FOREUM
Foundation for Research in Rheumatology

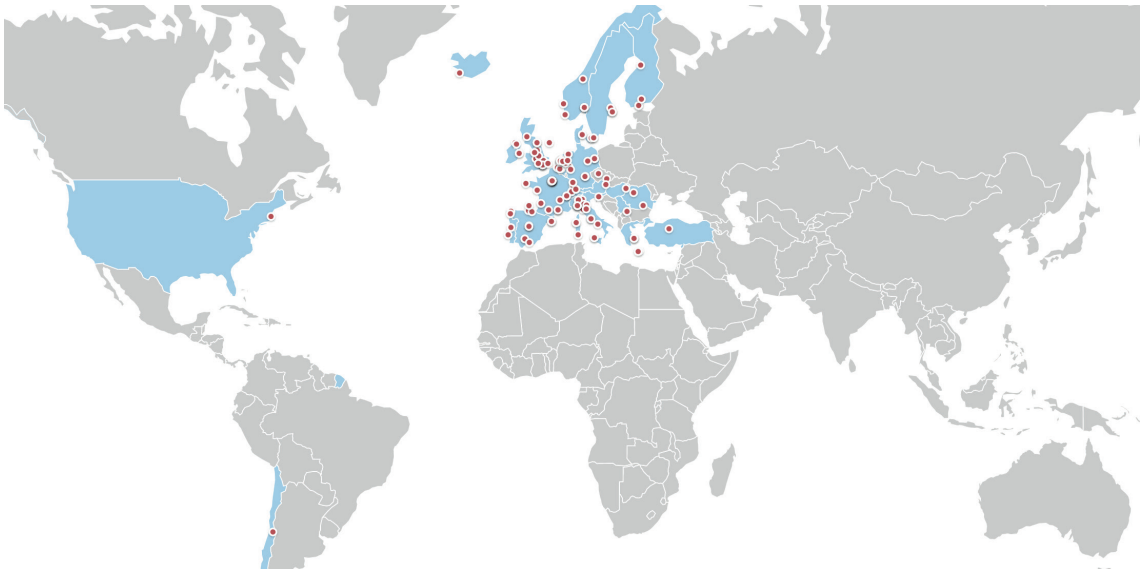
Promoting health through effective research in individuals with rheumatic and musculoskeletal diseases

September 2020

TABLE OF CONTENT

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: recognizing 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 2020 FOREUM funded more than 50 projects, totaling almost EUR 14 million in grants. FOREUM funded projects involve more than 100 research institutions across Europe, several networks as well as patient organizations.



Contact

FOREUM Foundation for Research in Rheumatology
Seestrasse 240
CH-8802 Kilchberg Switzerland
info@foreum.org
www.foreum.org

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:

Platinum

Pfizer, Lilly, UCB, AbbVie, Galápagos, Novartis

Silver

Gilead, Bristol-Myers Squibb

Bronze

Amgen, Roche, Boehringer Ingelheim

Donors

GSK – do more feel better live longer

FOREUM is supported by EULAR, the European League Against Rheumatism. 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.

Board of Trustees

- President: Gerd Burmester, Germany
- Vice-President: Paul Emery, United Kingdom
- Maxime Dougados, France
- Jiri Vencovsky, Czech Republic
- Julia Rautenstrauch, Switzerland

Executive Committee

- Chair: Prof. Désirée van der Heijde, The Netherlands
- Treasurer: Prof. Philip Conaghan, United Kingdom
- Carina Boström, Sweden
- Chris Denton, United Kingdom
- Tore Kvien, Norway
- Seza Ozen, Turkey
- Codruta Zabalan, Romania
- Non-voting members ex officio:
- EULAR President, Chair Scientific Committee, board members

Scientific Committee

- Chair: Prof. Georg Schett, Germany
- Heidi Bertheussen, Norway
- Dimitrios Boumpas, Greece
- Kimme Hyrich, United Kingdom
- Caroline Ospelt, Switzerland
- Carlo Salvarani, Italy
- Jérémie Sellam, France
- Annette de Thurah, Norway
- Lucy Wedderburn, United Kingdom
- Ana Vieira, Portugal

Secretariat

- Caroline Desiderio
- Patrizia Jud

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

Prof R Lories, KU Leuven, BELGIUM
rik.lories@uz.kuleuven.be

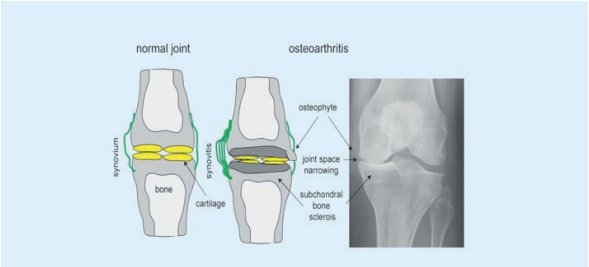
Funding and timeline

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

Publications

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

Objectives



Infl ammation 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.

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.
In accordance with the EULAR perspective on patient involvement, trained patients participate in the consortium meetings not only to update the community about our research but to add their perspective to the progress of the work.

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

Publications

- Ioan-Facsinay A, Kloppenburg M. Bioactive lipids in osteoarthritis: risk or benefit? Curr Opin Rheumatol. 2018 Jan;30(1):108-113. doi:10.1097/BOR.0000000000000463. PubMed PMID: 29035931. https://www.ncbi.nlm.nih.gov/pubmed/29035931
- Monteagudo S, Cornelis FMF, Aznar-Lopez C, Yibmantasiri P, Guns LA, Carmeliet P, Cailotto F, Lories RJ. DOT1L safeguards cartilage homeostasis and protectsagainst osteoarthritis. Nat Commun. 2017 Jun 19;8:15889. doi: 10.1038/ncomms15889. PubMed PMID: 28627522; PubMed Central PMCID: PMC5481839. https://www.nature.com/articles/ncomms15889
- Ioan-Facsinay A, Kloppenburg M. Osteoarthritis: Inflammation and fibrosis in adipose tissue of osteoarthritic joints. Nat Rev Rheumatol. 2017 Jun;13(6):325-326. doi: 10.1038/nrrheum.2017.53. Epub 2017 Apr 13. PubMed PMID: 28405000. https://www.nature.com/articles/nrrheum.2017.53
- Jónasdóttir HS, Brouwers H, Kwekkeboom JC, van der Linden HM, Huizinga T, Kloppenburg M, Toes RE, Giera M, Ioan-Facsinay A. Targeted lipidomics reveals activation of resolution pathways in knee osteoarthritis in humans. Osteoarthritis and Cartilage. 2017 Feb 8. pii: S1063-4584(17)30839-7. doi: 10.1016/j.joca.2017.01.018. [Epub ahead of print]. https://www.oarsijournal.com/article/S1063-4584(17)30839-7/fulltext
- van der Kraan PM, Berenbaum F, Blanco FJ, Cosimo de B, Lafeber F, Hauge E, Higginbottom A, Ioan-Facsinay A, Loughlin J, Meulenbelt I, Moilanen E, Pitsillidou I, Tsezou A, van Meurs J, Vincent T, Wittoek R, Lories R; EULAR Study group in OA. Translation of clinical problems in osteoarthritis into pathophysiological research goals. RMD Open. 2016 May 26;2(1):e000224. doi:10.1136/rmdopen-2015-000224. eCollection 2016. Erratum in: RMD Open. 2016 Oct7;2(2):e000224corr1. PubMed PMID: 27252894; PubMed Central PMCID: PMC4885448. https://rmdopen.bmj.com/content/2/1/e000224
- Brouwers H, von Hegedus J, Toes R, Kloppenburg M, Ioan-Facsinay A. Lipidmediators of inflammation in rheumatoid arthritis and osteoarthritis. Best Pract Res Clin Rheumatol. 2015 Dec;29(6):741-55. doi: 10.1016/j.berh.2016.02.003. Epub 2016 Mar 4. Review. PubMed PMID: 27107510. https://www.bprclinrheum.com/article/S1521-6942(16)00005-X/fulltext
- van der Kraan PM, Berenbaum F, Blanco FJ, Cosimo de B, Lafeber F, Hauge E, Higginbottom A, Ioan-Facsinay A, Loughlin J, Meulenbelt I, Moilanen E, Pitsillidou I, Tsezou A, van Meurs J, Vincent T, Wittoek R, Lories R; Translation of clinical problems in osteoarthritis into pathophysiological research goals. RMD Open. 2016 May 26;2(1):e000224. doi: 10.1136/rmdopen-2015-000224. eCollection 2016. https://rmdopen.bmj.com/content/2/1/e000224
- de Jong AJ, Kloppenburg M, Toes RE, Ioan-Facsinay A. Fatty acids, lipid mediators, and T-cell function. Front Immunol. 2014 Oct 13;5:483. doi: 10.3389/fimmu.2014.00483. eCollection 2014. Review. PubMed PMID: 25352844; PubMed Central PMCID: PMC4195378. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4195378/

Project team/centres

- Prof R Lories, KU Leuven, BELGIUM (lead)
- P L Meroni, University of Milano, ITALY
- O de Lucia, University of Milano, ITALY
- A Ioan- Facsinay, UMC Leiden, THE NETHERLANDS
- Z Szekanecz, University of Debrecen, HUNGARY

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

Project lead

F Lafeber, UMC Utrecht, THE NETHERLANDS
s.mastbergen@umcutrecht.nl

Funding and timeline

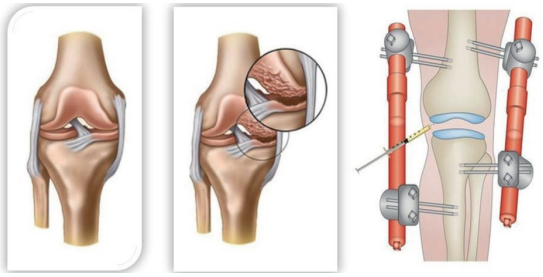
FOREUM research grant: EUR 300.000
Project duration: 2016–2019

Publications

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

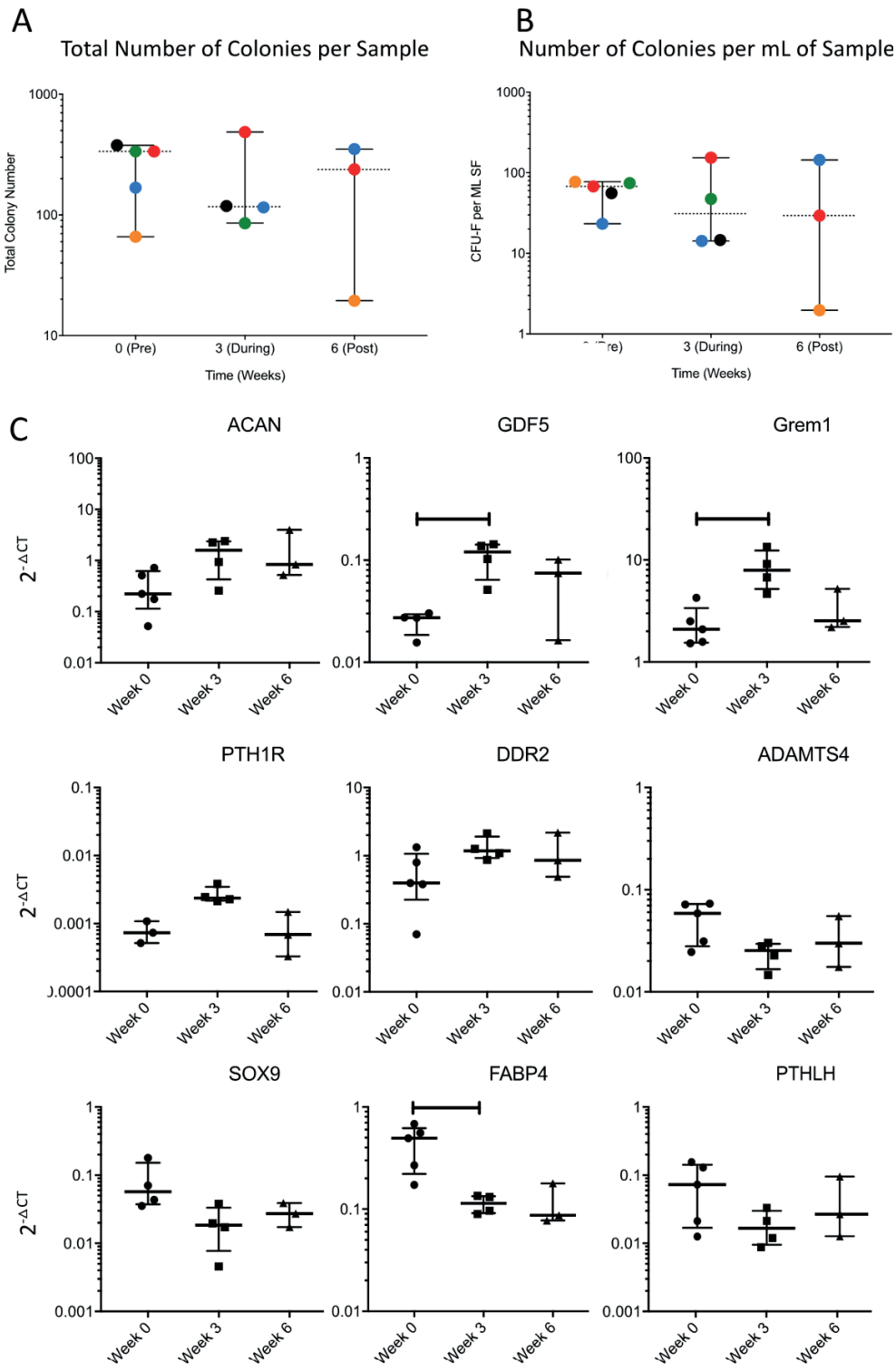


Figure 1: Changes in synovial fluid MSCs numbers and gene expressing profiles upon knee joint distraction. Bar indicates statistically significant changes ($p<0.05$).

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 sub-chondral 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

- Understanding joint preservation, new insights from knee joint distraction
  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
  Oral presentation at EORS 2019, Maastricht October 2019
- Analysis of mechano-sensitive pathway markers in the synovial fluid during joint distraction. Fiona E Watt, Benjamin Hamid, Cesar Garriga, Andrew Judge, Renata Hrusecka, Roel Custers, Floris Lafeber, Simon Mastbergen, Tonia Vincent joint last author
  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/

Project team/centres

- F Lafeber, UMC Utrecht, THE NETHERLANDS (lead)
- S Mastbergen, UMC Utrecht, THE NETHERLANDS
- D McGonagle, University of Leeds, UNITED KINGDOM
- F Berenbaum, Université Pierre et Marie Curie, FRANCE

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

Project lead

P Conaghan, University of Leeds, UNITED KINGDOM
p.conaghan@leeds.ac.uk

Funding and timeline

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

Publications

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

Objectives

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

– Bowes MA, Lohmander LS, Wolstenholme C, Vincent GR, Conaghan PG, Frobell RB. Marked and rapid change of bone shape in acutely ACL injured knees – an exploratory analysis of the KANON trial. Osteoarthritis and Cartilage, April 2019 Volume 27, Issue 4, Pages 638–645 https://www.oarsijournal.com/article/S1063-4584(19)30019-6/fulltext
– Barr AJ, Dube B, Hensor EM, Kingsbury SR, Peat G, Bowes MA, Sharples LD, Conaghan PG. The relationship between three-dimensional knee MRI bone shape and total knee replacement-a case control study: data from the Osteoarthritis Initiative. Rheumatology (Oxford) 2016;55(9):1585-93. http://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kew191

Project team/centres

– P Conaghan, University of Leeds, UNITED KINGDOM (lead)
– R Frobell, Lund University, SWEDEN

Micro RNAs as biomarkers in OA

Project lead

I Meulenbelt, UMC Leiden, THE NETHERLANDS
i.meulenbelt@lumc.nl

Funding and timeline

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

Publications

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 uL) 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.

Publications

R.C. Almeida, Y. Ramos, A. Mahfouz, E. Houtman, N. Lakenberg, G. Kloppenburg, P. Slagboom, R.G. Nelissen, M. Reinders, I. Meulenbelt. Integrative approach uncover microRNA interactome dysregulation in osteoarthritis cartilage. 315 DOI:
https://doi.org/10.1016/j.joca.2018.02.353
https://www.oarsijournal.com/article/S1063-4584(18)30453-9/abstract

Project team/centres

- I Meulenbelt, UMC Leiden, THE NETHERLANDS (lead)
- C Beyer, University Erlangen, GERMANY
- C Ospelt, University Hospital Zurich, SWITZERLAND

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
D Boumpas, University of Athens, GREECE
boumpasd@uoc.gr, dboumpas@bioacademy.gr

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

Publications
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.

Publications

– Grigoriou M, Banos A, et al. Transcriptome Reprogramming and Myeloid Skewing in Hematopoietic Stem and Progenitor Cells in Systemic Lupus Erythematosus. Ann Rheum Dis 2020;79:242-253 https://ard.bmj.com/content/79/2/242
– Bertsias G et al. Combined genetic and transcriptome analysis of patients with SLE: Distinct, targ-

etable signatures for susceptibility and severity. Ann Rheum Dis. 2019 Aug;78(8):1079-1089 https://ard.bmj.com/content/78/8/1079.long

– Nikolaos I Panousis, et al. Genomic dissection of Systemic Lupus Erythematosus: Distinct Susceptibility, Activity and Severity Signatures. doi: https://doi.org/10.1101/255109. Bioarxiv. https://www.biorxiv.org/content/10.1101/255109v1.full

Abstracts

– Filia A. et al RNA sequencing and machine learning techniques predict major organ involvement in patients with systemic lupus erythematosus. EULAR Meeting, Madrid, Spain. June 2019. Oral presentation and Best Abstract Award
– Filia A. et al Biomarkers for the activity of Systemic Lupus Erythematosus using RNA sequencing and machine learning techniques. European Conference on Computational Biology, Athens, Greece. September 2018.
– Banos A.*, Grigoriou M., Filia A., Giannouli S., Nikolopoulos D., Pieta A., Karali V., Mitroulis I., Verginis P., Boumpas DT., Disorders of the Hematopoietic Stem Cells in the Bone Marrow and Periphery of SLE Patients, 26th Panhellenic Rheumatology Congress, 6-9 December 2018, Athens, Greece
– Grigoriou M.*, Banos A., Filia A., Pavlidis P., Mitroulis I., Verginis P., Boumpas DT., Gene expression analysis of Hematopoietic Stem and Progentiors Cells in an experimental model of SEL: Disorders of the Myeloid Lineage, 26th Panhellenic Rheumatology Congress, 6-9 December 2018, Athens, Greece
– Grigoriou M.*, Verginis P., Nikolaou C., Pavlidis P., Dermitzakis E., Bertsias G., Boumpas DT., Banos A., Next Generation Sequencing in Hematopoietic Progenitors of murine SLE model reveals aberrant regulation of Cebp/a expression, 11th European Lupus Meeting, 21-24 March 2018, Dusseldorf, Germany
– Bertsias G, Panousis N, Gergianaki I, Tektonidou M, Trachana M, Pamfil C, Fanouriakis A, Dermitzakis E, Boumpas D. The genomic architecture of Systemic Lupus Erythemathosus (SLE) by RNA-seq: Distinct disease susceptibility, activity and severity signatures and extensive genetic effects on whole blood gene expression. Abstract EULAR 2017, Madrid – accepted as Oral Presentation.
– M. Grigoriou*, M. Anastasiou, P. Verginis, P. Pavlidis, C. Nikolaou, G. Bertsias, D.T. Boumpas, A. Banos, RNA-seq profiling of Hematopoietic Stem Cells in Murine Systemic Lupus Erythematosus (SLE): Validation and Functional characterization, 37th European Workshop for Rheumatology Research, March 2 – 4, 2017, Athens, Greece
– Banos A.*, Grigoriou M., Verginis P., Nikolaou C., Pavlidis P., Dermitzakis E., Bertsias G., Boumpas DT., Transcriptome Profiling by Next Generation Sequencing of Hematopoietic Progenitors in Murine Systemic Lupus Erythematosus (SLE), 10th European Lupus Meeting, 5-8 October 2016, Venice, Italy
– Banos A.*, Grigoriou M., Verginis P., Pavlidis P., Bertsias G., Boumpas DT., Gene Expression Analysis of Hematopoietic Stem Cells (HSCs) in Murine Systemic Lupus Erythematosus (SLE), Functional Genomics Workshop, 10-12th February 2016, St Thomas' Hospital Campus, King's College London, London, UK
– Banos A.*, Grigoriou M., Verginis P., Pavlidis P., Bertsias G., Boumpas DT., Transcriptome Profiling by Next Generation Sequencing of Hematopoietic Progenitors in Murine Systemic Lupus Erythematosus (SLE), 36th European Workshop for Rheumatology Research, February 25 – 27, 2016, York, United Kingdom

– A Banos, M Grigoriou, P Verginis, P Pavlidis, G Bertsias, DT Boumpas. Transcriptome profiling by next generation sequencing of hematopoietic progenitors in murine systemic lupus erythematosus (SLE). Ann Rheum Dis 2016; 75:A50.
– Grigoriou M., Verginis P., Bertsias G., Boumpas DT., and Banos A., The Role Of Hematopoietic Stem Cells (HSC) In Systemic Autoimmunity, 35th European Workshop for Rheumatology Research, March 5 – 7, 2015, Budapest, Hungary

Project team/centres

– D Boumpas, University of Athens, GREECE (lead)
– G Bertsias, University of Crete, GREECE
– F Hiepe, Charité Berlin, GERMANY
– C Pamfil, University of Medicine and Pharmacy, ROMANIA
– L Rönnblom, Uppsala University, SWEDEN
– T Vyse, King's College, UNITED KINGDOM

REFRACT – Refractory lupus nephritis: a tissue-based pathophysiological approach

Project lead

B Lauwerys, Cliniques Universitaires Saint-Luc, BELGIUM
bernard.lauwerys@uclouvain.be

Funding and timeline

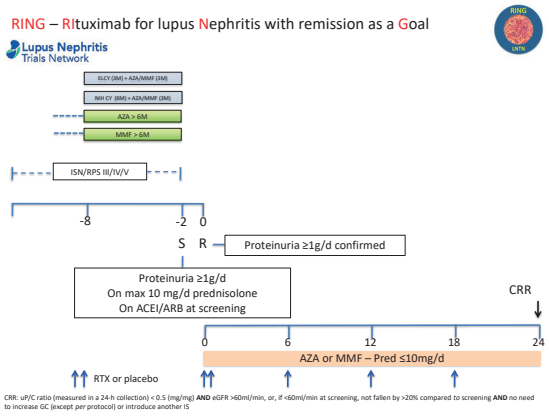
FOREUM research grant: EUR 298.860
Project duration: 2016–2019

Publications

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.

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.

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.

Publications

Pamfil C, Makowska Z, De Groof A, et al. Intrarenal activation of adaptive immune effectors is associated with tubular damage and impaired renal function in lupus nephritis. Annals of the Rheumatic Diseases Published Online First: 31 July 2018. doi: 10.1136/annrheumdis-2018-213485
https://ard.bmj.com/content/early/2018/07/30/annrheumdis-2018-213485

Project team/centres

- B Lauwerys, Cliniques Universitaires Saint-Luc, BELGIUM (lead)
- M Mahévas, Université Paris-Descartes, FRANCE
- R van Vollenhoven, Karolinska Institutet, SWEDEN
- D Jayne, University of Cambridge, UNITED KINGDOM
- R Cervera, Fundacio Clinic per a la Recerca Biomedica Barcelona, SPAIN
- P Remy, Université Paris-Est, FRANCE
- D Mazzoni, Lupus Europe, UNITED KINGDOM

NET-ting the autoreactive B cell memory by therapeutically targeting the humoral autoimmunity in patients with SLE

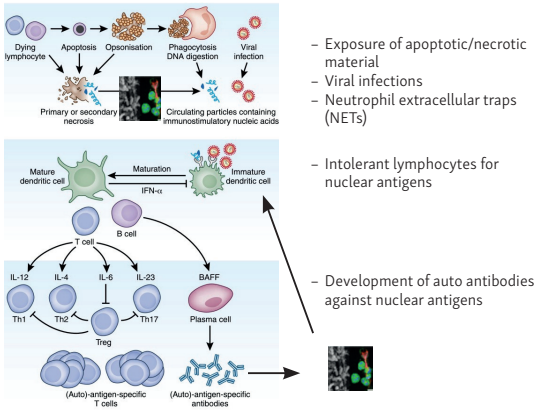
Project lead
Y K O Teng, UMC Leiden, THE NETHERLANDS
y.k.o.teng@lumc.nl

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

Publications
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 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.

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.

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 autoantigenic 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.

Publications

- van Dam LS, Osmani Z, Kamerling SWA, et al. A reverse translational study on the effect of rituximab, rituximab plus belimumab, or bortezomib on the humoral autoimmune response in SLE [published online ahead of print, 2020 Jan 17]. Rheumatology (Oxford). 2020;kez623. doi:10.1093/rheumatology/kez623 https://pubmed.ncbi.nlm.nih.gov/31951278/
- Laura S. van Dam, Tineke Kraaij, Sylvia W. A. Kamerling, Jaap A. Bakker, Uli H. Scherer, Ton J. Rabelink, Cees van Kooten, Y. K. Onno Teng. Intrinsically Distinct Role of Neutrophil Extracellular Trap Formation in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis Compared to Systemic Lupus Erythematosus. Arthritis Rheumatol, 71: 2047-2058. doi:10.1002/art.41047 https://onlinelibrary.wiley.com/doi/abs/10.1002/art.41047
- Laura S. van Dam, Eline J. Arends, Tineke Kraaij, Sylvia W.A. Kamerling, Ton J. Rabelink, Cees van Kooten, Y.K. Onno Teng. A high-throughput assay to assess and quantify neutrophil extracellular trap formation. J Vis Exp. 2019 Jan 29;(143). doi: 10.3791/59150.
- Laura S. van Dam, Eline J. Arends, Tineke Kraaij, Sylvia W.A. Kamerling, Ton J. Rabelink, Cees van Kooten, Y.K. Onno Teng. A high-throughput assay to assess and quantify neutrophil extracellular trap formation. J Vis Exp. 2019 Jan 29;(143). doi: 10.3791/59150.
- Van Dam L, Osmani Z, Kraaij T, et al. FRI0311 The effect of b cell targeted therapies on autoantibodies and excessive neutrophil extracellular trap formation in systemic lupus erythematosus patients. Annals of the Rheumatic Diseases 2018;77:692. https://ard.bmj.com/content/77/Suppl_2/692.2
- Laura S. van Dam, Ton J. Rabelink, Cees van Kooten, Y.K. Onno Teng. Clinical implications of excessive neutrophil extracellular trap formation in renal autoimmune diseases. Kidney Int Rep. 2018 Nov 19;4(2):196-211. doi: 10.1016/j.ekir.2018.11.005. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6365354/
- Dam LV, Kraaij T, Kamerling S, et al. SAT0015 Anca-associated vasculitis- and systemic lupus erythematosus-induced neutrophil extracellular traps have intrinsically different features. Annals of the Rheumatic Diseases 2017;76:774. https://ard.bmj.com/content/76/Suppl_2/774.1

Project team/centres

- Y K O Teng, UMC Leiden, THE NETHERLANDS (lead)
- L van Dam, UMC Leiden, NETHERLANDS
- R Voll, Albert Ludwig University Freiburg, GERMANY
- D Isenberg, University College London, UNITED KINGDOM

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

Project lead
A Bengtsson, Lund University, SWEDEN
anders.bengtsson@med.lu.se

Funding and timeline
FOREUM research grant: EUR 150.000
Project duration: 2016–2019

Publications
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.

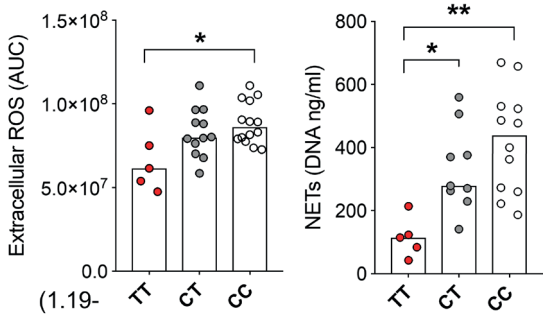


Figure 1. Extracellular ROS and NETs released of SLE neutrophils with different NCF1-339 genotypes stimulated with phorbol-myristate-acetate (PMA).

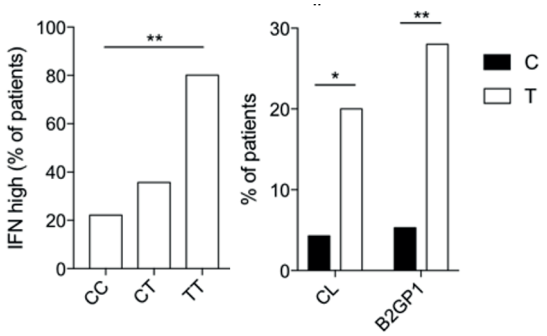


Figure 2. Serum IFN and anti-cardiolipin (CL) and anti-β2-glycoprotein-I in SLE patients with different NCF1-339 genotypes.

Patient voice

Close collaboration with patients who took part in the projects.

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.

Publications

- Olsson LM, Johansson AC, et al. A SNP in the gene NCF1 leading to a reduced oxidative burst is associated with SLE. http://dx.doi.org/10.1136/annrheumdis-2017-211287. http://ard.bmj.com/content/early/2017/06/12/annrheumdis-2017-211287
- Linge P, Arve S, Olsson LM, et al. NCF1-339 polymorphism is associated with altered formation of neutrophil extracellular traps, high serum interferon activity and antiphospholipid syndrome in systemic lupus erythematosus. Ann Rheum Dis. 2020;79(2):254-261. doi:10.1136/annrheumdis-2019-215820 https://pubmed.ncbi.nlm.nih.gov/31704719/

Project team/centres

- A Bengtsson, Lund University, SWEDEN (lead)
- Prof 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

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

U Syrbe, Charité, GERMANY
uta.syrbe@charite.de

Funding and timeline

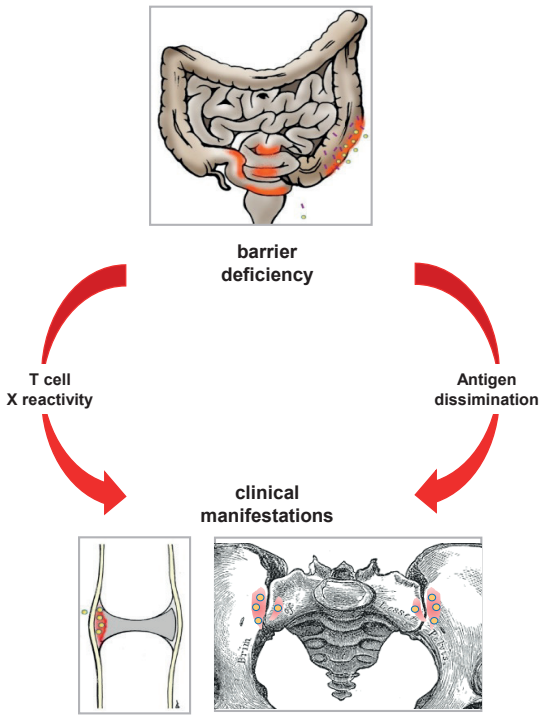
FOREUM research grant: EUR 300.000
Project duration: 2017–2020

Publications

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

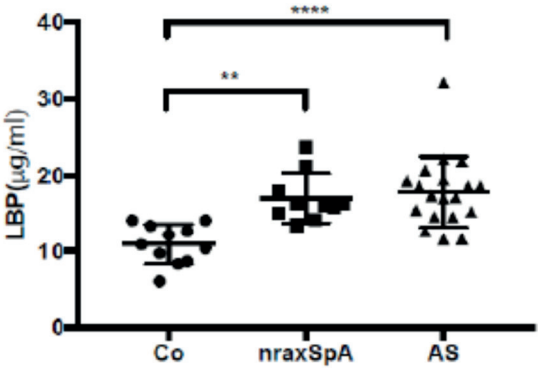
- lipopolyaccharide binding protein (LBP) is upregulated in axial SpA patients compa- red to controls.
- there is no difference according to disease state (i.e. nr-axial SpA and AS) and disease activity (i.e. BASDAIhigh and BASDAI low).
- In patients from GIANT cohort (Belgium) LBP serum levels were 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.

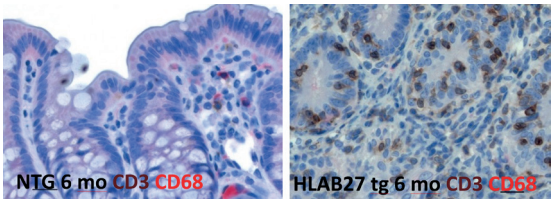
Mechanism of translocation in HLA-B27 tg rats

– 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

P Gardiner, Western Health and Social Care Trust, UNITED KINGDOM
pvgardiner@yahoo.co.uk

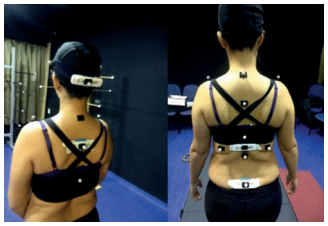
Funding and timeline

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

Publications

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

Objectives



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.

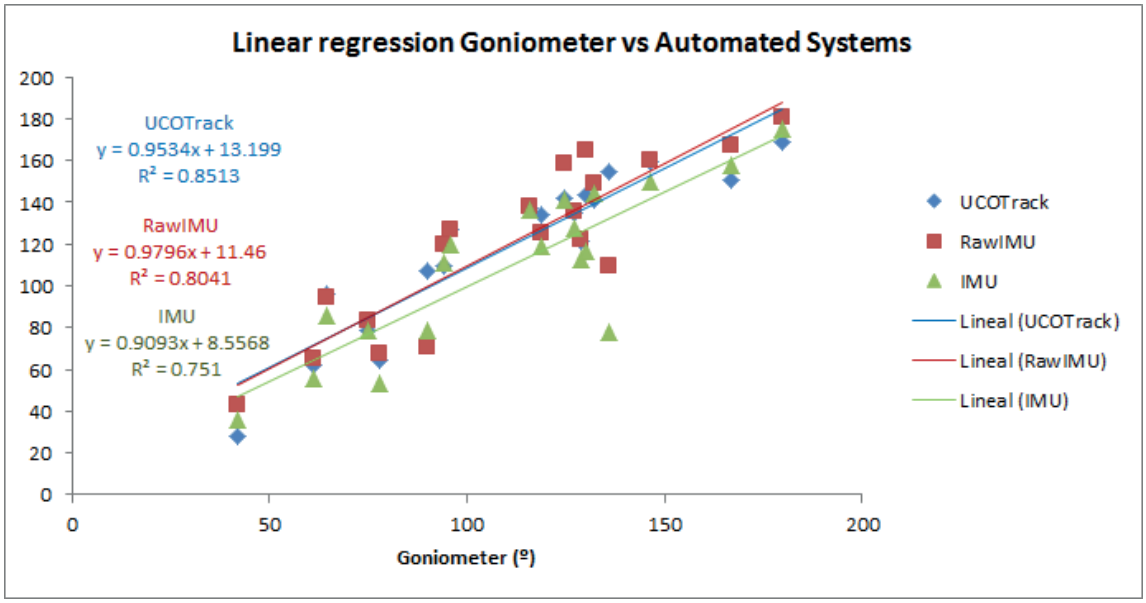
Final Results

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.



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.

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.

Publications

Validity and Reliability of a Sensor Based Electronic Spinal Mobility Index for Axial Spondyloarthritis Rheumatology 2020 doi: 10.1093/rheumatology/keaa122

EULAR Abstracts 2019

- THU0380: Lumbopelvic rhythm in patients with Axial Spondyloarthritis compared with low back pain and healthy subjects
- 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

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
- JL Garrido Castro, , 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

N Yeremenko, AMC Amsterdam, THE NETHERLANDS
n. g.yeremenko@amsterdamumc.nl

Funding and timeline

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

Publications

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.

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.

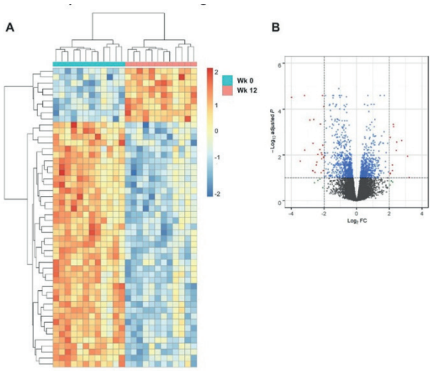


Figure 1. A. Hierarchical cluster analysis of differential expressed genes showing the log2 expression of the 100 most significantly regulated by the treatment with secukinumab genes. Normalized gene expression levels across samples are shown. B. A volcano plot. Red plots represented significant ($p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

Leukocytes cytokines responses

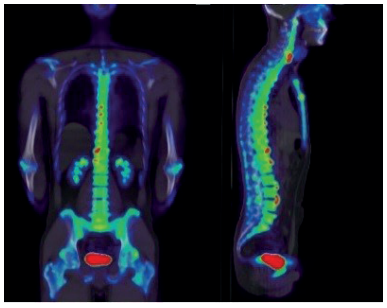
Analysis via whole-blood stimulation systems revealed that aTNF therapy induces profound changes in patients' innate immune response. Modular transcriptional repertoire analysis showed that aTNF therapy affects immune responses via direction of macrophage polarization and the inhibition of TNF- and IL-1-dependent 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).



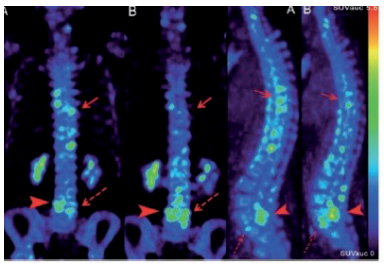


Figure 2. (A) An example of [18F]-fluoride accumulation throughout the spine at baseline in AS patient with clinically active disease. (B) Heterogeneous effect of aTNF therapy on [18F]-fluoride uptake

Figure 3. Baseline [18F]-fluoride accumulation in the cervical, thoracic and/or lumbar spine at locations such as anterior corners of vertebrae and in bridging syndesmophytes in an AS patient with clinically active disease started aIL-17A treatment.

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.

Publications

– Menegatti S, Bianchi E, Rogge L. Anti-TNF Therapy in Spondyloarthritis and Related Diseases, Impact on the Immune System and Prediction of Treatment Responses. Frontiers in Immunology. 2019 https://www.frontiersin.org/articles/10.3389/fimmu.2019.00382/full#h10
– Eleni Kampylafka, Isabelle d'Oliveira, Christina Linz, Veronika Lerchen, Fabian Stemmler, David Simon, Matthias Englbrecht, Michael Sticherling, Jürgen Rech, Arnd Kleyer, Georg Schett, Axel J. Hueber. Resolution of synovitis and arrest of catabolic and anabolic bone changes in patients with psoriatic arthritis by IL-17A blockade with secukinumab: results from the prospective PSARTROS study. Arthritis Res Ther. 2018 Jul 27;20(1):153. doi: 10.1186/s13075-018-1653-5 https://arthritis-research.biomedcentral.com/articles/10.1186/s13075-018-1653-5#Abs1

Project team/centres

– N Yeremenko, AMC Amsterdam, THE NETHERLANDS (lead)
– C Miceli, Institute Pasteur Paris, FRANCE
– L Rogge, Institute Pasteur Paris, FRANCE
– C van der Laken, VU Medisch Centrum, THE NETHERLANDS
– L Salij, Stichting Bechterew in Beweging, THE NETHERLANDS
– G van der Zalm, Stichting Bechterew in Beweging, THE NETHERLANDS
– D Simon, University Hospital, GERMANY

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

J Askling, Karolinska Institutet, SWEDEN
johan.askling@ki.se

Funding and timeline

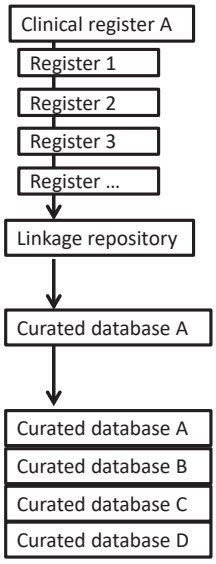
FOREUM research grant: EUR 297.685
Project duration: 2017–2020

Publications

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.



1. Enrichment through linkage to other registers in the same country
2. Curation (generic and project-specific)
3. Analyses (separately in each country or based on export of curated data from each country)

Objectives

To establish a standing network across the five Nordic Rheumatology registers, and to use this network for studies of clinical questions in Rheumatoid Arthritis (RA), Spondyloarthropathies (AS/SpA), and Pso- riatic Arthritis (PsA).

Interim Results

Within the collaboration, some 20 individual projects each addressing specific research questions have been initiated. Some have already been reported, many are ongoing. For instance, we have investigated the use and comparative effectiveness of TNF-biosimilars, the comparative effectiveness and safety of non-TNFi-biologics, and currently investigate the use of biologics in the context of pregnancies and in patients with malignancies, and treatment outcomes following biologics use in patients with spondyloarthropathies. As spin-offs of our collaboration, several additional projects have and are also being launched.

Patient voice

We have established a Patient Advisory Panel that has influenced the research agenda e.g., via the formulation of specific research questions. Liaison between the project and the national patient organizations on general issues such as data protection and perceptions of personal/data integrity, and, depending on focus, to suggest additional patient research partners for specific projects.

Publications

- 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. https://ard.bmj.com/content/78/3/320
- 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 biological registries, Scandinavian Journal of Rheumatology, DOI: 10.1080/03009742.2018.1444199 https://www.tandfonline.com/doi/full/10.1080/03009742.2018.1444199
- 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 https://rmdopen.bmj.com/content/4/1/e000655
- 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 [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10). https://acrabstracts.org/abstract/first-line-biological-treatment-in-ankylosing-spondylitis-prescription-rates-baseline-demographics-and-disease-activity-a-collaboration-between-biological-registers-in-the-five-nordic-counties/ https://www.tandfonline.com/doi/full/10.1080/03009742.2018.1444199
- 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/abstract/baseline-characteristics-and-rates-of-hospitalized-infections-in-pa-

tients-with-rheumatoid-arthritis-treated-with-non-tnf-inhibitors-in-denmark-and-sweden/

– 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
– 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
– 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
– 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

EULAR Abstracts 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

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

Project team/centres

– J Askling, Karolinska Institutet, SWEDEN (lead)
– M Lund Hetland, Rigshospitalet, DENMARK
– E Lie, Diakonhiemmet University of Oslo, NORWAY
– D Nordström, Helsinki University Gentral Hospital, FINLAND
– B Gudbjörnsson, University of Iceland, ICELAND

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

Project lead

H Chinoy, University of Manchester, UNITED KINGDOM
lorenzo.cavagna@unipv.it, hector.chinoy@manchester.ac.uk

Funding and timeline

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

Publications

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), instru- mental 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.

Performed steps

Systemic literature review for the identification of a first list of eligible variables.

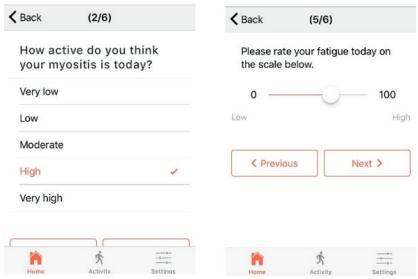
2019 Ongoing steps

– Eligible variables list submission to collaborating centers and experts for an in depth analysis and a possible up to date (clinicians and patients)

- Answers collection and analysis
- Preliminary criteria core set evaluation from steering committee members
- Final working group for the definition of the final core set of items (March-April 2019 in Pavia)

MyoPAD gait sensor

MyoPAD smartphone-based app interface



Other studies supported with the IMPROVEMENT project:

- ACR/EULAR Classification Criteria of antisynthetase syndrome (CLASS Project): we defined the list of participating centers, steering committee members, and the list of variables that should be included in the CRF
- The anti-MDAS antibodies project: characterization of anti-MDA5 antibodies positive patients in a non-Asian cohort. First paper submitted (analysis of 149 patients)
- The EARTH project (Early myositis Antibodies detection in Recent onset arthritis): addressed to evaluate the prevalence of myositis antibodies in a new setting, frequently overlapping with MSDs. Antibodies determination (target of 2.000 patients with early arthritis) is planned for the end of 2019
- The MyoPAD Study: The MyoPAD study aims to integrate mobile health technologies into routine myositis management, to improve recognition of worsening disease activity. The preliminary stages have been planned and data collection has begun.

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

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/

Project team/centres

- H Chinoy, University of Manchester, UNITED KINGDOM (lead)
- L Cavagna, Policlinico S.Matteo Foundation, ITALY
- L Wedderburn, University College London, UNITED KINGDOM
- M Gonzalez-Gay, Hospital Universitario Marqués de Valdecilla, SPAIN
- U Viora, Associazione Nazionale Malati Reumatici ANMAR, ITALY

European network of pregnancy registers in rheumatology (EuNeP)

Project lead

R Fischer-Betz , Heinrich-Heine University, GERMANY
strangfeld@drfz.de

Funding and timeline

FOREUM research grant: EUR 298.000
Project duration: 2017–2020

Publications

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

Concept

There is a high unmet need of robust data on the outcomes of pregnancies in women with inflammatory rheumatic diseases (IRD) and on the safety of a substantial number of drugs when used before or during pregnancy. The aim of our project is to combine existing data and to improve future pregnancy counseling by using better information on pregnancy outcomes and drug safety.

Therefore, experts from France, Germany, Norway and Switzerland who already run prospective pregnancy registers in women with IRD are brought together.

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

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.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 will be published as a EULAR recommendation. Currently, the joint data analysis is being prepared.

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

- Meissner Y, Strangfeld A, Costedoat-Chalumeau N, Forger F, Goll D, Molto A, Ozdemir R, Wallenius M, Fischer-Betz R. European Network of Pregnancy Registers in Rheumatology (EuNeP)-an overview of procedures and data collection. Arthritis Res Ther. 2019;21(1):241.
- Meissner et al. OP0326 Development of a standardized minimal core data set for pregnancy registers in rheumatology – results of a EULAR task force. Annals of the Rheumatic Diseases. 2019;78(Suppl 2):246-.
- Meissner Y, Strangfeld A, Costedoat-Chalumeau N, Förger F, Moltó A, Wallenius M, Fischer-Betz R. Defining a Standardized Core Data Set for Pregnancy Registers in Rheumatic Diseases – an European Approach [abstract]. Arthritis Rheumatol. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/defining-a-standardized-core-data-set-for-pregnancy-registers-in-rheumatic-diseases-an-european-approach/. Accessed March 28, 2019. https://acrabstracts.org/abstract/defining-a-standardized-core-data-set-for-pregnancy-registers-in-rheumatic-diseases-an-european-approach/
- Meissner Y, Strangfeld A, Costedoat-Chalumeau N, et al. 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). Annals of the Rheumatic Diseases 2018;77:824. https://ard.bmj.com/content/77/Suppl_2/824
- Meissner et al. Defining a standardized core data set for pregnancy registers in rheumatic diseases – an approach of the European Network of Pregnancy registers in rheumatology (EuNeP). 10th international conference on reproduction, pregnancy and rheumatic diseases, 2018

EULAR Abstracts 2019

- OP0326: Development of a standardized minimal core data set for pregnancy registers in rheumatology – results of a EULAR task force

EULAR Abstracts 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

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

Project team/centres

- R Fischer-Betz , Heinrich-Heine University, GERMANY (lead)
- A Strangfeld , German Rheumatism Research Centre, GERMANY
- N Costedoat-Chalumeau, Université Paris-Descartes, FRANCE
- A Molto , Groupe Hospitalier Cochin-Saint Vincent de Paul, FRANCE
- M Wallenius , University of Trondheim, NORWAY
- F Förger , University Hospital and University of Bern, SWITZERLAND
- Y Meissner, German Rheumatism Research Centre, GERMANY

Comorbidity in Juvenile Idiopathic Arthritis (JIA)

Project lead

N Wulffraat, UMC Utrecht, THE NETHERLANDS
j.f.swart@umcutrecht.nl

Funding and timeline

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

Publications

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.

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

– A clinical prediction model for estimating the risk of developing uveitis in patients with juvenile idiopathic arthritis
J.W. van Straalen1, G. Giancane2,3, Y. Amazrhar1, Nikolay Tzaribachev4, Calin Lazar5, Yosef Uziel6, Albena Telcharova – Mihaylovska7, Claudio Len8, Angela Miniaci9, Alina Lucica Boteanu10, Giovanni Filocamo11, Mariel Viviana Mastri12, Thaschawee Arkachaisri13, Maria Greca Magnolia14, Esther Hoppenreijs15, S. de Roock1, N.M. Wulffraat1, Nicolino Ruperto2*, J.F. Swart1*, for the Paediatric Rheumatology International Trials Organisation (PRINTO) Submitted and under review

EULAR Abstracts 2019

– OP0058: Development of inflammatory bowel disease during treatment with Etanercept in patients with Juvenile Idiopathic Arthritis
http://scientific.sparx-ip.net/archiveeular/

Project team/centres

– N Wulffraat, UMC Utrecht, THE NETHERLANDS (lead)
– J Swart, UMC Utrecht, THE NETHERLANDS
– K Hyrich, University of Manchester, UNITED KINGDOM
– M Lunt, University of Manchester, UNITED KINGDOM
– L Kearsley-Fleet, University of Manchester, UNITED KINGDOM
– N Ruperto, Istituto Giannina Gaslini, ITALY
– G Giancane, IRCCS Istituto G. Gaslini, ITALY
– K Minden, Charité Berlin, GERMANY
– J Klotsche, Charité Berlin, GERMANY
– G Horneff, Charité Berlin, GERMANY
– W Costello, European Network for Children with Arthritis ENCA, IRELAND
– C Schoemaker, Dutch JIA parent organisation, THE NETHERLANDS

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

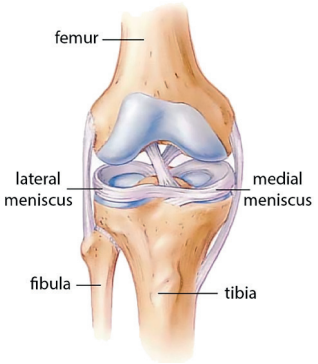
Novel treatment targets in early-stage OA

Project lead
M Englund, Lund University, SWEDEN
martin.englund@med.lu.se

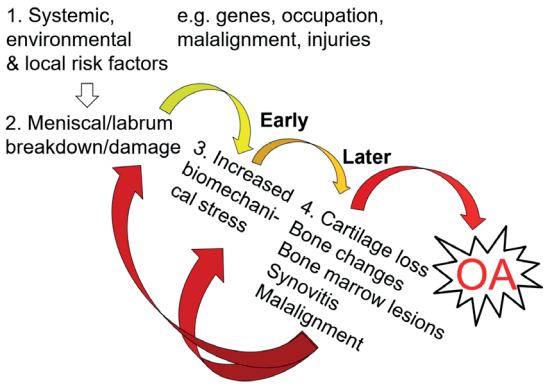
Funding and timeline
FOREUM research grant: EUR 600.000
Project duration: 2018–2021

Publications
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.
Our 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. We further 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.



Objectives
We will characterize the early molecular and structural changes associated with meniscal breakdown and knee OA. By studying the meniscus and synovial fluid from patients with torn menisci using mass spectrometry and novel micro CT imaging techniques, we will identify protein changes that accompany meniscus breakdown. We will further follow-up on a sub-

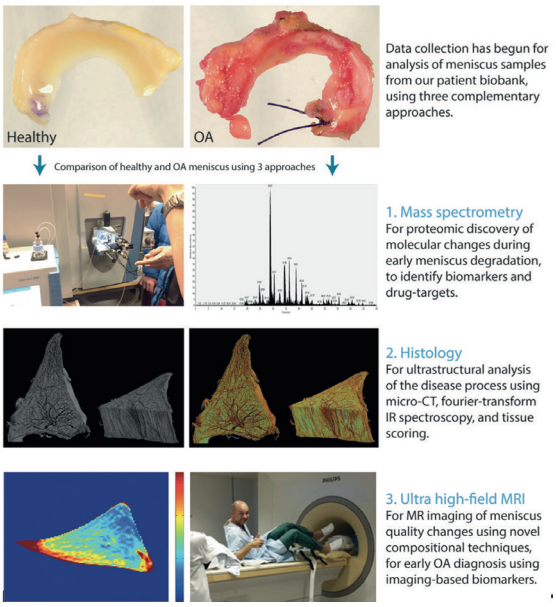


set of these patients at risk for future OA, using ultra high-resolution 7-Tesla magnetic reso-nance imaging (MRI). This technique will enable us to visualize the earliest structural features associated with OA disease progression.

Combining our results from these two me- thods, we aim to pinpoint the molecular chan- ges in the meniscus that are associated with development of OA. This will help us identify new biomarkers for early diagnosis of OA, as well as discover new targets for pharmaceuti- cal intervention against meniscal breakdown and OA disease.

Patient voice

We have two patient research partners, who have visited Lund to meet our team and discuss our project. We have received their positive feedback on our initial work, and will continue working with them as our studies continue.



Publications

- Ultra-high field magnetic resonance imaging parameter mapping in the posterior horn of ex vivo human menisci. Olsson E, Folkesson E, Peterson P, Önnerfjord P, Tjörnstrand J, Hughes HV, Englund M*, Svensson J*. Osteo-arthritis Cartilage. 2019 Mar;27(3):476-483. *shared senior authors https://www.oarsijournal.com/article/S1063-4584(18)31556-5/abstract
- Differential protein expression in human knee articular cartilage and medial meniscus using two different proteomic methods: a pilot analysis. Folkesson E, Turkiewicz A, Englund M, Önnerfjord P. BMC Musculoskelet Disord. 2018 Nov 29;19(1):416. * shared senior authors https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-018-2346-6#Abs1

EULAR Abstracts 2019

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

EULAR Abstracts 2020

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

Project team/centres

- M Englund, Lund University, SWEDEN (lead)
- P Önnerfjord, Lund University, SWEDEN
- V Hughes, Lund University, SWEDEN
- A Turkiewicz, Lund University, SWEDEN
- E Folkesson, Lund University, SWEDEN

– N Ali, Lund University, SWEDEN
– E Olsson, Lund University, SWEDEN
– J Svensson, Lund University, SWEDEN
– M Nieminen, University of Oulu, FINLAND
– S Saarakkala, University of Oulu, FINLAND
– I Kestilä, University of Oulu, FINLAND
– E Oei, Erasmus MC Rotterdam, THE NETHERLANDS

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

Project lead

R Seror, Université Paris Sud , FRANCE
raphaele.se@gmail.com

Funding and timeline

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

Publications

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.

Objectives

This project aims to investigate the role of new environmental factors and of potential interactions between the genetic background and specific environmental factors in the development of RA and/or preclinical phases of RA.

Interim Results

RA cases validation

In the French prospective general population cohort (E3N). Among the 98,995 included women, we identified and validated self-reported RA cases 3 methods including a specific validation questionnaire, a medical chart review (where available) and the use of the reimbursement database. Among the 3,192 identified potential cases, 964 RA cases were validated, including 698 incident cases and 266 prevalent cases. Of them, 314 (32.6%) were seropositive cases, 23 (2.4%) seronegative and 627

(65.0%) had unknown antibody status. Mean age at diagnosis was 57.4 ± 13.9 years (40.9 ± 10.4 years for prevalent cases, and 63.8 ± 9.0 for incident cases).

Chronic Diarrhoea and Risk of Rheumatoid Arthritis
In the E3N cohort, we assessed the relationship between gastrointestinal disorders and the risk of further development of RA. We observed that chronic diarrhea was associated with an increased risk of subsequent RA development (HR 1.70, 95% CI: 1.13–2.58), particularly among ever-smokers (HR 2.21, 95% CI: 1.32–3.70), independently of dysthyroidism or dietary habits. These data fit with the mucosal origin hypothesis of RA, where interaction between intestinal dysbiosis and smoking could occur at an early stage to promote emergence of autoimmunity, followed years later by clinical disease.
Adherence to the Mediterranean diet and risk of RA
In the E3N cohort, we assessed the relationship between adherence to the Mediterranean diet and risk of RA. We observed that, among ever-smokers, MD score was associated with a decreased risk of RA (HR for 1-point increase of MD score: 0.91; 95% CI: 0.84 to 0.99, P = 0.03).
Hormonal exposure and risk of RA
In the E3N cohort, we assessed the relationships between hormonal exposures and the risk of RA in women. We observed that Early age at menopause (<45 yrs) was associated with an increased risk of RA, particularily in women exposed to tobacco. By contrast, exogenous hormonal exposures were not.

Patient voice

Patients will be involved at each step: For case validation, for interpreting/discuss results of research, and they will help providing key message derived from research results to other patients. Patients from dif- ferent countries will be involved to input different view and perspectives.

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.
– Nguyen Y, Mariette X, Salliot C, Gusto G, Boutron-Ruault MC, Seror R. Chronic Diarrhoea and Risk of Rheumatoid Arthritis: Findings from the French E3N-EPIC Cohort Study. Rheumatology (oxford), 2020 (in press)

Project team/centres

– R Seror, Université Paris Sud , FRANCE (lead)
– D van der Woude, UMC Leiden, NETHERLANDS
– C Boutron, Gustave Roussy Institute, FRANCE
– D Alpízar-Rodríguez, Hôpitaux Universitaires de Genève, SWITZERLAND
– P Preiss, Association France Polyarthrite, FRANCE

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

Project lead

A Catrina, Karolinska Institutet, SWEDEN
anca.catrina@ki.se

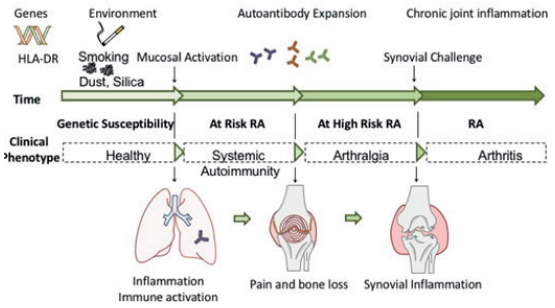
Funding and timeline

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

Publications

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

– Joshua et al. Association between number and type of different ACPA fine specificities with lung abnormalities in early, untreated rheumatoid arthritis, submitted
– Ljungberg et al. Secretory anti-citrullinated protein antibodies in serum associate with lung involvement in early rheumatoid arthritis, submitted
– Gerasimicik et al. The periodontal pathogens P. gingivalis and A. actinomycetemcomitans antigens are detected in synovial tissues and correlate with citrullination in patients with rheumatoid arthritis, submitted

Project team/centres

– A Catrina, Karolinska Institutet, SWEDEN (lead)
– D van Schaardenburg, University of Amsterdan, NETHERLANDS
– J Nam, University of Leeds, UNITED KINGDOM
– 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

Project lead

G Bertsias, University of Crete, GREECE
gbertsias@uoc.gr

Funding and timeline

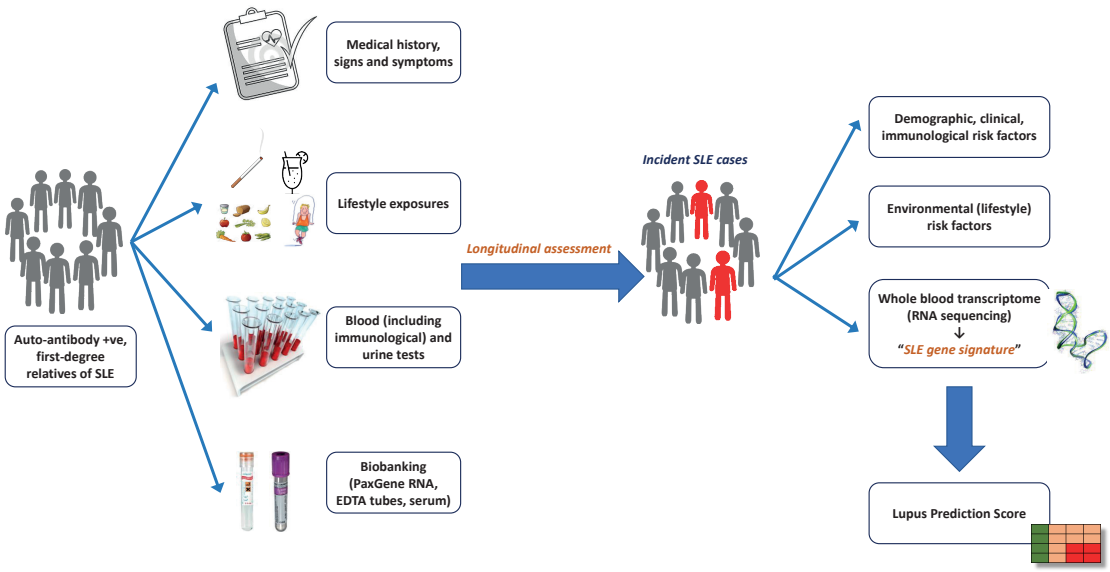
FOREUM research grant: EUR 400.000
Project duration: 2018–2021

Publications

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.

Interim Results

The study protocol, including the questionnaires for assessment of environmental factors and the biosampling strategy, has been approved by all participating centres and IRBs.
Among more than 300 screened individuals, a total 254 at-risk individuals (93% women, 99% Caucasians, aged 36±12 years) have been included (complete data and biosampling) and enrolment/monitoring is still ongoing. Forty individuals (16%) have first-degree relative(s) with SLE. During follow-up of 15.2 ± 7.2 months, a total 15 individuals (5.9%) have progressed into classified (incident) SLE. An interim analysis of demographic, clinical and biological (RNA-seq) data is currently underway.

Publications

- In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: 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.
- 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.
- EULAR 2020 Poster Presentation (Poster no. 4468). A multicenter "at-risk" cohort for the discovery of environmental, clinical and molecular predictors for the transition into systemic lupus erythematosus (SLE).

EULAR Abstracts 2020

- THU0014: Comparative transcriptome analyses across tissues and species identify targetable genes for human Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN)
- FRI0155: A multicenter "at-risk" cohort for the discovery of environmental, clinical and molecular predictors for the transition into systemic lupus erythematosus (SLE)
  http://scientific.sparx-ip.net/archiveeular/

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.

Project team/centres

- G Bertsias, University of Crete, GREECE (lead)
- A Stara, Arthritis Foundation Crete, GREECE
- A Tincani, University of Brescia, ITALY
- 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

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

D Noël, Université de Montpellier, FRANCE
daniele.noel@inserm.fr

Funding and timeline

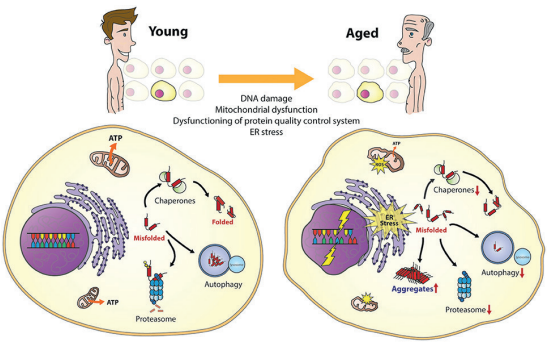
FOREUM research grant: EUR 600.000
Project duration: 2018–2021

Publications

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 and to the feedback of two patient experts of one-day visit of a research laboratory on OA has been made.
- WP2. Several types of samples in 3 non-clinical models of mice and humans with OA have been collected and are under evaluation for expression of senescence markers in various articular tissues.
- WP3. Different in vitro (stem cells, chondrocytes) and in vivo (mouse, zebrafish) models of senescence have been developed. Senolytics are being evaluated in those models.

– WP4. A preliminary screening was performed with a repurposing library to identify Senolytics and Pro-autophagy modulators in human chondrocytes. Several candidates are available for further validation.

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

– Boulestreau J, Maumus M, Rozier P, Jorgensen C, Noël D. Mesenchymal stem cell derived extracellular vesicles in aging. Frontiers in Cell and Developmental Biology, 2020; 8: 107
– 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.
– Tachikart Y, Malaise O, Mumme M, Jorgensen C, Brondello JM. Seno-suppressive molecules as new therapeutic perspectives in rheumatic diseases; Biochem Pharmacol 2019; 165: 126-133.
– 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.
– Vinatier C, Domínguez E, Guicheux J, Caramés B. Role of the Inflammation-Autophagy-Senescence Integrative Network in Osteoarthritis. Front Physiol. 2018; 25; 9: 706.

Project team/centres

– D Noël, Université de Montpellier, FRANCE (lead)
– C Jorgensen, Université de Montpellier, FRANCE
– X Houard, Université Pierre et Marie Curie, FRANCE
– F Berenbaum, Université Pierre et Marie Curie, FRANCE
– C Caramés Perez, Hospital Teresa Herrera, SPAIN
– L Comole, Arthritis Courtin Fondation, FRANCE
– J Guicheux, Université de Nantes, FRANCE
– C Vinatier, Université de Nantes, FRANCE
– F Rannou, Centre Universitaire des Saints-Pères, FRANCE
– 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

J Lord, University of Birmingham, UNITED KINGDOM
j.m.lord@bham.ac.uk

Funding and timeline

FOREUM research grant: EUR 599,881
Project duration: 2018–2021

Publications

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

Concept

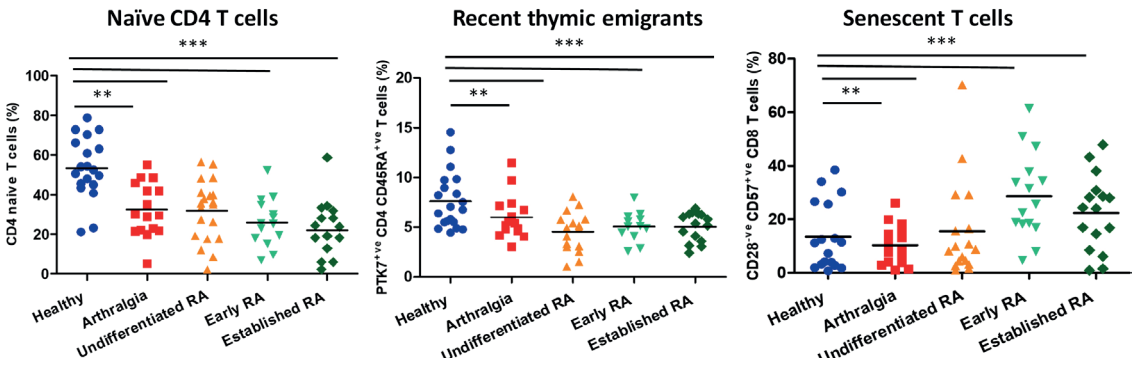
Age is a major risk factor for rheumatoid arthritis (RA), yet we understand little of the role ageing processes play in RA pathogenesis. Why this matters is that if ageing processes are a driver for RA, then improved understanding of the mechanisms involved may reveal innovative approaches to prevention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

Objectives

We 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. We 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. We will also assess immune phenotype at the various stages of disease development to see if this occurs early or is a consequence of disease.

Interim Results

The interim data suggest that thymic atrophy, increased neutrophil and regulatory monocyte counts occur early in disease, but the build up of senescent cells is more likely a consequence of disease. We have also completed analysis of published data on DNAm in established RA and the manuscript will be submitted in late April.



Patient voice

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

Project team/centres

- J Lord, University of Birmingham, UNITED KINGDOM (lead)
- K Raza, University of Birmingham, UNITED KINGDOM
- A Pratt, University of Newcastle, UNITED KINGDOM
- A Catrina, Karolinska Institutet, SWEDEN
- 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

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

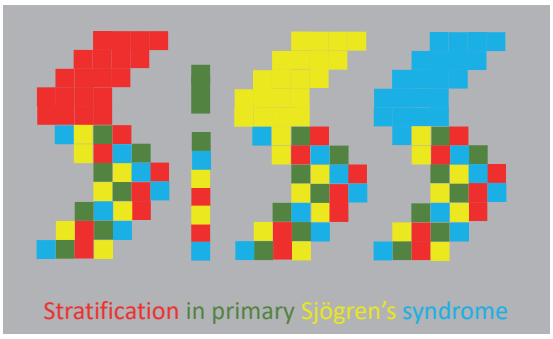
Project lead
W-F Ng, Newcastle University, UNITED KINGDOM
wan-fai.ng@ncl.ac.uk

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

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

Concept
Primary Sjögren's syndrome (PSS) is a chronic complex immune-mediated rheumatic disease with no effective treatment to date. PSS affects 0.05-0.1% of the adults. A key barrier to therapeutic development is the marked heterogeneity in clinical manifestations and pathobiological profiles among PSS patients. We have recently described a strategy to stratify PSS patients into four subtypes with distinct clinical phenotypes and transcriptomic signatures.

Objectives
The proposal aims to further characterise the clinical significance and the underpinning pathotypes of 4 PSS subtypes. The specific objectives are:



1. To understand the natural history of the different PSS subtypes.
2. To validate the transcriptomic signatures of the PSS subtypes and re-calibrate (if necessary) for non-UK cohorts.
3. To further characterise the underpinning pathobiological profiles of the four PSS subtypes
4. To explore whether the four subtypes respond differently to treatments by reanalysing data from two clinical trials (JOQUER (hydroxychloroquine) and TRACTISS (Rituximab)

Interim Results
- Biological differences between the four key PSS subtypes confirmed in the French and Scandinavian cohorts.
- We have established these PSS subtypes are relatively stable over time.
- Transcriptional differences between the PSS subtypes confirmed.
- Patient advisory board established and patient-driven pro-forma for health outcome data in development. (English and French versions completed, awaiting finalization of the Norwegian and Swedish translations)

– Historical clinical trials data reanalyzed which revealed differential responses to rituximab and hydroxychloroquine between the four substypes
– Serum protein profiling of the subtypes ongoing
– Preparation of collection of longitudinal outcome in progress

Patient voice

We formed a patient advisory board – comprising 7 patient research partners from 4 participating countries - to advise on what information to collect to best describe the burden that PSS brings to their daily lives. The health economist Dr Peter McMeekin joined us to facilitate group discussion in developing the pro-forma for data collection. We have invited 3 patient research partners to join our steering committee to provide guidance and oversight of the whole proposal.

Publications

Tarn JR, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. Lancet Rheumatology. 2019 Oct 1;1(2):PE85-E94.

Project team/centres

– W-F Ng, Newcastle University, UNITED KINGDOM (lead)
– D Lendrem, Newcastle University, UNITED KINGDOM
– J-E Gottenberg, Strasbourg University, FRANCE
– R Seror, Université Paris Sud , FRANCE
– V Devauchelle-Pensec, Brest University, FRANCE
– A Saraux, Brest University, FRANCE
– S Bowman, University of Birmingham, UNITED KINGDOM
– F Barone, University of Birmingham, UNITED KINGDOM
– B Fisher, University of Birmingham, UNITED KINGDOM
– G Nordmark, Uppsala University, SWEDEN
– U Landegren, Uppsala University, SWEDEN
– R Omdal, Stavanger University Hospital, NORWAY
– M Bombardieri, Queen Mary University London, UNITED KINGDOM
– P McMeekin, , UNITED KINGDOM
– J Tarn, UNITED KINGDOM
– E Traianos, UNITED KINGDOM
– P McMeekin, UNITED KINGDOM
– V Macrae, UNITED KINGDOM

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

Project lead

N Pipitone, Azienda Unità Sanitaria Locale, ITALY
nicolo.piptone@ausl.re.it

Funding and timeline

FOREUM research grant: EUR 600.000
Project duration: 2018–2022

Publications

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

Concept

The present research aims to develop and validate biomarkers whose quantification in temporal artery biopsies (TABs) might predict response to glucocorticoids and tocilizumab in patients with giant cell arteritis (GCA) and to stratify patients according to molecular signatures in TABs. Glucocorticoids are the standard of care in GCA but about 40% of patients relapse when glucocorticoids are tapered. Tocilizumab plus glucocorticoids has recently been proven effective at increasing the percentage of GCA patients in remission and sparing glucocorticoids.

Objectives

– Identification of biomarkers in TABs whose quantification may allow to predict at diagnosis patients' response to glucocorticoids and tocilizumab.
– Stratification of GCA patients according to molecular signatures in TABs and correlation of such signatures to the clinical characteristics of patients.
– Validation of the potential predictors and signatures.

The long-term objective is to create the basis for a therapeutic approach in patients with GCA, tailored to molecular characteristics in TABs at diagnosis, aiding physicians to achieve the best outcome in each patients (maximum efficacy with minimal adverse effects) in the shortest time.

Patient voice

One Italian (AMRER) and two Spanish (FEP and LIRE) associations of patients are involved as patient research partners (PRPs). Patient associations in France and Switzerland will be further involved.

EULAR guidelines for Patient Research Partners (PRP) inclusion have been followed. We have discussed the design of the project and the burden for patients with the PRPs integrating their feedback. PRPs will be involved in all phases of the project.

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)
– S Croci, Azienda Unità Sanitaria Locale, ITALY
– 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
– P Villiger, University Hospital Bern, SWITZERLAND
– D Conti, Associazione Malati Reumatici Emilia Romagna, ITALY
– J Baquero, Foro Español de Pacientes, SPAIN
– Dr V Romero, Liga Reumatologica Española, SPAIN
– Dr L Carmona, Liga Reumatologica Española, SPAIN

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

D Lazarevic, Clinic of Pediatrics, SERBIA
lazarevic.gaga@gmail.com

Funding and timeline

FOREUM research grant: EUR 125.00
Project duration: 2018–2021

Publications

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.

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

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

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. They should be involved in public engagement and inform wider society using different media if this project meets the needs of JIA patients.

Project team/centres

- D Lazarevic, Clinic of Pediatrics, SERBIA (lead)
- J Vojinovic, Pediatric Rheumatology Department, SERBIA
- C Malattia, Istituto Giannina Gaslini, ITALY

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

Project lead
E Sag, Hacettepe University, TURKEY
sag.erdal@gmail.com

Funding and timeline
FOREUM research grant: EUR 150.00
Project duration: 2018–2021

Publications
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

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.

Publications

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/

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.

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

B Burja, University Medical Centre Ljubljana, SLOVENIA
blaz.burja@gmail.com

Funding and timeline

FOREUM research grant: EUR 150.00
Project duration: 2018–2021

Publications

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

Concept

Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown cause, which leads to disability and may cause premature death. SSc is characterized by massive accumulation of extracellular matrix proteins (=fibrosis) in skin and internal organs with permanent loss of organ function. Decreasing/reversing fibrosis in patients with SSc can improve the prognosis of this devastating disease. Targeting metabolic pathways could reduce the production of extracellular matrix proteins by fibroblasts in SSc. This represents a promising new treatment strategy in SSc.

Objectives

We aim at exploring the crosstalk between metabolic and epigenetic pathways in SSc fibroblasts to uncover new anti-fibrotic treatment strategies. We will explore dysregulation of metabolic pathways in SSc fibroblasts and determine, whether metabolic substrates, such as aKG and glutamine influence the epigenetic state and pro-fibrotic activities of SSc fibroblasts. Targeting metabolic pathways might reverse epigenetic alterations and halt fibrosis in SSc with direct implications for drug discovery in SSc.

Interim Results

TGFβ-activated skin fibroblasts from healthy controls and SSc patients exhibit changes in key regulatory enzymes of energy metabolism and mitochondrial dysfunction (e.g. HIF1alpha, PGC-1alpha). Observed dysregulations of TCA cycle metabolites could influence the activity of epigenetic enzymes (e.g. JMJD3) utilizing metabolic co-factors and lead to pro-fibrotic activation.

Metabolic perturbations caused by extrinsic addition of metabolite dimethyl-alpha ketoglutarate (aKG) and diethyl succinate affected the activity of the JMJD3-mediated H3K27me3, resulting in different expression of profibotic targets (e.g. collagen I, alpha-smooth muscle actin).

Publications

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/

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.

Project team/centres

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

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, comorbidities 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

P Duffau, CHU of Bordeaux, FRANCE
patrick.blanco@chu-bordeaux.fr

Funding and timeline

FOREUM research grant: EUR 595'000
Project duration: 2019–2022

Publications

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. Our group made 3 findings of particular interest that could link SLE pathogenesis and atherosclerosis-associated immune dysregulation: 1/ we identified specific immunometabolites (circulating nucleotide-derived metabolites), which are increased in the circulation of SLE patients. These immunometabolites trigger a constitutive inflammasome activation resulting in aberrant IL1-β production. Given that IL1-β inhibition was reported to significantly reduce CV events without altering lipid levels, we propose that these immunometabolites may represent novel candidate biomarkers of CV risk stratification in SLE. 2/ we identified OX40L as an important costimulatory molecule implicated in follicular helper T cell (Tfh) activation in SLE. Interestingly, OX40L polymorphism has been associated to both SLE and atherosclerosis, and Tfh have been recently shown to accelerate atherosclerosis progression. 3/ Immune complexes-activated platelets sustain aberrant immune response in SLE and block immunosuppressive functions of regulatory T cells (Tregs). Selectins and Tregs cell dysfunction are well accepted players in atherosclerosis pathogenesis. Thus there are multiple pathways that are shared between SLE and atherosclerosis and that may results in an increased risk of CV-associated morbidity in SLE patients. 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.

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
- G Ruiz-Irastorza, Hospital Universitario Cruces, SPAIN
- R Voll, Albert Ludwig University Freiburg, GERMANY

Comorbidities in Osteoarthritis

Project lead

W Zhang, University of Nottingham, UNITED KINGDOM
weiya.zhang@nottingham.ac.uk

Funding and timeline

FOREUM research grant: EUR 600'000
Project duration: 2019–2022

Publications

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.

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 (Figure 1).
In the UK, people with physician diagnosed OA were more likely to develop multimorbidity (≥2 other diseases) (Figure 2). 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

– Swain S, Sarmanova A, Mallen C, Kuo CF, Coupland C, Doherty M, Zhang W. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). Osteoarthritis and Cartilage. 2020.
– Swain 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). 2019.

EULAR Abstracts 2020

– OP0074: Multimorbidity clusters, determinants and trajectories in Osteoarthritis in the UK: findings from the Clinical Practice Research Datalink
http://scientific.sparx-ip.net/archiveeular/

Project team/centres

– W Zhang, University of Nottingham, UNITED KINGDOM (lead)
– S Bierma-Zeinstra, Erasmus MC Netherlands, NETHERLANDS
– M Englund, Lund University, SWEDEN
– D Prieto-Alhambra, Autonomous University of Barcelona, SPAIN
– Carol Copland
– Michael Doherty
– Jos Runhaar, NETHERLANDS
– Anne Kamps, NETHERLANDS
– Kenneth Pihl, SWEDEN
– Helen He, SPAIN

Characterising comorbidity in patients with RA in Europe: a multi-national federated analysis of big healthcare data

Project lead
D Prieto-Alhambra, University of Oxford, UNITED KINGDOM
daniel.prietoalhambra@ndorms.ox.ac.uk

Funding and timeline
FOREUM research grant: EUR 200'000
Project duration: 2019–2020

Publications
www.foreum.org/projects/?id=160

Concept
There is a need to better understand how comorbidity and frailty affect people with RMDs. Comorbidity usually increases with age, with the elderly and frail most affected. Often, patients with RMDs gather comorbidities that can have a negative effect on achieving both early diagnosis but also good responses to treatment. Some early data suggest that certain types of comorbidity may be seen in certain groups of people. Furthermore, although evidence suggests that comorbidities reduce the chances of good treatment responses, it remains unclear whether this is due to direct effects of comorbidities on RMDs, or through other mechanisms, such as for example the concurrent use of multiple medications.

Objectives
There is scarce data on how comorbidity and frailty affect patients with rheumatoid arthritis (RA). Registry data provide an exceptional opportunity, and common data models will enable multinational federated collaboration. We will develop and test a structured approach for the assessment of comorbidity in people with RA in Europe.

Patient voice
Two patient research partners and PARE members (Irene Pitsillidou and Savia de Souza) are named co-applicants in our proposal. They will be involved as research partners throughout all stages of the application: from the ethics applications to study completion, data interpretation and dissemination. At least one Expert Patient will be included in the steering group and will take part in the project-management meetings. Patients will be involved at every stage of the research cycle and will be co-authors on publications/conference abstracts.

Project team/centres

- D Prieto-Alhambra, University of Oxford, UNITED KINGDOM (lead)
- K Hyrich, University of Manchester, UNITED KINGDOM
- D Courvoisier, Hôpitaux Universitaires de Genève, SWITZERLAND
- E Nikiphorou, King's College London, UNITED KINGDOM
- A Strangfeld , German Rheumatism Research Centre, GERMANY
- M Pombo, University Hospital Santiago de Compostela, SPAIN
- J Závada, Charles University Prague, CZECH REPUBLIC
- M Svoboda, Masaryk University Brno, CZECH REPUBLIC

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**, the second in **2019**, and out of 17 letters of intent 8 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
- "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

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

Project lead

M Aspari, Aarhus University, DENMARK
au611635@uni.au.dk

Funding and timeline

FOREUM research grant: EUR 50'000
Project duration: 2019–2020

Publications

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. In this project, we plan to examine SSc cohorts, fibroblast cultures with antibodies to co inhibitory molecules by using techniques of flowcytometry, ELISA, PCR studies. Measurements and analysis of changes to matrix proteins and inflammatory proteins.

Objectives

The purpose of this project is to examine T cell exhaustion and their role in the outcome of dSSc, with the focus on CiR and their ligands. Fibroblasts play a crucial role in the pathogenesis of dSSc, this project will also elucidate how TEX and CiR are regulated in co-cultures with T cell and autologous dSSc fibroblasts.
Additionally, their levels will be compared to well-known disease parameters and pseudo-parameters in dSSc. To establish the role of T cell exhaustion in SSc.

Interim Results

ELISA

ResultsThe mean of sPD-1 level was increased (136pg/ml) among dcSSc patients in comparison to healthy controls. Comparison of sPD-1 levels in patients on DMARDs with those without treatment demonstrated significant effect of immunosuppressive therapies, with mean sPD-1 95.1 pg/ml among patients on DMARD compared to 216.7 pg/ml among those on no treatment (p=0.0178). There was association between sPD-1 and mRss (p=0.04) and FVC (p=0.04).
Mean sLAG-3 levels were significantly lower among dcSSc patients (394.6 pg/ml) vs healthy controls (740.8 pg/ml, p=0.0001). sLAG-3 was inversely associated with disease duration (p=0.04). There was a trend for association between sLAG-3 and mRss, with higher levels of sLAG-3 seen in

patients with higher skin score (p=0.06),and between sLAG-3 levels and presence of tendon friction rubs (TFR) (mean sLAG-3 366.3 ng/ml among patient without TFR and 531.5 ng/ml among those with TFR, p=0.08). There was highly significant difference in the sTIM-3 levels between healthy controls (mean 4721.9 ng/ml) and dcSSc patients (8728.0 ng/ml, p<0.0001). There was a trend for association between anti-Scl70 (ATA) positivity and sTIM-3 levels (p=0.0944). Hb levels showed significant association with sTIM-3, with higher Hb levels associated with lower sTIM-3 levels (p=0.02).

FLOWCYTOMETRY

Pilot flowcytometry studies showed that the proportion of CD4+ T cells expressing PD1 were markedly increased in SSc patients compared to healthy volunteers and Rheumatoid Arthritis patients. There was increased expression of both TIGIT and TIM3 in the CD4+ T cells. (Figure 1) Similarly, the co-expression of these receptors on the CD4+ T cell population was elevated compared to healthy volunteers. (figure 2)

Publications

EULAR Abstracts 2020

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

Patient voice

The experimental nature of our research proposal limits the potential contribution of patient research partners. However, A project taskforce will be setup at Aarhus University based on EULAR recommendations during the course of this project . This taskforce would consist of both patients and doctors involved in the project. Regular meetings and consultations with patients will be held as part of the taskforce's schedule. Patient input in terms of both sample collection and suggestions will be taken into consideratio.

Project team/centres

- M Aspari, Aarhus University, DENMARK (lead)
- B Deleuran, Aarhus University, DENMARK
- D Abraham, University College London, UNITED KINGDOM
- Stinne Greisen, Stinne Greisen Department of Biomedicine, Aarhus University, DENMARK
- Voon H. Ong, UCL Medical School, Royal Free Campus, UNITED KINGDOM
- Christopher P. Denton, UCL Medical School, Royal Free Campus, UNITED KINGDOM

Incidence and outcome of cardiovascular disease in patients with inflammatory joint diseases

Project lead

A Semb, Diakonhjemmet Hospital, NORWAY
anne.kerola@helsinki.fi

Funding and timeline

FOREUM reserach grant: EUR 50'000
Project duration: 2020–2021

Publications

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. We establish a Norwegian Cardio-Rheuma register with data on the whole Norwegian population >18 years including all patients with IJD from 2008 – 2017 through linkage between Norwegian national registers. The design is observational cohort study and individuals with and without IJD will be compared. Our research team has obtained concession from the Norwegian General Data Protection Regulation (GDPR) (16/00482-11/CDG) to establish the Norwegian Cardio-Rheuma register, and the project has been recommended by the South East Health Authority Ethical Committee (2016/588) and by the Data Protection Officer, Oslo University Hospital (2016/924) and a GDPR including DPIA evaluation has been performed (5/12-2019).

Objectives

- To evaluate CVD morbidity and mortality in patients with RA, AS and PsA compared to the general population. We will study prevalence, incidence and outcome of the most common CVDs, and explore trends in CVD mortality and morbidity during the 10-year period.
- To compare the prevalence of CVD in users and non-users of biologic disease-modifying antirheumatic drugs in patients with IJD and the general population.
- 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 stable coronary heart disease (CHD) or after acute coronary syndrome (ACS) vs. general population controls with stable CHD or after ACS and the effect on CVD outcome.

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

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. We aim 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 Department of Rheumatology in Diakonhjemmet Hospital also has an established rheumatology patient
Council, who will be consulted for relevant user input and presentation of results. We will actively seek to disseminate results from the projects to patients through lay summaries and presentations at patient organizations meetings.

Project team/centres

- A Semb, Diakonhjemmet Hospital, NORWAY (lead)
- A Kerola, University of Helsinki, FINLAND
- M Kauppi, Päijät-Häme Central Hospital, FINLAND
- T Nieminen, Päijät-Häme Central Hospital, FINLAND
- E Haarvardsholm, Diakonhjemmet Hospital, NORWAY
- S Rollefstad, Department of Rheumatology, Diakonhjemmet Hospital, NORWAY
- G Wibetoe, Department of Rheumatology, Diakonhjemmet Hospital, NORWAY
- Eirik Ikdahl, Department of Rheumatology, Diakonhjemmet Hospital, NORWAY

Epigenetic regulation by DAMPs underlying trained immunity in health and disease

Project lead
K Laskari, Athens University Medical School, GREECE
katerina_laskari@yahoo.gr

Funding and timeline
FOREUM research grant: EUR 50'000
Project duration: 2019–2020

Publications
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 analysisof trascriptomic and epigenetic changes leading to innate immune memory (month 6-12)

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 potential therapeutic targets and strategies will clearly benefit the patients.

Project team/centres

– K Laskari, Athens University Medical School, GREECE (lead)
– P Sfikakis, Athens University Medical School, GREECE
– Prof. Dr. O Distler, University of Zurich, SWITZERLAND

Exploring treatment response in AS versus non-radiographic axSpA

Project lead

X Michelena Vegas, Hospital Universitari de Bellvitge, SPAIN
xmichelena@bellvitgehospital.cat

Funding and timeline

FOREUM research grant: EUR 50'000
Project duration: 2019–2020

Publications

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.

Objectives

Primary objective: 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.
Secondary objective: To explore treatment response to bDMARDs at 1 year as well as drug survival according to radiographic status (nr-axSpA vs r-axSpA)

Interim Results

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.

Publications

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/

Patient voice

The research team is directly involved with patient initiatives such as the National Ankylosing Spondylitis Team (NASS) and has discussed the objectives and preliminary results with patient representatives. The results from this project will aid in the understanding of axSpA as a single disease entity and promote better access to bDMARDs for axSpA patients.

Project team/centres

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

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
C Bruni, University of Florence, ITALY
cosimobruni85@gmail.com

Funding and timeline
FOREUM research grant: EUR 50,000
Project duration: 2020–2021

Publications
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

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)
- Prof. Dr. 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
A Paoletti, Paris-Saclay University, FRANCE
audreypaoletti@gmail.com

Funding and timeline
FOREUM research grant: EUR 50,000
Project duration: 2020–2021

Publications
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.

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
- M Kurowska-Stolarska, University of Glasgow, UK
- I McInnes, University of Glasgow, UK

Tissue Profiling of the Th17 Gene Activity in AS

Project lead

D Simone, Università della Campania Vanvitelli, ITALY
davide.simone@ndorms.ox.ac.uk

Funding and timeline

FOREUM research grant: EUR 50,000
Project duration: 2020–2021

Publications

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

Concept

Ankylosing Spondylitis (AS) is a chronic immune-mediated disease that affects various musculoskeletal 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

Project lead

P Studenic, Medical University of Vienna (MUV), AUSTRIA
paul.studenic@muv.ac.at

Funding and timeline

FOREUM research grant: EUR 50,000
Project duration: 2020–2021

Publications

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).

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 andto 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.

Project team/centres

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

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
F dell'Accio, Queen Mary University of London, UNITED KINGDOM
fdellaccio@gmail.com

Funding and timeline
FOREUM research grant: EUR 50.000
Project duration: 2019–2022

Publications
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

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.

Project team/centres

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

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

Project lead

R Landewé, University of Amsterdam, THE NETHERLANDS
landewe@rlandewe.nl

Funding and timeline

FOREUM research grant: EUR 226'186
Project duration: 2020–2023

Publications

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.

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
- SA 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

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

The second call was launched in **2020**, and out of 71 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)

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

Project lead
F Costantino, Université Versailles Saint-Quentin, FRANCE
felicie.costantino@inserm.fr

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

Publications
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.

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
A Croft, University of Birmingham, UNITED KINGDOM
a.p.croft@bham.ac.uk

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

Publications
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.

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.

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

S Dudli, University of Zurich, SWITZERLAND
stefan.dudli@usz.ch

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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

We aim to identify molecules that cause inflammation and scarring of vertebral bone marrow, processes that contribute to chronic low back pain. Once we have identified these molecules and understand how they cause inflammation and scarring of the bone marrow, we will test different drugs that stop this undesired painful reaction in the bone marrow.

Patient voice

We will form a supervising committee with patient representatives from local low back pain organizations and a few key opinion leaders. 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)
- Prof. Dr. O Distler, University of Zurich, SWITZERLAND

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

Project lead

M Jani, University of Manchester, UNITED KINGDOM
meghna.jani@manchester.ac.uk

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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-related morbidity/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

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, , UNITED KINGDOM
– C Lowe, , UNITED KINGDOM

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

Project lead

G Cavalli, IRCCS San Raffaele Hospital, ITALY
cavalli.giulio@hsr.it

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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.

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

R Lucas, Universidade do Porto, PORTUGAL
rlucas@med.up.pt

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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 ection 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)
- M Talih, Universidade do Porto, PORTUGAL
- A Rocha, INSEC TEC, PORTUGAL
- M J Santos, Portuguese Society of Rheumatology, PORTUGAL
- E Frazão Mateus, PARE, PORTUGAL
- C Cooper, University of Oxford, UK
- Dr L Carmona, Liga Reumatologica Española, SPAIN

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

Project lead
E Nikiphorou, King's College London, UNITED KINGDOM
enikiphorou@gmail.com

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

Publications
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)
– A Cope, King's College London, UNITED KINGDOM
– F Ibrahim, King's College London, UNITED KINGDOM
– R Williams, King's College London, UNITED KINGDOM

PMR Research On Disease Mechanisms In Synovium (PROMIS)

Project lead

K Van der Geest, University Medical Center Groningen, THE NETHERLANDS
k.s.m.van.der.geest@umcg.nl

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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.

Project team/centres

- K Van der Geest, University Medical Center Groningen, THE NETHERLANDS (lead)
- E Brouwer, University Medical Center Groningen, THE NETHERLANDS
- M Boots, University Medical Center Groningen, THE NETHERLANDS
- P Heeringa, UMC Groningen, THE NETHERLANDS
- L Geurts - van Bon, ZGT Hospital, THE NETHERLANDS
- D Boumans, ZGT Hospital, THE NETHERLANDS

A New Concept of ANCA-Associated Vasculitis (ANCA)

Project lead

D van der Woude, UMC Leiden, NETHERLANDS
dvanderwoude@lumc.nl

Funding and timeline

FOREUM research grant: EUR 200.000
Project duration: 2020–2023

Publications

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.

Project team/centres

- D van der Woude, UMC Leiden, NETHERLANDS (lead)
- S Rooijakkers, Medical Microbioloy, Utrecht, THE NETHERLANDS
- P Heeringa, UMC Groningen, THE NETHERLANDS
- Y K O Teng, UMC Leiden, THE NETHERLANDS

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

Project lead
JC Guéry, University of Toulouse, FRANCE
jean-charles.guery@inserm.fr

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

Publications
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.

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.

Project team/centres
- JC Guéry, University of Toulouse, FRANCE (lead)
- C Chizzolini, University of Geneva, SWITZERLAND
- L Frasca, Istituto Superiore di Sanità, ITALY

Validation of sex-dependent molecular pain mechanisms in OA

Project lead

T Vincent, University of Oxford, UNITED KINGDOM
tonia.vincent@kennedy.ox.ac.uk

Funding and timeline

FOREUM research grant: EUR 568.000
Project duration: 2020–2023

Publications

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.

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 Institute, 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

M Wahren-Herlenius, Karolinska Institute, SWEDEN
marie.wahren@ki.se

Funding and timeline

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

Publications

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".

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.

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

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

Project lead
I Ceccherini, IRCCS Istituto Giannina Gaslini, ITALY
isa.c@unige.it

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

Publications
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 hospedalization)
- 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

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.

Project team/centres

- I Ceccherini, IRCCS Istituto Giannina Gaslini, ITALY (lead)
- M Gattorno, IRCCS Istituto Giannina Gaslini, ITALY
- P Uva, IRCCS Istituto Giannina Gaslini, ITALY
- S Croci, Azienda Unità Sanitaria Locale, ITALY
- P L Meroni, University of Milano, ITALY
- A Cavalli, Fondazione Istituto Italiano di Tecnologia (IIT), ITALY

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

Project lead
J L Pablos, Hospital 12 de Octubre, SPAIN
jlpablos@h12o.es

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

Publications
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 fator 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.

Patient voice

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

Project team/centres

- J L Pablos, Hospital 12 de Octubre, SPAIN (lead)
- M Galindo, Hospital 12 de Octubre, SPAIN
- R Garcia, Hospital 12 de Octubre, SPAIN
- E Paz, Hospital 12 de Octubre, SPAIN
- R Perona, Hospital 12 de Octubre, SPAIN
- L Sastre, Hospital 12 de Octubre, SPAIN

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

M Englund, Lund University, SWEDEN
martin.englund@med.lu.se

Funding and timeline

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

Publications

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

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.

Project team/centres

- M Englund, Lund University, SWEDEN (lead)
- K Magnusson, Norwegian Institute of Public Health (NIPH), NORWAY
- S Bierma-Zeinstra, Erasmus MC Netherlands, NETHERLANDS

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

Project lead

Y-M Pers, CHU Montpellier, FRANCE
ym-pers@chu-montpellier.fr

Funding and timeline

FOREUM research grant: EUR 75,000
Project duration: 2020–2021

Publications

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: Recruitement 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

- Y-M Pers, CHU Montpellier, FRANCE (lead)
- P Louis-Plence, INSERM UMR1183, FRANCE
- J M Brondello, INSERM UMR1183, FRANCE
- F Berenbaum, Université Pierre et Marie Curie, FRANCE
- H Marotte, CHU Saint-Etienne, FRANCE
- M Khoury, Clínica Universidad de los Andes, CHILE
- 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

Project lead
V Welsh, Keele University, UK
v.welsh@keele.ac.uk

Funding and timeline
FOREUM research grant: EUR 99.195
Project duration: 2020–2022

Publications
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)

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 in-

flammatory 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

– Burja B. et.al., reveals a role of dimethyl-α-ketoglutarate in TGFβ-driven cytoskeleton regulation and myofibroblast differentiation, Poster SAT0292, EULAR 2020
– Burja B. et.al., The Metabolic Intermediate Alpha-Ketoglutarate Suppresses the TGFβ-driven Profibrotic Responses of Dermal Fibroblasts, Poster 1043, ACR 2019
– Burja B. et.al., Metabolic Intermediate Alpha-Ketoglutarate Attenuates TGFβ-driven Profibrotic Responses of
– Dermal Fibroblasts, Oral and Poster presentation at the 16th International Workshop on Scleroderma Research

Project team/centres

– V Welsh, Keele University, UK (lead)
– C Burton, Keele University, UK
– K Jordan, Keele University, UK
– J Bailey, Keele University, UK
– M Frisher, Keele University, UK
– C Mallen, Keele University, UK