ patients
- Compare the immunosenescence of COVID-19+ patients to a reference inflammatory disease with immunosenescence (active RA)
- Specify the specific gene expression of the immunosenescence induced in patients infected by SARS-Cov-2

Goals/Milestones
- WP1: Recruitment of patients
- WP2: Multiparametric cytometry experiments
- WP3: Single Cell Analysis
- WP4: Coordination and management of the project / reporting

Patient Voice

Patients with RA may be at particular risk for COVID-19 as they show an intrinsically higher risk for infections. On the other hand, among RA treatments, JAK inhibitors or IL-6 targeting drugs may counteract CRS and immunosenescence by protecting RA patients from deleterious outcomes. Thus, a better understanding of the mechanisms of immunosenescence observed in RA compared to the patterns associated with SARS-Cov-2 is important and may validate the use of senolytic drugs such as Jak inhibitors, already available in RA patients.

Project Team/Centres

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- I Picot, AFPric, FRANCE

Assessing the impact of COVID-19 on Rheumatic and Musculoskeletal Disorders in primary care: an observational study of UK national primary care electronic health records

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Funding and Timeline
FOREUM research grant: EUR 99.195
Project duration: 2020–2021

Project Url
www.foreum.org/projects/?id=198

Concept

The COVID-19 pandemic has led to a paradigm shift in the way primary care operates and patients with non-COVID related symptoms are managed. Almost all patients are managed remotely. Routes to refer patients routinely for specialist care have been paused. This study aims to use primary care electronic healthcare records to explore changing trends in the prevalence and incidence of consultations for rheumatic musculoskeletal disorders (RMDs), prescribing of analgesia, and the incidence and time to diagnosis of rheumatoid arthritis (RA) and juvenile idiopathic arthropathy (JIA) in the pre- peri- and post- pandemic periods.

Objectives

The study objective is to assess the impact of the COVID-19 pandemic on patients experiencing RMDs including changes in consultation patterns, analgesic prescribing and timely referral for new presentations of inflammatory RMDs.

Goals/Milestones

- receiving data from CPRD (Sep-20)
- completing database preparation and starting data analysis (Dec-20 and Jan-21)
- completing analysis of pre- and peri-COVID-19 data for hypotheses (Jul-21)
- receiving further data from CPRD (Sept-21)
- completing database preparation (Dec-21)
- completing analysis of peri- and post COVID-19 time periods (May-22)
- writing results with a final PPIE meeting (May-22)
- submitting conference abstracts (Jun-22) and publications to peer-reviewed journals (Jul-22)
- engagement with external agencies to promote RMD health (Jul-22)

Final Results

Consultations for musculoskeletal conditions fell sharply during March 2020 and returned to pre-pandemic levels by October 2021. However, the proportion of consultations in which analgesia was prescribed rose steeply in March 2020 and then returned to pre-pandemic trajectory by December 2021.

The incidence of rheumatoid arthritis and juvenile idiopathic arthritis reduced from March 2020 and then rose again, though not to pre-pandemic rates. Referral rates to specialist services for patients with suspected inflammatory arthritides reduced between February 2020 and May 2020 before recovering by October 2021. Time to diagnosis of RA from first consultation was longer in the early pandemic and late pandemic periods. Time between referral and diagnosis of RA was longest for those who received a diagnosis in the late pandemic period in the pre-pandemic period. Residents of the most deprived areas experienced the longest time between first consultation and RA diagnosis.

Lay Summary

COVID-19 pandemic changed healthcare access and delivery. Patients had healthcare consultations remotely. Doctors could only refer patients to specialists for urgent problems.

We assessed the impact of these restrictions on the care of patients living with musculoskeletal symptoms (for example, pain). We measured:

1) consultations for musculoskeletal conditions, 2) prescriptions of pain-relieving medicines, and 3) referral patterns to specialist healthcare services for diagnosis and treatment of inflammatory arthritis, including rheumatoid and juvenile idiopathic arthritis.

We looked at anonymized health records of 6 million people who had consulted their primary care team with a musculoskeletal condition. We compared three time periods:

pre-pandemic (April 2017-February 2020), early pandemic (March 2020–August 2020), and later pandemic (September 2020–October 2021).

Fewer consultations for musculoskeletal conditions occurred in the early pandemic period, but this returned to pre-pandemic levels by October 2021. More pain-relieving medicines were prescribed to patients who consulted during the early-pandemic period compared to pre-pandemic , but prescribing patterns returned to pre-pandemic levels by October 2021. Referrals to specialists continued at the same rate across all time periods. It took longer for patients to be diagnosed with rheumatoid arthritis in the early and later pandemic periods, particularly for residents in more deprived areas.

Healthcare services to support diagnosis and management of musculoskeletal conditions must remain open and accessible during healthcare crises. This would help to avoid high levels of pain-relieving medicine and their associated side effects and ensure early diagnosis of rheumatoid arthritis which requires rapid treatment to prevent worsening symptoms.

Patient Voice

This work is essential to investigate the indirect impact of the COVID-19 pandemic on the care of patients with RMDs. Identifying trends in consultation, analgesic prescribing, and diagnosis of inflammatory RMDs will provide evidence to underpin future pandemic planning to enable access to non-pharmacological management options and to ensure those with inflammatory RMDs are identified and referred to specialist care in a timely manner in order to maximize long term outcomes.

Publications

– Welsh, Victoria, Claire Burton, Kelvin Jordan, James Bailey Mr, Kayleigh Mason, Ram Bajpai, Christian Mallen, Martin Frisher, and Danielle Van Der Windt. 2022. "MuSculoskeletal paiN durIng the COVID-19 PandEmic:
An Observational Study of UK National Primary Care Electronic Health Records (the SNIPE Study)." OSF. October 20. doi:10.17605/OSF.IO/RJ56X.
https://osf.io/rj56x/

Project Team/Centres

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– K Jordan, Keele University, UNITED KINGDOM
– J Bailey, Keele University, UNITED KINGDOM
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– C Mallen, Keele University, UNITED KINGDOM

2020

Call for Fatigue and Pain

Fatigue and pain are central manifestations of many different forms of Rheumatic Musculoskeletal Diseases (RMDs). Fatigue and Pain, alone or in combination, are associated with substantial impairment of the life quality of patients with RMD and therefore constitute a major clinical challenge. Despite their importance, our knowledge on the nature of fatigue and pain in RMDs, their mechanisms, clinical impact and management, is more than limited to date and new research efforts in this field are required. Furthermore, the relation between inflammatory activity and fatigue as well as pain in RMDs is often not linear suggesting additional factors that control the burden of fatigue and pain in RMDs.

The call was launched in **2020**, and out of 41 letters of intent 3 projects were selected for funding:

- Targeting nociplastic pain in arthritis
- Autoimmune and molecular mechanisms for pain and fatigue in fibromyalgia
- Exploring the effects of a combined exercise programme on pain and fatigue outcomes in people with systemic sclerosis

Targeting nociplastic pain in arthritis

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Funding and Timeline
FOREUM research grant: EUR 599.908
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=201

Concept
Pain is the main disabling symptom in arthritis. Inflammation and tissue damage cause nociceptive pain, which normally improves with injury healing and disease control. Many patients develop nociplastic pain, which persists in the absence of inflammation and tissue damage. It was discovered that, in mice, ablating Nav1.8-expressing nociceptors preserves nociceptive pain but prevents the establishment of nociplastic pain. By comparing the transcriptome of patients with prevalently nociceptive versus prevalently nociplastic pain from highly characterized prospective cohorts and cross-referencing with transcriptomics data in animal models of rheumatoid arthritis, osteoarthritis and nociplastic pain, the group will identify transcripts associated with the development of nociplastic pain. After an in-silico analysis to predict and prioritize key molecular players amenable for targeting, the group will use gain- and loss-of-function experiments in animal models to determine which of these genes/pathways are essential for the transition from nociceptive to nociplastic pain.

Objectives
Objective 1. Identification of signatures of nociplastic vs nociceptive pain using transcriptomics data from patient cohorts and animal models.
Objective 2. Prioritization strategy for candidate gene targets.
Objective 3. Validation of drug targets in animal models of pain, osteoarthritis and inflammatory arthritis.

Goals/Milestones
1-12 months: completion and analysis of transcriptomics data
18 months: prioritization of targets
24 months: completed in vitro validation of at least 5 targets.

Patient Voice

A large proportion of patients with arthritis and all patients with fibromyalgia are disabled by nociplastic pain, resulting in absenteeism, huge costs and loss of work capacity worth billions. Treating nociplastic pain would restore the work capacity of these patients, their quality of life and independence.

Publications

– Caxaria S, Kouvatsos N, Eldridge SE, Alvarez-Fallas M, Thorup AS, Cici D, Barawi A, Arshed A, Strachan D, Carletti G, Huang X, Bharde S, Deniz M, Wilson J, Thomas BL, Pitzalis C, Cantatore FP, Sayilekshmy M, Sikandar S, Luyten FP, Pap T, Sherwood JC, Day AJ, Dell'Accio F. Disease modification and symptom relief in osteoarthritis using a mutated GCP-2/CXCL6 chemokine. EMBO Mol Med. 2023 Jan 11;15(1):e16218. doi: 10.15252/emmm.202216218. Epub 2022 Dec 12. PMID: 36507558; PMCID: PMC9832835.
https://www.embopress.org/doi/full/10.15252/emmm.202216218

Project Team/Centres

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– C Pitzalis, Queen Mary, University of London, UNITED KINGDOM
– M Lewis, Queen Mary, University of London, UNITED KINGDOM
– N Eijkelkamp, Utrecht University, NETHERLANDS
– A Pandit, University Medical Center Utrecht, THE NETHERLANDS
– A Moqrich, Institute of Marseille, FRANCE

Autoimmune and molecular mechanisms for pain and fatigue in fibromyalgia

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 599.950
Project duration: 2021–2024

Project Url

www.foreum.org/projects/?id=202

Concept

Although there is a wide range of symptoms, the main somatic symptoms of Fibromyalgia (FM) are chronic musculoskeletal pain and physical and cognitive fatigue. There is an urgent need to advance our understanding of the underlying cellular and molecular mechanisms of FM pain and fatigue in order to identify new therapy solutions. The group will conduct metabolomic and lipidomic studies in serum samples from women with FM to identify factors that correlate with pain, fatigue and/or antibodies (IgG). The project will use animal models and in vitro systems to further explore if candidate factors that are elevated in FM samples contribute to pain and fatigue and examine the benefit of exercise and pharmacological interventions. The direct reverse translation of clinical findings will allow to generate conclusions of high predictive value/validity.

Objectives

Question:
Are changes in lipid metabolism and mitochondrial function in sensory neurons and muscle contributing to pain and/or fatigue – and are there links to autoimmunity?
Objective 1. Examine metabolic and lipidomic profile in FM in relation to IgG and clinical symptoms.
Objective 2. Determine whether transfer of IgG from FMS alters metabolism and mitochondrial function in mice and whether such changes are related to induction of pain and physical fatigue.
Objective 3. Determine whether candidate lipids or other serum factors influence nociceptor excitability, and to examine the impact of pharmacological interventions and exercise on FM IgG-induced nociceptor excitability, muscle pathophysiology and behaviour.

Goals/Milestones

1. Metabolomic/lipidomic analysis of 120 FM/HC (cohort A).
2. Validation of the identified pain/fatigue relevant factors in 200 FM/HC samples (cohort B) and establishment of their relation to IgG antibodies, pain sensitivity and skin innervation.
3. Metabolomic/lipidomic analysis blood, muscle, DRG and brain from FM/HC IgG injected mice.
4. Comparison of changes in lipids/metabolites between human and mouse samples.
5. Results from in vivo and in vitro muscle fatigue studies.
6. Results from intervention studies (exercise and pharmacology).
7. Analysis of Ca2+-measurements in DRG neurons.
8. Electrophysiological studies of single units in skin-nerve preparation.
9. Webinar for patient organizations in Sweden, Finland, UK summarizing research and findings
10. Submit popular scientific summary/highlight to patient organizations' newsletters

Patient Voice

FM antibodies and fatty acids of relevance for disease mechanism in FM will be identified and validated. The FM antibodies could be used for development of diagnostic tests for subgrouping FM patients, a prerequisite for patient tailored treatment strategies. The increased understanding of disease relevant substances and how various interventions can reverse their negative effects can potentially lead to the development of new treatment strategies for FM.

Project Team/Centres

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- K Kultima, Uppsala University, SWEDEN
- D Andersson, King's College London, UNITED KINGDOM
- P Tavi, University of Eastern Finland (UEF), FINLAND

Exploring the effects of a combined exercise programme on pain and fatigue outcomes in people with systemic sclerosis

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 387.216
Project duration: 2021–2024

Project Url

www.foreum.org/projects/?id=203

Concept

As yet, the effects of a feasible, long-term, tailored exercise programme on pain and fatigue in people with SSc have not been explored. Therefore, this project will carry out a multicentre (n=5) research clinical trial to assess the effect of a previously-established, supervised 12-week combined (aerobic and resistance training) exercise programme on pain and fatigue. The 26-month study will recruit 180 people with SSc that will be allocated randomly to two groups. Group A will perform the exercise programme parallel to standard care and Group B will receive the standard care alone.

Objectives

- To investigate the effects of the proposed intervention on digital pain and fatigue of people with SSc.
- To investigate the effects of the proposed intervention on QoL, depression, cardiorespiratory fitness, strength of people with SSc.
- To investigate the effects of the proposed intervention on the digital structural vascular changes in people with SSc.

Goals/Milestones

Months 1-3: Study set up
Months 4-20: Recruitment, baseline assessments, exercise intervention and follow ups.
Months 21-23: Data analysis.
Months 24-26: Dissemination of findings and study close down. (Report to stakeholders, leaflet for the general public, approx. 4 manuscripts)

Patient Voice

Participant inclusion: 1) People diagnosed with Systemic Sclerosis experiencing RP; 2) Being over 18 years old; and 3) Patients should be able to perform the prescribed exercise programme.
Benefits for patients:

- Reduction of pain and fatigue.
- Improvement in QoL, overall fitness, social life.
- Prevention of open wounds in fingers and infections/hospitalisations.
- Education on benefits of exercise on overall health gained through participation in exercise programme.

Publications

- Mitropoulos, A., Boström, C., Mattsson, M., Kouidi E., Dimitroulas T., I. E. Liem S., P. M. Vliet Vlieland T., de Vries-Bouwstra J.K., Jacobsen S., Cuomo G., Akil M. & Klonizakis M. Exploring the effects of a combined exercise programme on pain and fatigue outcomes in people with systemic sclerosis: study protocol for a large European multi-centre randomised controlled trial. Trials 23, 962 (2022).
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  https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06853-1#citeas
- Anifanti M, Teloudi A, Mitropoulos A, Syrakou N, Pagkopoulou E, Triantafyllidou E, Boström C, Diederichsen LP, Cuomo G, Dimitroulas T, Klonizakis M, Kouidi E. Right Ventricular Morphology and Function after Exercise Training in People with Systemic Sclerosis: A Randomized Controlled Pilot Study. Life (Basel). 2023 Feb 15;13(2):545. doi: 10.3390/life13020545. PMID: 36836902; PMCID: PMC9958927.
  https://pubmed.ncbi.nlm.nih.gov/36836902/

Project Team/Centres

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- S Jacobsen, Copenhagen University, DENMARK
- G Cuomo, L. Vanvitelli University, ITALY
- E Kouidi, Aristotle University of Thessaloniki, GREECE

2021

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a particularly challenging rheumatic and musculoskeletal disease (RMD). While being in the shadow of rheumatoid arthritis for many years, scientific interest in PsA has gradually risen. But the current knowledge on the pathophysiology, clinical presentation and diagnosis and treatment of PsA is still limited. Acknowledging these unmet needs FOREUM announced a call for innovative ideas and projects to increase our knowledge in PsA in order to instigate high-quality research in this severe and underrecognised disease in Europe.

The call was launched in **2021**, and out of 20 Letters of Intent three projects were selected for funding:

- The contribution of Stromal cells in shaping the Synovial MicroEnvironment of Psoriatic arthritis: pathogenetic mechanisms, Heterogeneity, and prognosis (StroPHe)
- BarrieR Integrity loss in Gut as driver of Host tissue Tropism and outcome in PsA: the BRIGHT concept
- Identifying the mechanisms and biomarkers of transition from Psoriasis (PsO) to Psoriatic Arthritis (PsA)

The contribution of Stromal cells in shaping the Synovial MicroEnvironment of Psoriatic arthritis: pathogenetic mechanisms, Heterogeneity, and prognosis (StroPHe)

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 591'960
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=211

Concept

Recent evidence appreciating the contribution of stromal cell heterogeneity in pathophysiology emerges as a new opportunity to stratify arthritic diseases and develop more targeted clinical tools. The project group postulates that different synovial fibroblast (SF) profiles determine the nature of Synovial MicroEnvironment (SME), and fuel the development of different types of arthritic diseases by exhibiting differential sensitivity to inflammatory stimuli. The ensuing transcriptional responses dictate the changes in the cellular composition of the diseased SMEs, characterizing the distinct pathological and clinical findings in each arthritic phenotype. Consistent with the hypothesis, the group aims to explore the stromal-mediated causalities in Psoriatic Arthritis (PsA) and delineate the PsA-specific SF profile. With the integrative transcriptomic and functional analyses, the group aspires to assist the generation of the distinct stromal codes governing arthritic diseases.

Objectives

To address the project's hypothesis, the group will follow a human/mouse integrative analysis, combining the high-resolution analysis of PsA-affected synovia with molecular and functional analysis on the pathogenic contribution of the SFs ex vivo and in modeled PsA. With this analysis the aim is to:

- Provide the stromal cell atlas of PsA synovium at single cell level and identify synovial stromal signatures which uniquely characterize PsA
- Functionally assess the pathogenicity of the stromal responses in a new A20 mutant mouse model (A20Znf7) that develops PsA-like arthritis, characterized by peripheral arthritis, dactylitis, nail pathology and enthesitis.
- Predict and preclinically examine new therapeutic strategies and targets, based on genetic and functional evidence

Goals/Milestones

Milestone I: The PsA synovium at single cell level
Milestone II: The stromal codes of inflammatory arthritides
Milestone III: Pathogenic mechanisms in modelled PsA:
focusing on stromal compartment
Milestone IV: Delivery of A20-ZnF7 protein domain as a therapy to suppress PsA

Patient Voice

The expected results will inform healthcare innovation and benefit the patients by providing targeted biomarkers for segregating inflammatory arthritides, and testing novel therapeutics. Moreover, the high-resolution analysis will be deposited in public databases, serving as a key resource for the formation and validation of additional mechanistic hypotheses.

Project Team/Centres

- M Armaka, Biomedical Sciences Research Center Alexander Fleming, Vari, GREECE (lead)
- R Micheroli, University Hospital Zurich, SWITZERLAND
- G van Loo, VIB Center for Inflammation Research & Ghent University, BELGIUM

BarrieR Integrity loss in Gut as driver of Host tissue Tropism and outcome in PsA: the BRIGHT concept

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600'000
Project duration: 2021–2024

Project Url

www.foreum.org/projects/?id=212

Concept

Psoriatic arthritis (PsA) is clinically heterogeneous, showing inflammation of the peripheral joints, spine, entheses, fingers and toes, skin or nails. Whilst there is substantial overlap in the underlying immunobiology driving inflammation in any of these sites, there are also marked differences. However, the reasons for these differences are unclear. The BRIGHT consortium hypothesizes that intestinal microbiota shape immune responses in the early stages of PsA thereby driving clinical heterogeneity. To address this, the group will investigate (i) how gut barrier integrity, intestinal dysbiosis, disease subtype and severity relate in patients; (ii) whether there are differences in the cellular sources that produce or respond to IL-23 and IL-17 production, using deep phenotyping of blood, gut, joint and skin; and (iii) whether PsA intestinal microbiota shape IL-23 and/or IL-17-dependent responses and treatment, using animal models of axial and peripheral forms of PsA.

Objectives

Obj.1: How do gut barrier integrity, intestinal dysbiosis, disease subtype and severity in PsA relate?
Obj.2: Do similar cellular sources produce or respond to IL-23 and IL-17 in different tissues (blood, skin, gut, joint) in PsA?
Obj.3: Do intestinal microbiota shape IL-23/IL-17 dependent responses in axial and peripheral forms of PsA?

Goals/Milestones

Objective 1
M1, months 01 - 12: Serum analysis of GIANT cohort
M2, months 06 – 18: PsA gut histopathology
M3, months 12 – 24: Link to microbiota and PsA phenotype
Objective 2
M4, months 01 – 24: Patient recruitment and sample collection
M5, months 04 – 30: Deep phenotyping by scRNAseq and flow cytometry
Objective 3

M6, months 01 – 36: Experimental animal studies in germ-free, gnotobiotic and knockout models
M7, months 27 – 36: Manuscript submission
M8, months 30 – 36: Symposium

Patient Voice

Several million adults in Europe live with PsA, which significantly affects their quality of life. The group hopes that their findings will start to reveal the gut as a potential critical determinant of peripheral versus spinal disease subtype in patients with PsA. This would generate a shift in the way we think about the diagnosis, disease outcome and response to treatment in PsA.

Project Team/Centres

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– K Venken, VIB Center for Inflammation Research & Ghent University, BELGIUM

Identifying the mechanisms and biomarkers of transition from Psoriasis (PsO) to Psoriatic Arthritis (PsA)

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 599'850
Project duration: 2021–2024

Project Url

www.foreum.org/projects/?id=213

Concept

The key unmet clinical needs in Psoriasis (PsO) and Psoriatic Arthritis (PsA) management include (i) prognostic biomarkers of progression from PsO-to-PsA and (ii) improved understanding of pathogenic mechanisms of transition from skin-to-joint disease. Provision of these will lead to earlier diagnosis and treatment – with better prognosis – of PsA, and aid development of novel drug targets which prevent rather than treat PsA. This project aims to uncover heterogeneity of PsO/PsA by establishing its comprehensive functional cellular and molecular atlas of blood, skin and synovium, and to uncover the mechanisms and biomarkers of the evolution from PsO-to-PsA. This aim will be addressed by an international team of clinical and basic science researchers with synergistic patient cohorts, tissue biopsy repository and diverse computational and experimental expertise.

Objectives

A) To delineate the cellular and molecular atlas of the disease trajectory from PsO-to-PsA using single cell multi-omic profiling.
B) To investigate the role of candidate PsO/PsA shared cell clusters/pathways in initiating joint pathologies by using in vitro synovial organoids or tissue digests with pathway inhibitors.
C) To identify the biomarkers of progression from PsO-to-PsA by integrating the cellular atlas of PsO with longitudinal clinical outcomes (including PsA development or not).

Goals/Milestones

Milestone 1:
Providing candidate pathways determining the transition from PsO-to-PsA.
Milestone 2:
Identification of the molecular mechanisms of PsO-to-PsA transition.
Milestone 3:
Identification of the Biomarkers of PsO-to-PsA transition.

Patient Voice

This project will help identify at-risk PsO patients for earlier diagnosis of PsA, and improve treatment options of patients with PsA. If the biomarkers of PsOto-PsA transition identified in this study are confirmed by other Rheumatology centres across the world, this can lead to a change of EULAR treatment recommendation for PsO patients to favour earlier drug intervention.
In addition, this project will provide new knowledge on the mechanisms of PsO-to-PsA transition.

Publications

Kurowska-Stolarska, M., Alivernini, S. Synovial tissue macrophages in joint homeostasis, rheumatoid arthritis and disease remission. Nat Rev Rheumatol 18, 384–397 (2022). https://doi.org/10.1038/s41584-022-00790-8
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Project Team/Centres

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- S Alivernini, Fondazione Policlinico Universitario A. Gemelli IRCCS, ITALY
- S Siebert, University of Glasgow, UNITED KINGDOM
- T Otto, University of Glasgow, UNITED KINGDOM
- O Distler, University of Zurich, SWITZERLAND

2021

Call for Career Research Grants

FOREUM is committed to promote the best talents in the field of rheumatic and musculoskeletal diseases (RMD). Consistent with these goals FOREUM issued a new call that aims to fund excellent young researchers promoting innovative ideas and supporting high quality research projects covering basic and clinical science projects related to RMDs. Scientific excellence is the key eligibility criterion for this career research grant initiative, which aims to foster independent science and intends to develop new research leaders in the field.

The third call was launched in **2021**, and out of 71 letters of intent 4 projects were selected for funding:

- Failing maternal-fetal tolerance in SLE: finding the molecular mechanisms behind pregnancy complications
- Role of Innate Lymphoid Cells in Rheumatoid Arthritis
- Pro-fibrotic role of IgG4 antibodies in the pathogenesis of IgG4-related disease
- Cognitive phenotypes in immune mediated inflammatory diseases: a trans-diagnostic approach

Failing maternal-fetal tolerance in SLE: finding the molecular mechanisms behind pregnancy complications

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200'000
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=214

Concept

Pregnant women with systemic lupus erythematosus (SLE) have an increased risk of maternal complications and adverse fetal outcomes. To better predict and prevent adverse outcomes of SLE pregnancies, it is crucial to understand the underlying biological processes.
Failing maternal-fetal tolerance is thought to play an important role in the increased risk for pregnancy complications in SLE patients. However, it is unknown which mechanisms mediate maternal-fetal tolerance and how the dysregulated immune system in SLE affects this process.
This study will identify potential therapeutic targets based on the mechanisms underlying failing maternal-fetal tolerance in SLE. Furthermore, it will deliver potential biomarkers for early detection of developing complications. Thereby, the findings in this study will contribute to the improvement of SLE pregnancy outcomes with benefits for both mother and child.

Objectives

The overall objective of this research is to delineate which cellular processes mediate failing maternal-fetal tolerance in SLE patients. Furthermore, the aim is to define potential biomarkers for earlier detection of complications. The group hypothesises that the abnormally regulated immune system in SLE patients causes aberrant interactions at the maternal-fetal interface, resulting in failure of immunological tolerance.
AIM 1: Compare the cellular distribution and activation state of placental cells from women with SLE with healthy women
AIM 2: Analyze cell-cell interactions at the maternal-fetal interface
AIM 3: Identify peripheral blood biomarkers associated with failing maternal-fetal tolerance

Goals/Milestones

Milestone 1: ethics approved (Year 1, end of Q2)
Milestone 2: all patients included (Year 2, end of Q4)
Milestone 3: scRNA sequencing done (Year 2, end of Q2)
Milestone 4: optimization and validation of organoid models – publication 1 (Year 1, end of Q4)
Milestone 5: mechanisms and biomarkers identified – publication 2 (Year 3, end of Q4)

Patient Voice

This study greatly advances our understanding of the processes leading to pregnancy complications in SLE patients. This is a crucial first step in better predicting and improving pregnancy outcomes for SLE patients, for example by monitoring the cells identified in the final part of our project in the blood of women with SLE. This work will also be a benefit for future research to develop intervention strategies to reduce pregnancy complications.

Project Team/Centres

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Role of Innate Lymphoid Cells in Rheumatoid Arthritis

Project Lead
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Funding and Timeline
FOREUM research grant EUR 200'000
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=215

Concept
Rheumatoid Arthritis (RA) severely impacts the life of affected individuals and current treatments are not effective in all patients. Fibroblast-like synoviocytes (FLS) are joint stromal cells which serve a key role in joint destruction during RA. Therefore, inflammatory mediators promoting FLS-driven joint destruction are considered important drug targets in RA. The group has evidence supporting a previously unrecognized mechanism of FLS activation by group 2 innate lymphoid cells (ILC2s), which challenges the current dogma regarding the role of ILC2 in RA. Thus, the objective is to determine if joint-localized ILC2 play a pathogenic, rather than protective, role in RA by promoting FLS-driven joint damage.

Objectives
Aim 1. To establish the role of AREG-producing ILC2 in arthritis.
Aim 2. To establish the presence of AREG-producing ILC2 in human RA.
Aim 3. To demonstrate that ILC2-derived AREG promotes FLS aggressiveness.

Goals/Milestones
- Month 12: Established the pathogenic role of AREG-producing ILC2 in experimental arthritis (aim 1.1). Obtained initial evidence for an enrichment of AREG-producing ILC2 within the synovium of RA patients (aim 2.1 and 2.2).
- Month 24: Established that AREG-producing ILC2 activates a joint destructive behaviour in FLS in vivo (aim 1.2) and in vitro (aim 3.1).
- Month 30: Completed the analysis of AREG-producing ILC2 in human synovium (aim 2) and established that AREG-producing ILC2 promote cartilage degradation by RA FLS (aim 3.2).
- Month 36: Finalisation and publication of obtained results.

Patient Voice

Results from this project will establish a novel mechanism of disease in RA and thereby lead to the identification of new therapeutic targets, which can be exploited for the generation of new and effective therapies for RA and improve the lives of individuals affected by this disease.

Project Team/Centres

– M Svensson, University of Gothenburg (UGOT), SWEDEN (lead)

Pro-fibrotic role of IgG4 antibodies in the pathogenesis of IgG4-related disease

Project Lead
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Funding and Timeline
FOREUM research grant EUR 200'000
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=216

Concept
IgG4-related disease (IgG4RD) is a fibrotic disorder of unknown etiology named for the peculiar accumulation of IgG4 antibodies in affected organs. Depletion of IgG4 producing B-lymphocytes after treatment with rituximab reverses myofibroblast activation in affected tissues suggesting that B-lymphocytes and IgG4 antibodies might directly contribute to tissue fibrosis in this condition. The project will demonstrate overlooked fibrotic properties of IgG4 antibodies and to explore the therapeutic potential of their inhibition.

Objectives
With the present research project we aim:
1. to demonstrate a direct pro-fibrotic effect of IgG4 antibodies from IgG4RD patients
2. to identify fibrotic molecular properties of IgG4 antibodies from IgG4RD patients
3. to explore the therapeutic potential of inhibiting the pro-fibrotic activity of IgG4 antibodies
In addition, the project will include a parallel work package conceived to engage patients over and beyond voluntary sample donation and discussion of scientific outputs. In particular, we will take advantage of this FOREUM Call and collaborate with experienced PRP in order to:
4. to identify IgG4RD specific "patient reported outcomes" (PRO) and develop the first ad hoc QoL questionnaire for IgG4RD (IgG4RD QoL).

Goals/Milestones
Milestone 1: Demonstration of a pro-fibrotic effect of IgG or IgG subclasses
Milestone 2: Identification of fibrotic molecular properties of IgG or IgG subclasses
Milestone 3: Identification of novel possible therapeutic targets
Milestone 4: Development of a Quality of Life Questionnaire for IgG4RD

Patient Voice

By implementing a patient-specific "work package", our study will actively involve experienced Patient Research Partners and a large number of patients with IgG4RD in the full research project. This ideal enterprise will proficiently raise
awareness on clinical and psychological instances that have never been systematically addressed before in IgG4RD, thus outlining a new era of personalized medical care tailored on patients' needs and based on targeted therapeutic approaches.

Project Team/Centres

- E Della Torre, San Raffaele Hospital (SRH), ITALY (lead)
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- I Galetti, Gruppo Italiano Lotta alla Sclerodermia (GILS), ITALY
- A Vieira, Liga Portuguesa Contra as Doenças Reumáticas, PORTUGAL
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Cognitive phenotypes in immune mediated inflammatory diseases: a trans-diagnostic approach

Project Lead
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Funding and Timeline
FOREUM research grant EUR 197'124
Project duration: 2021–2024

Project Url
www.foreum.org/projects/?id=217

Concept

Accumulating evidence from small-scale studies suggests that people with immune mediated inflammatory diseases (IMIDs) have an increased risk of cognitive impairment (CI), but limited data are available from population studies. CI enormously impacts quality of life, but at present there is little understanding of the magnitude of CI or which sociodemographic, biological and medical factors are associated with CI in the IMIDs, meaning there is no research to direct intervention development. The IMIDs in this study are: rheumatoid arthritis, systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, psoriasis, inflammatory bowel disease.
This analysis of the UK-Biobank dataset will be the largest study of CI in the IMIDs, providing the first definitive evidence of the extent of CI in this group. Furthermore, risk factors for CI identified within this project can be used to direct intervention development.

Objectives

- To define the magnitude of cognitive impairment in people with IMIDs, using a harmonised battery of cognitive assessments
- To identify cognitive phenotypes in the IMIDs, and explore how these phenotypes are related to diagnosis
- To perform a phenotypic scan for factors associated with cognitive impairment / phenotypes in the IMIDs

Goals/Milestones

- 8 months (August 2022): received data, recruited a PPI group and held first meeting
- 14 months (March 2023): cleaned data and performed first descriptive analysis
- 20 months (September 2023): performed machine learning and identified cognitive phenotypes
- 26 months (March 2024): performed phenome-wide scan and identified factors associated with cognition in the IMIDs
- 32 months (September 2024): project completion, academic papers published, lay summaries written and disseminated to patient groups

Patient Voice

This will be the largest assessment of cognitive impairment in the IMIDs to date, providing an accurate description of cognitive impairment in these conditions, leading to it becoming a recognised symptom of the IMIDs. Furthermore, identifying factors that are linked with cognitive impairment could pave the way for the development of interventions to improve or prevent cognitive impairment in the IMIDs. Lastly, if lifestyle is linked with cognitive impairment in the IMIDs, this will provide motivation for positive health behaviour changes.

Project Team/Centres

- J Gwinnutt, University of Manchester (UoM), ENGLAND (lead)
- S Verstappen, University of Manchester (UoM), ENGLAND
- A MacGregor, University of East Anglia (UEA), Norwich, ENGLAND
- D Montaldi, University of Manchester (UoM), ENGLAND
- J Simpson, Patient Partner
- J Rollestone, Patient Partner

2021

Call for international exchange 1-year fellowships

FOREUM is committed to funding and promoting scientific research into rheumatic and musculoskeletal diseases (RMD) and has a goal to foster links between rheumatology units in different countries. Consistent with these goals is the establishment of a call for international exchange fellowships that have the specific objective of facilitating the development of research capacity and training high-caliber applicants in RMD research.

The third call for a 1-year fellowship was launched in 2021 and out of 11 letters of intent 3 projects were selected for funding:

- Amlexanox as a potential novel therapeutic option for SLE
- Deciphering the interactions between gut microbiome components and the host during spondyloarthritis: insights from a Gut-on-Chip model
- Characterization of Synovial Fibroblast Subtypes

Amlexanox as a potential novel therapeutic option for SLE

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2022–2023

Project Url
www.foreum.org/projects/?id=222

Concept
In SLE, plasmacytoid dendritic cells produce type I interferon (IFN-I) in response to RNA- and DNA-containing immune complexes via activation of endosomal toll-like receptors 7 and 9. B cells are important players in SLE pathogenesis and are directly activated by the IFN-I protein and indirectly by IFN-I induced release of B cell activating factor (BAFF) by monocytes. The cytokine BAFF is essential for B cell activation, differentiation, and survival, and high serum BAFF levels have been associated with SLE disease activity. Although inhibition of both IFN-I and BAFF has been shown to have beneficial effects in clinical trials, such therapies do not relieve all patients from symptoms and complications. TANK-binding kinase 1 (TBK-1) is an important signalling hub leading to IFN-I production and subsequent induction of interferon stimulated genes such as BAFF.

Objectives
The hypothesis is that Amlexanox, by acting as a TBK-1 inhibitor, can be used as a novel therapeutic option to treat SLE by inhibiting IFN-I and IFN-I induced BAFF production. This hypothesis will be investigated by three specific objectives with the following aims:

- To determine whether Amlexanox has the potential to inhibit IFN-I release and IFN-I induced BAFF production, by using peripheral blood mononuclear cell cultures from healthy volunteers and patients collected at the home and the host center.
- To investigate whether IFN-I and BAFF increase B cell survival, proliferation, and differentiation, by analysis with high-dimensional flowcytometry and automated ELISA systems.
- To identify pathways through which Amlexanox can affect B cell survival.

Goals/Milestones

At 3 months: the effect of Amlexanox on IFN-I and IFN-I induced BAFF production has been determined.
At 6 months: the effect of IFN-I and BAFF on B cell survival, differentiation and proliferation has been assessed and an abstract will be submitted for presentation at the annual EULAR meeting.
At 9 months: the effect of Amlexanox on B cell survival pathways has been determined.
At 12 months: at least one manuscript will be submitted for publication.

Patient Voice

Researchers at the host institute are actively working together with ENCA (European Network for children with arthritis), Lupus Europe and the NVLE (Dutch patient organization for Lupus and other rheumatic diseases). A patient research partner associated with the Swedish Rheumatism Association is also engaged in the project. The patient partners will be actively involved throughout the study and communicate the results to the patient organizations.

Project Team/Centres

– A Björk, Karolinska Institute, SWEDEN (lead)
– M Versnel, Erasmus MC, NETHERLANDS

Deciphering the interactions between gut microbiome components and the host during spondyloarthritis: insights from a Gut-on-Chip model

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2022–2023

Project Url
www.foreum.org/projects/?id=232

Concept

Spondyloarthritis (SpA) encompasses several inflammatory rheumatic diseases that frequently harbor overt or subclinical intestinal inflammation. Dysbiosis, characterized by an overabundance of the Ruminococcus gnavus species, has recently been demonstrated in the intestinal microbiota of patients affected by SpA and correlates positively with disease activity. A thorough understanding of the microbiota-host interaction mechanisms in SpA is lacking due to the intrinsic limitations of standard cellular models. Organ-on-Chip systems have been recently developed thanks to the integration of nanotechnologies and microfluidics. The application of a laminar flux in two separate channels adjacent to a cell culture patch would allow the prolonged interaction between bacteria (including anaerobes) and patient-derived intestinal epithelium, closely mimicking interactions that occur in vivo.

Objectives

The primary objective of this project is to set up a relevant microphysiological model of gut epithelium in SpA based on colon organoids and Gut-on-Chip technology. Furthermore, we aim to determine how different strains of Ruminococcus gnavus and other relevant members of the gut microbiota directly isolated from SpA patients or healthy controls interact with gut epithelial cells and modulate the inflammatory response in order to assess a possible causal link.

Goals/Milestones

The main goals along the timeline are the following:

- Three months: the samples will be collected from patients and healthy controls; organoids lines will be established, Gut-on-Chip platform will be put in operation using standard colon epithelial cell line;
- Six months: the collection of the samples will be completed; the Gut-on-Chip platform will be fine-tuned culturing epithelium derived from patients and healthy controls organoids; experimental assays will be performed to accomplish the primary objective of the project.
- Nine months: co-culture of epithelium derived from patients and healthy controls organoids with

relevant microbiota products or bacterial strains (in particular, we will focus on R. gnavus); experimental assays to accomplish the other objectives of the project;
– Twelve months: data analysis and reporting.

Patient Voice

This project aims to create a reliable model for the study of the interactions between intestine and microbiota in patients with SpA. After validation, the far-reaching output of our project will provide some important advantages for patients suffering from SpA. First, this model will give the opportunity to experiment with new treatments, in particular those that can have an effect on the intestinal microbiota (such as antibiotics and probiotics), to understand if patients suffering from SpA can obtain an improvement in their condition. Second, it will allow the ex vivostudy of the sensitivity to the pharmacological treatments available, allowing to select the best treatment before administering it to the patient. These applications fall within the field of "tailored medicine". At the present stage, the project is based on the use of a microphysiological platform, and there are no clinical outcomes directly related to the patient. Thus, the patients were not involved in the experimental design. Biological samples will be used from adequately informed subjects who have explicitly given their consent, respecting all the regulations in force regarding the ethics of biomedical research, and approval by the local authorities has been obtained. Future clinical protocols based on the model developed in this project will certainly benefit from the full involvement of patient partners in the research team.

Project Team/Centres

– G Natalello, Catholic University of the Sacred Heart, ITALY (lead)
– M Breban, Université de Versailles Saint-Quentin-en-Yvelines, FRANCE
– T Bazin, Université de Versailles Saint-Quentin-en-Yvelines, ITALY
– P Langella, INRAE Université Paris-Saclay, FRANCE
– C Cherbuy, INRAE Université Paris-Saclay, FRANCE
– M A D'Agostino, Catholic University of the Sacred Heart, ITALY

Characterization of Synovial Fibroblast Subtypes

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 50.000
Project duration: 2022–2023

Project Url
www.foreum.org/projects/?id=223

Concept
Disease modifying anti-rheumatic drugs have revolutionized RA therapy, expanded life expectancy, and dramatically improved the quality of patients' lives. However, it is estimated that a significant number of patients display inadequate response, whereas others experience severe side effects. As evidence grows that RA patients with a "fibroid pathotype" respond less effectively to treatment, the need to develop therapeutic targets for influencing the activated stroma increases. Previous studies have highlighted the potential role of four distinct synovial fibroblast subtypes in the propagation of RA inflammation, warranting further investigation. This project aim is to further explore the functional differences of the synovial fibroblast subtypes and assess whether POSTN+ SF and CXCL14+SF are functional antagonists with opposite roles in the inflammatory process in RA. Furthermore, we aim to elucidate the spatial distribution of the fibroblast subtypes as well as their interaction with immune cells in the microenvironment of the synovial tissue from RA patients. Our approach would provide insight into the pathogenic role of the stroma and the different fibroblast subtypes and could be the trigger for uncovering novel therapeutic targets.

Objectives
This project aims to:
– Explore the functional differences between the synovial fibroblast subtypes.
– Analyze the interactions between immune cells and synovial fibroblasts.

Goals/Milestones
M1: Established cell sorting protocol to sort all 4 SF subtypes – at 2 months
M2: Functional differences between SF subtypes assessed – at 6 months
M3: Impact of CXCL14 + and POSTN + SF on other cell types assessed – at 12 months

Patient Voice

During the stay at the host center, the fellow will work together with a patient buddy. At the beginning and every three months, one-to-one meetings will be organized to discuss the project and its progress (virtual and/or visits to the lab).

Project Team/Centres

- M Toitou, University Hospital of Heraklion, GREECE (lead)
- Prof. dr. med. C Ospelt, University Hospital Zurich, SWITZERLAND
- P Sidiropoulos, University of Crete

2021

Remission and Flare

Remission and Flare: New potent drugs and novel disease management strategies lead to higher remission rates in patients suffering from various rheumatic and musculoskeletal diseases (RMDs) such as rheumatoid arthritis, spondyloarthritis and systemic autoimmune disorders such as systemic sclerosis (SSc) or systemic lupus erythematosus (SLE). However, remission or low-disease activity can often not be sustained, resulting in disease activity flares. Such new bouts of inflammation have an important and complex burden on the patient such as increases in pain and loss of joint function, risks for structural damage and disability, fewer therapeutic options and specific management strategies. Disappointment, struggle to remain hopeful about outcomes of disease, new absenteeism with impact on employment options, have an additional impact on the burden of disease. Hence, flares are much more than just an increase in inflammatory disease activity, and should be considered in a holistic context. Our scientific understanding of flares in the various RMDs remains limited. It is still difficult to predict and manage flares as they necessitate complex therapeutic decisions with sufficient attention towards the holistic psychosocial context. Therefore, research into mechanisms, evaluation, management and prevention of flares are necessary to provide good answers to the patient community and to sustain the health of our patients.

The call was launched in 2021 and out of 51 letters of intent 3 projects were selected for funding:

- Sustained drug-free remission in rheumatoid arthritis: immunological and patient perspectives
- Signs of danger: extrafollicular, auto-reactive B cell responses as drivers of disease flares in AAV
- Dissecting the cellular and molecular atlas of Rheumatoid Arthritis (RA) in sustained remission to identify pathways maintaining Remission and Triggering Flares

The SustaINed drug-Free remissiON in rheumatoId Arthritis (SINFONIA) project

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 599.536
Project duration: 2023–2026

Project Url

www.foreum.org/projects/?id=228

Concept

Sustained drug-free remission (SDFR) is achievable in up to 50% of patients with rheumatoid arthritis (RA) in drug-induced remission. However, methods to predict SDFR, its immunological basis, and its impact from a patient perspective remain unknown. The goal of this proposal is to address these unmet needs in three distinct yet complementary work packages (WPs). In WP1, we aim to validate our prototype cytokine biomarker of SDFR using our existing sample biobanks. In WP2, we aim to explore and understand specific mechanisms that potentiate SDFR as implicated by our pilot data, namely: the abundance, phenotype and function of CD4+ regulatory T cells (Tregs) and ACPA-expressing B cell subsets; and markers of regulatory macrophage and intestinal barrier function. In WP3, we aim to understand the impact of living with SDFR from a patient perspective using qualitative methodology. If successful, our project will support a future clinical efficacy trial of biomarker-driven drug cessation in RA remission, a paradigm shift in the management of RA. Furthermore, new insights into the immunobiology of SDFR could identify novel approaches to treat and prevent RA flare, and understanding the lived experience of SDFR will help to guide patient-clinician discussions around drug cessation.

Objectives

WP1 – Cross-validation of biomarkers of SDFR.
WP2 – Longitudinal molecular and cellular characterisation of SDFR.
WP3 – Understanding the lived experience of SDFR from a patient perspective.

Goals/Milestones

- Clinical review and blood sample donation from SDFR patients from our clinical cohorts (completion April 2025)
- Cytokine biomarker validation (completion April 2024)
- Treg suppression assays (completion August 2025)
- B cell flow cytometry assays (completion August 2025)

– Macrophage and intestinal barrier marker assays (completion August 2025)
– Qualitative patient interviews (completion April 2025)
– Manuscript preparation and dissemination (completion Jan 2026)

Patient Voice

Patient research partners form an integral component of this project, and cut across all proposed activities. Our patient research partners will:

– Be members of the Project Steering Group
– Be involved in the preparation of documents for ethical approvals, including writing and editing patient information sheets
– Help to develop WP3 topic guides and analyse qualitative data, checking the validity of themes identified
– Help in the dissemination of the results of our study, from being named authors on publications through to oral and written presentations to lay audiences.

Project Team/Centres

– K Baker, Newcastle University, UNITED KINGDOM (lead)
– A Anderson, Newcastle University, UNITED KINGDOM
– A van der Helm-van Mil, Leiden University, THE NETHERLANDS
– A Kleyer, Friedrich-Alexander University, GERMANY
– A Pratt, Newcastle University, UNITED KINGDOM
– G Schett, Friedrich-Alexander University, GERMANY
– H U Scherer, Leiden University, THE NETHERLANDS
– J Wason, Newcastle University, UNITED KINGDOM
– J D Isaacs, Newcastle University, UNITED KINGDOM
– J Rech, Friedrich-Alexander University, GERMANY
– R Toes, Leiden University, THE NETHERLANDS
– T Rapley, Northumbria University, UNITED KINGDOM
– J Taylor
– O Diamond
– W Broderick
– B Maat
– K Guethlein

Signs of danger: auto-reactive B cell responses as drivers of disease flares in AAV

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 599.976
Project duration: 2023–2026

Project Url
www.foreum.org/projects/?id=233

Concept

ANCA-associated vasculitides (AAV) are characterized by recurrent, chronic small vessel inflammation and deleterious organ damage. Early disease control by targeted treatment has improved considerably, but the most important clinical challenge now is the recognition and control of flares. This project aims to delineate the immunological basis of disease flares and disease persistence in AAV patients. We have observed that individual AAV patients (in contrast to healthy individuals) can harbour large populations of B cells expressing IgM-ANCA, and that IgM-ANCA can strongly activate complement. Based on this preparatory work, we hypothesize that auto-reactive B cell responses reflect a so far undetermined layer of immunological disease activity in AAV, with IgM B cell responses driving flares. To test this novel hypothesis, the project unites three AAV expert centres that combine unique expertise and technology in autoreactive B cell biology, well-defined cohorts with longitudinal follow-up and biological samples, and patient representatives experienced in supporting translational research. The expected end-product is an immunological definition of (imminent) disease flares in AAV and a novel measure of disease activity. This addresses directly the scope of the call and will be crucial to guide future trials aiming at testing strategies for optimal control of disease.

Objectives

We hypothesize that phenotypic characteristics of the autoreactive MPO-ANCA B cell response, and in particular the presence and/or activation of IgM MPO-ANCA B cells, reflect immunological processes that drive disease flares.

To test this hypothesis, we formulate the following objectives:

- To define MPO-ANCA B cells and their characteristics as disease-specific markers that reflect immunological disease activity (IDA) in different phases of MPO-AAV.
- To evaluate the association between dynamic changes of IgM MPO-ANCA in serum and defined clinical phenotypes, in relation and addition to IgG MPO-ANCA.

– To generate the molecular tools to unravel potential triggers initiating and maintaining the activation of MPO-ANCA B cells.
– To evaluate the perception by patients of the novel concept of IDA in AAV versus clinical disease activity based on defined, patient-reported outcomes (PROs).

Goals/Milestones

– MS1: (Month 6) initiation meeting, technology transfer, PRP training and advise accomplished.
– MS2: (Month 12) PROs defined and distributed to defined patient groups.
– MS3: (Month 30) patient/PRO recruitment completed; cellular and serum analyses performed.
– MS4: (Month 30) BCR repertoire analysis performed; mAb generated and tested.
– MS5: (Month 36) data integration and analysis completed; manuscripts prepared.

Patient Voice

All centres will recruit patients for cellular analyses and select sera from their biobanks/cohorts. PRPs from all centres will receive training via foundation Tools2use (http://www.tools2use. eu/; Dr. Maarten de Witt). PRPs will be actively contributing to WP4 as full collaborating partners.

Project Team/Centres

– H U Scherer, Leiden University, THE NETHERLANDS (lead)
– R Toes, Leiden University, THE NETHERLANDS
– Y O Teng, Leiden University Medical Center, THE NETHERLANDS
– V Malmström, Karolinska Institutet, SWEDEN
– I Gunnarsson, Karolinska Institutet, SWEDEN
– A Bruchfeld, Karolinska Institute, SWEDEN
– C D. Pusey, Imperial College London, UNITED KINGDOM
– S P McAdoo, Imperial College London, UNITED KINGDOM

Dissecting the cellular and molecular atlas of Rheumatoid Arthritis (RA) in sustained remission to identify pathways maintaining Remission and Triggering Flares

Project Lead

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Funding and Timeline

FOREUM research grant: EUR 600.000
Project duration: 2023–2026

Project Url

www.foreum.org/projects/?id=231

Concept

There is a knowledge gap in the understanding of mechanisms and predictors of flare in remission RA and we hypothesize that synovial tissue in disease remission exhibits heterogeneity in cellular and molecular pathways, and this determines clinical outcome after treatment tapering/cessation (remission maintenance or flare). Dissecting this heterogeneity will provide: (i) biomarkers to develop testable machine-learning (ML) models that accurate predict disease flares, and uncover (ii) cellular mechanisms responsible for maintenance of remission or flare. To test this hypothesis, we will establish a comprehensive cellular and molecular synovial tissue atlas of remission RA, achieved with different therapeutics. This will aid discovery of (a) cell clusters/pathways driving flare or sustaining remission, and (b) provide an evidence-base to develop ML tools to predict flares that will be tested longitudinally in a biopsy-driven clinical study. To test the functional roles of distinct cell clusters that distinguish synovium of those who flared from those who maintained in remission, we will investigate their pathogenic or inflammation resolving functions using human synovial organoid system. In summary, this project will uncover tissue biomarkers of flare that will help in management of patients' flares with current therapeutics and provide novel targets for therapeutic intervention to enhance the resolution/repair processes that could transform remission into long-term state.

Objectives

This study proposal will have the following research objectives:
A) To establish the cellular and molecular atlas of remission RA achieved with different therapeutics aimed to identify (i) cell clusters/pathways driving disease flare or maintaining remission and (ii) provide an evidence base for developing ML tools for predicting flares.
B) To test the performance of a ML-derived algorithm on longitudinal remission RA cohort in a biopsy-driven study.
C) To dissect the cellular and molecular mechanisms of remission maintenance and joint flares.

Goals/Milestones

Milestone 1: To establish the cellular and molecular atlas of remission RA achieved with different therapeutics, providing (i) biomarkers fordeveloping ML-based algorithm predicting disease flare, and (ii) molecular mechanisms driving maintenance of remission versus flare.
Milestone 2: Biopsy-driven study will validate power of the ML algorithm in predicting maintenance of remission or onset of flare.
Milestone 3: To establish the role of tissue resident and infiltrating myeloid-stromal cell interactions in induction of flare or maintenance of remission.

Patient Voice

Two PRP from Associazione Persone con Malattie Reumatiche e Rare and from the CONARTRITIS were recruited. They will provide their insight into project progression at biannual meetings. For example, they will help in preparation of the factsheet describing this study, which we will be given to patients during consenting for biopsy and testing ML tool. To develop the communication skills of research fellows and to maintain the focus of the project onto the priorities of the patient, each research fellow will be allocated a PRP. The PRPs will also have an important role in providing lay language for effective dissemination of discoveries at educational meetings for patients and public.

Project Team/Centres

- S Alivernini, FPG IRCCS – Università Cattolica del Sacro Cuore, ITALY (lead)
- M Kurowska-Stolarska, University of Glasgow, UNITED KINGDOM
- M Jose Artero, ConArtritis, Coordinadora Nacional de Artritis.
- A Celano, APMARR (Associazione Pazienti con Malattie Reumatiche e Rare)
- J Bacardit, Newcastle University, UNITED KINGDOM
- J D Cañete, Hospital Clinic and Fundació Clinic per la Recerca Biomèdica, SPAIN

2022

Call for Career Research Grants

FOREUM is committed to promote the best talents in the field of rheumatic and musculoskeletal diseases (RMD). Consistent with these goals FOREUM issued a new call that aims to fund excellent young researchers promoting innovative ideas and supporting high quality research projects covering basic and clinical science projects related to RMDs. Scientific excellence is the key eligibility criterion for this career research grant initiative, which aims to foster independent science and intends to develop new research leaders in the field.

The fourth call was launched in 2022, and out of 57 letters of intent 4 projects were selected for funding:

- Gut-derived metabolites and modulation of pathogenic B-cell responses in JIA
- Harnessing cell energy metabolism to suppress salivary gland inflammation in Sjögren Syndrome
- Deciphering synovitis in systemic sclerosis
- EPI-ILD: Epigenetics aspects of rheumatic diseases associated interstitial lung disease

Immunomodulation of pathogenic B-cell responses by gut-derived metabolites in Juvenile Idiopathic Arthritis

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 198.350
Project duration: 2023–2026

Project Url
www.foreum.org/projects/?id=234

Concept
Accumulating evidence demonstrates that pathogenic changes at the gut-site, such as dysbiosis of the gut-microbiota, drives inflammation in the synovium of patients with autoimmune arthritis. However, the exact nature of the gut-derived signals that condition the pro-arthritogenic potential of inflammatory cells are yet to be clarified. Here, using juvenile idiopathic arthritis (JIA) as a model, I will investigate whether, and how, specific metabolites, whose production is controlled by the gut-microbiota and/or diet, impact B-cell pathogenicity in JIA. The findings from this proposal will generate new insights into the mechanisms controlling the gut-joint axis in childhood arthritides.

Objectives
This proposal will test the hypothesis that the availability of gut-derived metabolites drives B-cell pathogenicity in autoimmune arthritis via two research objectives:
Objective 1: Identify gut-derived metabolites that are associated with altered B-cell phenotype in JIA.
Objective 2: Ascertain the mechanisms by which candidate metabolites modulate pro-arthritogenic B-cell function in vivo.

Goals/Milestones
Milestones before project start date (1st of Feb 2023):
– Recruit research assistant; 2) Complete recruitment for JIA patients and controls.

Milestones during 36-month project timeline:
– Measure candidate metabolites in JIA and perform B-cell immunophenotyping on matched blood samples;
– Assess potential of different diets to alter B cell function and severity of experimental arthritis.
– Prepare grant applications for further funding and to grow research group.

Patient Voice

Patient research partners have been extensively consulted during the design and drafting of this project to make it relevant to patients/families, make sure it is understandable, as well as on the research methods and patient facing documents (see non-technical summary for detailed information). Patient partners will be consulted at all the major milestones, and throughout the project to ensure maximal dissemination to the wider JIA community.

Project Team/Centres

- E Rosser, UCL Division of Medicine, University College London (lead)
- C Wright, Versus Arthritis YPFS
- S Douglas, Scottish Network for Arthritis in Children
- D Wilson, JIA-at-NRAS
- R Beesley, Juvenile Arthritis Research

Harnessing cell energy metabolism to suppress salivary gland inflammation in Sjögren Syndrome

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2023–2026

Project Url
www.foreum.org/projects/?id=225

Concept

Background – Sjögren Syndrome (SS) is a systemic autoimmune disease characterized by inflammation of lacrimal and salivary glands (SG). SG epithelial cells (SGEC) play a key role in sustaining inflammation in SS. However, the mechanisms responsible for the inflammatory activation of SGEC remain largely undetermined. Our line of research indicates that SGECs in SS exhibit profound changes in cell energy metabolism (eg, increased autophagy, glycolysis, and TCA cycle activation), as well as downstream upregulation of adhesion molecules and increased cytokine production (eg, IL-6). Based on these findings, we hypothesize that altered cell energy metabolism of SGEC is a central and targetable driver of SG inflammation in SS.

Objectives

AIM 1: to dissect the metabolic activation of SGECs in SS.
AIM 2: to dissect the pro-inflammatory epigenetic changes in SGECs.
AIM 3: to determine the therapeutic potential of targeting SGEC energy metabolism.

Goals/Milestones

Milestone 1, Month 12 (AIM 1): characterization of metabolic activation of SGECs in SS.
Milestone 2, Month 24 (AIM 2): characterization of epigenetic changes in SS SGECs.
Milestone 3, Month 36 (AIM 3): testing of strategies suppressing SGECs inflammatory activation.

Patient Voice

ANIMASS (Associazione Nazionale Italiana Malati Sindrome di Sjogren) is the main non-profit SS patient association in Italy (http://www.animass.org/AMRI). ANIMASS had a key role in informing the priorities of the present research study: specifically, the lack of effective therapies to restore secretory function was perceived as a critically unmet need by SS patients, who strongly advocated

for the development of therapeutic alternatives to the currently available but scarcely effective immunotherapies. Tight and productive collaborative ties between our Institution and ANIMASS will be key to the conduction of this study and will ensure constant referral of individuals with suspected SS to our dedicated Clinic, as well as active involvement in outreach activities.

Project Team/Centres

– S Colafrancesco, Sapienza University, ITALY (lead)

Deciphering synovitis in systemic sclerosis

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 200.000
Project duration: 2022–2025

Project Url
www.foreum.org/projects/?id=224

Concept

In single-cell RNA sequencing, activated signaling pathways were largely different between SSc and RA synovial fibroblasts with enrichment in TGF and interferon pathways in SSc. To provide a comprehensive atlas of cell populations and activated pathways in the SSc synovium: Single cell RNA sequencing will be analyzed to characterize the phenotype of synovial cells and activated pathways in SSc versus RA. Using bioinformatics packages, we will also analyze and visualize communication and cell-cell interactions in SSc synovium. Activated pathways and cell-cell interactions will be confirmed by immunohistochemistry in synovial tissues. Specific functions and cell-cell interaction will be assessed in 3D culture. This work will allow, for the first time, a detailed characterization of synovitis in SSc at the cellular and molecular levels.

Objectives

– establish a comprehensive atlas of cell populations and pathways activated in the SSc synovium
– characterize the biology of SF in SSc
– identify potential drivers of cellular activation in SSc arthritis.

Goals/Milestones

– Milestone 2: Analysis of the cytokines/chemokines driving the phenotype of SSc SF (M12-M 18)
– Milestone 3: Manuscript about synovitis in SSc at tissue and cellular levels (M15-M21)
– Milestone 4: Analysis of functional changes characterizing SSc SF(M12-M24)
– Milestone 5: Identification of therapeutic targets in SSc arthritis (M18-M30)
– Milestone 6: Manuscript about therapeutic targets in SSc arthritis(M30-M36)
– Milestone 7: Training of patients research partners (M6) and regular meetings every 3 months

Patient Voice

Three SSc patients are involved in this project, two have undergone synovial biopsy and one is a member of the Swiss Scleroderma Association responsible for the Berne group. A patient journalist was consulted to improve the synovial biopsy protocol and to write the lay summary. Regular

meetings with patients are organised to better target the needs and expectations of patients and to improve the visibility of the project. They will visit the laboratory on 16 September 2022 as part of the open day for patients and will receive research training in collaboration with the USZ clinical trials centre in early 2023.
As part of this funding, the first results and perspectives were presented to the French patients at the ASF medical day and will be presented to the Swiss patients next year.
A report will be written, which will be published in the Scleroderma Patient Journal. These oral and written presentations allow patients to be informed about the progress and results of the project, to give their opinion and to contact us later if necessary (contact details provided).

Project Team/Centres

– M Elhai, University Hospital Zürich, SWITZERLAND (lead)

EPI-ILD: Unravelling myeloid epigenetic signatures in Interstitial Lung Disease associated to Rheumatoid Arthritis and Systemic Sclerosis.

Project Lead
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Funding and Timeline
FOREUM research grant: EUR 199.418
Project duration: 2023–2026

Project Url
www.foreum.org/projects/?id=227

Concept

The optimisation of diagnostic and stratification tools, as well as a better understanding of disease pathogenesis and standardized therapeutic strategy in interstitial lung diseases (ILD) associated to rheumatoid arthritis (RA) and systemic sclerosis (SSc), represent an important translational and clinical unmet need in the field of Rheumatology. This project aims at identifying myeloid epigenetic signatures associated with RA-ILD and SSc-ILD, studying their role on myeloid phenotypes and tissue infiltration in disease, and identification of myeloid biomarkers for early stratification of patients with RA. By addressing this knowledge gap in the field of RA- and SSC-ILD, we believe that this work will facilitate the identification of new therapeutic targets and early biomarkers; which together will facilitate patients' stratification, clinical trials and clinical management.

Objectives

The project aims at:

- identifying RA- and SSc-ILD monocytes epigenetic signatures and their impact on gene and inflammatory pathways expression using ChIPseq and RNAseq;
- understanding these signatures' contribution to myeloid cells function and phenotypes across both circulating and tissue compartments using multiome single cell RNAseq and single cell ATACseq analysis associated to in vitro fibroid-myeloid compartments co-culture experiments;
- confirming identified epigenetic profiles as biomarkers in a cohort of early RA with up to 10 years follow-up and available biosamples.

Goals/Milestones

This project will be divided in 3 work packages addressing the 3 main objectives delivered each year. Results will be shared with the scientific community through presentations at conferences and publication of a manuscript.

Patient Voice

A core group of patients will be involved throughout the entire project as part of a pilot committee

along with myself, Prof Carl Goodyear and the technician employed through this grant.
We will have the following aims:
– focus on promoting patient/public engagement (Dissemination),
– study deliverables (Management)
– implementation phase to include engagement with patient board members of patient advocacy groups such as Glasgow Arthritis Involvement Network (GAIN).

Furthermore, we plan to develop Patient-Interactive-Workshops, to host a patient-judged competition where researchers will present their research in lay terminology. Finally, during the project, outputs will be disseminated to patients via social media, newsletters, and lay presentations at patient-oriented conferences (EULAR PARE/National Workshops/Research into Inflammatory Arthritis Centre Versus Arthritis RACE patients events).

Project Team/Centres

– A Najm, University of Glasgow, UNITED KINGDOM (lead)
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